THE INFLUENCE OF FORMATION CONDITIONS ON THE PROPERTIES OF LITHIUM TITANATE

by

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ABSTRACT

Lithium titanate (Li$_2$TiO$_3$) has been prepared by heating the mixture of lithium carbonate powder and titanium dioxide powder at molar ratio 1:1 at four different formation temperatures (680, 720, 820 and 920°C) for 24 hours. The samples produced were evaluated and characterized by determining the density, loss of weight on heating, particle size and surface area, etc., and by employing IR spectroscopy, X-ray diffraction, dielectric spectroscopy and solid NMR. In addition, the in-vitro release of lithium and the release mechanism of powders produced have been studied. The formation temperatures were found to affect the crystal growth on the surface of lithium titanate particles and to give three different slow release profiles of lithium in vitro (slow, intermediate and fast). An increase in the temperatures resulted in a great decrease in the release rate of lithium, especially for the first hour. No differences were found in density, loss of weight on heating and particle size of the samples made at 720°C or higher. The chemical reaction at 680°C was incomplete. The surface areas of these powders differed greatly.

Factors such as heating time, particle size of lithium carbonate and the quantity of the mixture were also investigated. These factors were found to affect mainly the in-vitro release of lithium from the powder, but did not affect the properties of the powder, since the factors influenced primarily the crystallization of lithium titanate.

Different tablet formulations were prepared by wet granulation, using different binders and channelling agents. The in-vitro release of lithium and the effects of the tablet weight and size were studied. A zero order of release was obtained from erodible/non-disintegrating tablets and a first order release from disintegrating tablets. The release rates of lithium from the tablets produced, however, did not exceed the release rate of lithium titanate powder.

From the study of the properties of the lithium titanate samples, general and additional specifications were proposed.
In memory of the life in United Kingdom

.....
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</tr>
<tr>
<td>Photos 3.19</td>
<td>SEM of lithium titanate samples prepared at 920°C, Group III (Batch No. 1, 2 and 3)</td>
</tr>
<tr>
<td>Photos 3.20</td>
<td>SEM of lithium titanate samples prepared at 920°C, Group III (Batch No. 4 and 5)</td>
</tr>
<tr>
<td>Photos 5.1</td>
<td>SEM images of lithium titanate made at different formation temperatures</td>
</tr>
</tbody>
</table>
List of Symbols

A  Sample integrator counts
A_{cal}  Calibration integrator counts
A_{cs}  Cross section area of nitrogen molecule
C  Capacitance of the material
C'  A constant which is a function of the heat of the nitrogen
C_{Li}  Lithium content in the product produced in percentage
C_t  Theoretic value of lithium content of lithium titanate
d  Density of the sample
F  Affinity or exchange ratio between lithium ion and hydrogen ion
G  Conductance of the material
L  Loss of weight on heating in percentage
l  Distance between two metal electrodes
M_a  Nitrogen molecular weight
N  Avogadro's number
P(\%)  Purity of the product produced in percentage
P  Partial pressure of nitrogen
P_a  Saturated vapour pressure of nitrogen
P_a  Ambient pressure
Q_{Li}  Amount of lithium added
Q_p  Weight of final product obtained
R  Gas constant (82.1 ml/atmdy.mol)
S_t  Total surface area of the sample
Specific surface area of the sample

Absolute temperature (K)

True volume of the sample

Calibration volume

Weight of the sample

Weight of the mixture of lithium carbonate and titanium dioxide before heating or weight of the mixture used

Weight of the mixture of lithium carbonate and titanium dioxide after heating or weight of lithium titanate produced

Weight of adsorbate (nitrogen) adsorbed on the sample

Weight of nitrogen adsorbed at a coverage of one monolayer

A loss factor

Permittivity of the material

Permittivity of free space

Part of relative permittivity representing the "leakage" or "loss"

Part of relative permittivity representing the capacitance decreasing

The relative permittivity

The permittivity at infinite frequencies

Frequency
CHAPTER 1

INTRODUCTION
Psychiatric disorders are described as abnormal mental states. The causes are complex and unknown. They may be a result of disturbance from one or more of the following interrelated factors (Brophy et al, 1985): (1) Biological function, (2) Psychodynamic maladaptation, (3) Learned behaviour and (4) Social and environmental conditions. There are about fourteen types of common psychiatric disorders such as depression and mania, stress and adjustment disorders, anxiety and dissociative disorders etc.

The treatment of the psychiatric disorders depends on the psychiatric assessment of each individual patient. The approaches generally are medical measures, psychologic techniques, social and environment manipulation and behavioral techniques or the combination of above approaches. Medications and convulsive therapy are commonly used in the treatment. The medications involve use of different types of the therapeutic drugs such as antipsychotic drugs (e.g. chlorpromazine), lithium (e.g. lithium carbonate) and antidepressant drugs (e.g. phenelzine).

The medical use of lithium can date back to 1841 when it was first introduced by Lipovoitz (Gershon, 1973) to treat uraemia, renal calculi, gout, rheumatism and other disorders. In 1949, the use of lithium in psychiatry was discovered by John Cade. Two years later, it was reported that the treatment of manias with lithium had reached roughly 25 to 30% success (Gershon, 1973). Since then, lithium has become the first choice of treatment in mania. To date, the use of lithium has dramatically affected both diagnosis and treatment in psychiatry. Lithium has been found to be effective not only in the treatment of acute manic episode, but also in maintenance therapy of bipolar disorder, prophylaxis of recurrent depression and in a number of other conditions such as acute depression, antidepressant augmentation, schizoaffective disorder, schizophrenia, alcoholism and aggressive states (Jefferson, 1990). The status of lithium therapy in psychiatry, as described by Johnson (1987), are that lithium would continue to occupy its position as a leading treatment modality in therapy for a long time, a position which can only become strengthened as more is learned about the kind of administration regimens which enable maximum clinical effectiveness to
be achieved with a minimum number of problems.

1.2 AFFECTIVE DISORDERS AND THE TREATMENT WITH LITHIUM

1.2.1 Affective disorders

A. Mania

A manic episode is a mood change characterized by elation with hyperactivity, overinvolvement in life activities, low irritability threshold, flight of ideas, easy distractibility and little need for sleep. Atypical manic episodes can also include gross delusions, paranoid ideation of severe proportions and auditory. Hallucinations are usually related to some grandiose perception. The episodes begin abruptly and may last from several days to months. The prevalence of mania was estimated to range between 0.1 and 0.8 per 1000 of the population (Jampala, 1987; Brophy, 1991).

B. Depression

Depression, like anxiety, is ubiquitous and is a reality of everyday life. It is recognized that the following symptoms are present in most depression: lowered mood (varying from mild sadness to intense feeling of guilt, worthlessness and hopelessness), difficulty in thinking, loss of interest, somatic complaints and anxiety. On some severe depressions presents psychomotor retardation or agitation, withdrawal from activities and suicide ideation. When the depression is appropriate to a life event and is not of major magnitude, specific treatment is not necessary. In general, there are three major groups of depressions: (1) Reactive to psychosocial factors, (2) Depressive disorders and (3) Bipolar disorders (manic and depressive episodes). Recent study indicated that as many as one in ten Americans may experience depression at some point in their life. The worldwide annual prevalence of depression by WHO (World Health Organization) is about 3 to 5% population (100 million people) (Charney et al, 1988).
C. Affective disorders

Depression and mania are classified together as affective disorders. Both are predominantly disorders of mood (Brophy, 1985 and Tsuang et al, 1987), representing two extremes of a continuum and occurring at different times in the same individual. Individuals suffering from both mania and depression at different times are described as having a bipolar affective disorder. When either mania or depression occurs alone, the condition may be referred to as a unipolar affective disorder.

1.2.2 Treatment with lithium

As a prophylactic drug for bipolar affective disorder, lithium significantly decreased the frequency and severity of both manic and depressive attacks in about 80% of patients (McCue et al, 1988). In the acute phase of the illness, manic patients are usually treated with neuroleptics (e.g. chlorpromazine, haloperidol) first until the acute manic symptoms are under control, and then followed by lithium treatment as soon as possible since the neuroleptics are not generally suitable for maintenance treatment of manic patients, as they have toxic side effects with long-term use and do not invariably prevent recurrence of mania (Jampala, 1987). Lithium has been suggested as a potential antidepressant for certain depressed patients. It was concluded that lithium is more effective in bipolar depressives than in unipolar depressives (Goodwin et al, 1972 and Baron et al, 1975). Recently, FDA (Food and Drug Administration in USA) has approved lithium for use in treatment of acute mania and in maintenance therapy of bipolar disorder. The clinical indication of lithium stated in BNF (British National Formula, 1993) is that lithium salts are used in the treatment and prophylaxis of mania, in the prophylaxis of bipolar disorder and recurrent depression (unipolar disorder).

Although presently lithium remains the treatment of choice for these two conditions, the likelihood of probable benefit from lithium use exists in other conditions such as herpes, aplastic anemia, aids, etc. (Jefferson, 1990)

The effectiveness of lithium therapy is related to the serum lithium concentration. It is usually recommended that the serum lithium concentration should
be within the range from 0.4 to 1.0 mmol Li⁺/litre to achieve a clinical response. Lithium dosing requirements vary depending on the phase of the patient’s affective illness and age. Current data suggest that the amount of lithium required to control an acute manic episode (0.9 mmol/l to 1.4 mmol/l) is much greater than the amount of lithium necessary to prevent subsequent episodes of either depression or mania (0.4 to 0.6 mmol/l) (Perry et al., 1983, 1984 & 1987 and Lesar et al., 1985). The side effects of the treatment with lithium are also related to the serum lithium level. When the plasma level are greater than 1.5 mmol/l, the treatment may produce toxic effects including tremor, ataxia, dysarthria, renal impairment, convulsions and even death. Plasma concentrations in excess of 2.0 mmol/l require emergency treatment. Therefore, it is important to determine the optimum range of the serum lithium concentration for each individual patient. Since lithium salts have such a narrow therapeutic/toxic ratio (therapeutic index), the plasma lithium level should be monitored and doses should be adjusted at 12 hours after the preceding dose and during the treatment period.

Lithium salts (lithium carbonate and lithium citrate) are available on the market in capsules, tablets and syrup dosage forms. The latter is for patients in whom compliance is a problem. All the dosage forms for lithium treatment are administrated orally. The adequacy of a particular lithium dosage for the individual patient is best determined by the serum level achieved and the individual clinical response.

1.3 LITHIUM

1.3.1 Chemistry

Lithium is the first member of the family of alkali metal and designated as Group IA in the periodic table of elements with an atomic number of 3. It is the lightest metallic element (specific gravity, 0.534). As a consequence, the chemistry of the alkali metals is essentially that of the +1 ion (Li⁺). Because of its large ionic radius in aqueous solution, it exhibits a similarity to calcium and magnesium of the neighbouring group IIA of the alkaline metals (Frianeza-Kulberg, 1987). The salts of lithium ion share some characteristics with those of sodium and potassium, but not others.
1.3.2 Pharmacology

The pharmacologic properties, therapeutic as well as prophylactic of lithium salts are attached solely to the lithium ion.

The general biology and pharmacology of the lithium ion was reviewed in detail by Schou (1957, 1969 and 1978). Lithium is not a sedative, depressant or euphoriant, which differentiates lithium from all other psychotropic agents.

The mechanism of action of lithium ion as an antimanic and mood stabilizing agent remains uncertain, perhaps because the cause of the illness itself is unclear. Initially, lithium was suspected to compete with Na⁺ and K⁺. However, lithium is not an adequate substitute for sodium in the "sodium pump" and can not maintain membrane potentials, because lithium ion has a relatively small gradient of distribution across biological membranes (Gilman et al, 1980 and Dollery, 1991). It is not known whether an important interaction occurs between lithium (at therapeutic level) and the transport of other monovalent or divalent cations by nerve cells.

Some in-vitro studies have suggested that the lithium ion may compete with or displace magnesium from molecular sites on enzymes, receptors and other effects (Birch, 1976, 1982, 1987, 1988; Birch et al, 1986), because of the chemical similarity between lithium and magnesium.

1.3.3 Pharmacokinetics

Lithium ion is readily and almost completely absorbed from the gastrointestinal tract (>97% oral absorption). Lithium is not protein bound. Once absorbed, lithium is subsequently distributed throughout body water, both intra and extracellularly. Its distribution volume approximates to the body water volume (50-90% of body weight), but concentrations in white matter, thyroid and bones are several-fold higher than the plasma concentration (Thornhill, 1981 and Poust, 1987). Entry into the cerebrospinal fluid is relatively slow and the equilibrium concentration is about 40% of that in the plasma concentration. Lithium is eliminated exclusively by the kidneys. It is filtered at glomerulus and reabsorbed almost like sodium in the proximal tubules, but normally
it is not reabsorbed in the distal parts of the nephron. Sodium loading produces a small enhancement of lithium excretion, but depletion by any diuretic promotes a clinically important degree of retention of lithium.

The serum concentration curve of lithium taken orally (the only route of administration used in practice for the therapy) shows rapid absorption, dependent on the drug formulation. Different formulations can affect the absorption markedly. After intake of an aqueous solution, the peak concentration occurs within about 30 minutes. After conventional tablets, the absorption is variable, starting at about 30 minutes with a maximum after 4-5 hours. After slow release tablets, there is broad maximum at 5 hours. After the peak a biphasic fall occurs, the rapid $\alpha$-phase lasts about 1.15 hours which is followed by a slower $\beta$-phase with a half life ranging from 8 to 45 hours (a mean of 24 hours) (Gillman et al, 1980; Amdisen et al, 1977 & 1986; Goodnick et al, 1981; Poust 1987 and Dollery 1991).

1.4 ORAL SUSTAINED/CONTROLLED RELEASE SYSTEMS

1.4.1 General

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of active drugs to patients, using various pharmaceutical dosage forms, which are known as conventional delivery systems. The characteristic of the oral conventional dosage forms such as tablets, pellets, capsules, etc., is that of providing an immediate release of active drug when the form is administrated. Therefore, to achieve maintenance of the drug concentration within the therapeutic range needed for treatment, it is often necessary to take the dosage form several times a day. This results in a great fluctuation in drug blood levels [see Fig.1.1(a)]. The fluctuation may lead to the production of a toxic level with undesirable effects, especially for those drugs with narrow therapeutic index and long half life.

Oral sustained/controlled release systems were introduced in the early sixty’s. Since then, new techniques for preparation of the system have been developed and advanced. These techniques are capable of controlling the rate of drug delivery,
Fig. 1.1 Plasma drug concentration-profiles  

a: multi-dose conventional tablets or capsule formulation  
b: single dose of conventional formulation, sustained release formulation and controlled release formulation
sustaining the duration at therapeutic activity, and/or targeting the delivery of drug to a tissue (Chien, 1983, 1987 & 1989). These types of systems are designed to release active drug at a slower rate or a constant rate to achieve the therapeutic level and to maintain it within the therapeutic window with less fluctuation [see Fig. 1.1(b)], and therefore to reduce the side effect and dosing frequency.

Both sustained and controlled release systems are similar in terms of the duration of drug action. However, there is a difference between these two types of systems. The sustained release drug delivery system is described as a pharmaceutical dosage form formulated to retard the release of a therapeutic agent and to ensure its plasma profile is sustained in duration. The onset of its pharmacologic action is often delayed and the duration of its therapeutic effect is sustained. The controlled release drug delivery system has the same characteristic, but it additionally implies a predictability and reproducibility in the drug release kinetics.

The difference between sustained and controlled release systems is illustrated in Fig. 1.2, which is the plasma profiles of phenylpropanolamine in human. A sustained release drug delivery system (Dexatrin) yields a sustained (but not constant) plasma profile with a longer duration than that achieved by a solution formulation. A controlled release system (Acutrin) provides a constant steady state plasma level with further prolongation of the duration (Chien, 1992a).

In general, the sustained/controlled release drug delivery systems attempt to sustain drug action at a predetermined rate, to localize drug action and to target drug action. In practice, the release systems (in most case) create a sustained or a constant plasma concentration of drug within the body over an extended period of time. The primary objectives of the systems are to ensure safety (minimization of undesirable side effects associated with fluctuation in drug level) and to improve efficacy of drugs as well as patient compliance.

1.4.2 Advantages and disadvantages

A. Advantages

The ideal sustained/controlled release systems should have the following
Fig. 1.2 Comparative plasma profiles of phenylpropranolamine (PPA) from oral solution formulation (soln.), sustained release (Dexatrim) and controlled release (Acutrim) formulations (Chien, 1992)
advantages.

1) Reducing fluctuations in plasma drug levels, and therefore improving safety and minimizing side effects of the drug
2) Reducing dosing frequency, and therefore increasing the patient compliance and decreasing the total amount of drug used
3) Achieving a more uniform pharmacological response
4) Avoiding irritation in gastrointestinal tract
5) Avoiding the night time dosing

B. Disadvantages

Several disadvantages of the systems were discussed in details by Welling et al (1987). They are summarized as follows.

1) **High cost**

   More sophisticated technology must be employed in preparation of the systems than that used in conventional dosage forms.

2) **Dose dumping**

   A phenomenon whereby the relatively large quantity of medication in some controlled release formulations is rapidly released, introducing potentially toxic quantities of drug into the system circulation. However, it should not be a problem with good manufacturing practice and the types of rigid control.

3) **Reduced potential for dosage adjustment**

   It can be a major disadvantage of some sustained/controlled release systems. It can be improved by formulating the product in a variety of strengths or in a form that can easily be subdivided without losing sustained/controlled release properties.

4) **Increased potential for first-pass clearance**

   The potential for reducing drug availability due to first-pass metabolism is greater with sustained/controlled release formulations than with conventional dosages. Hepatic metabolism is a saturable process. The higher the oral dose, the greater the possibility of saturating hepatic drug metabolizing enzymes. The smaller the dose, or
the slower the dose is released from the preparation, the smaller possibility of saturating first-pass metabolism.

5) Reduced drug absorption

It is an intrinsic disadvantage with all oral release dosage forms. Apart from the obvious limitation of gastrointestinal (GI) residence time, a sustained/controlled formulation is likely to cause a fraction of administrated drug to be released in regions of the GI tract that are distal to the optimum absorption region of the small intestine if the release rate is too slow. The problem is related to the GI physiology, which is increasingly recognised and will be discussed in detail in the following section 1.4.4.

1.4.3 Preparation of oral sustained/controlled release systems

The methods or techniques used in preparation of oral sustained/controlled release drug delivery systems are dependent on the design of the system (i.e., types of the systems) and the properties of drugs. Based on the principles applied in the release systems, oral sustained/controlled release drug systems can be classified into three main types: (A) Rate-preprogrammed release systems, (B) Activation-modulated release systems and (C) pH-independent release systems. The preparation of these types of release systems are briefly discussed below.

A. Rate-preprogrammed release systems

The release of active drug from the systems at specific rate profiles is accomplished by controlling the molecular diffusion or dissolution through the barrier medium within or surrounding the system. Two methods are usually applied in the preparation: (1) coating a core (particles, granules, pellets, and tablets) containing active drugs with different types of polymers to form different polymeric film membranes and (2) dispersing active drug directly into a matrix such as polymers or fatty materials which are insoluble in gastrointestinal fluid. The rate of drug released can be controlled by regulating the concentration of the polymers used in the system.

The method (1) is usually used in membranes permeation controlled release systems which consist of two types: (i) non gastric fluid-erodible and (ii) gastric fluid
resistant intestine-targeted. The type(i) is usually prepared by first compressing a water soluble drug, in combination with appropriate pharmaceutical excipients, into a core tablet and then coating the tablet with a layer of non-GI-erodible polymer (i.e. a copolymer of vinyl chloride and vinyl acetate), which also contains a small amount of water soluble pore-forming agents or plasticizer (i.e. magnesium lauryl sulphate). During the course of GI transit, the pore-forming agents are dissolved by the gastrointestinal fluid to form a microporous membrane. The type(ii) is prepared by coating core tablets of the drug with a combination of an intestinal fluid-insoluble polymer (i.e. ethycellulose) and an intestinal fluid-soluble polymer (i.e. methylcellulose). When the coated tablet arrives in the intestinal tract, the intestinal fluid-soluble polymer is dissolved to form a microporous membrane. The rate of drug released can be controlled and predetermined by the microporous membrane.

The method (2) is often used in the matrix diffusion controlled release system. The system is prepared by blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chains, or mixing a drug solid with a fatty material (i.e. beeswax) at melting temperature. The resulting drug-polymer dispersion is then moulded or extruded to form a drug dosage form of various shapes and sizes. It may also be prepared by formulating the drug into tablets, using hydrophilic polymer (i.e. hydroxypropyl methylcellulose, water swellable) as a binder. The rate of drug release from the matrix system is dependent on time and on the rate of drug diffusion.

B. Activation-modulated drug delivery systems

In this group of controlled release drug delivery systems, the release of drug is activated by some physical, chemical or biochemical processes. The processes mainly used in the preparation are physical and chemical means such as osmotic or hydrodynamic pressure and ion-exchange, respectively. The principles of osmotic and hydrodynamic release systems are similar, but different energy sources are introduced to force the drug to release through a delivery orifice. Only liquid formulation can be applied in the hydrodynamic pressure system. In ion-exchange system, the active drug should be ionic or ionizable, which allows to form a complex with an anionic or
cationic ion-exchange resin. The rate of drug release is controlled by regulating the process applied or energy input and the size of delivery orifice.

Osmotic pressure is used as the driving force to generate constant drug release in osmotic systems. The system is prepared by applying a semipermeable membrane around a core of an osmotically active drug or a core of an osmotically inactive drug in combination with an osmotically active salt (i.e. sodium chloride). The drug core can be either a solution or a solid formulation. The drug is activated to release in a solution form at a constant rate through a special delivery orifice drilled by laser or by a high-speed mechanical drill. When the system is exposed to water or any body fluid, water will flow into the core due to an osmotic pressure difference across the coating membrane. The rate of drug release is modulated by controlling the gradient of osmotic pressure.

Hydrodynamic pressure is also a potential energy source for controlled the release of active drugs (Micahaels, 1979 and Sheth et al, 1984). The system can be prepared by enclosing a collapsible drug compartment containing a liquid drug formulation inside a rigid shape retaining housing. The space between the drug compartment and external housing contains a laminate of swellable, hydrophilic cross-linked polymer (i.e. polyhydroxyalkyl methacrylate) which absorbs the gastrointestinal fluid through the annular openings in the bottom surface of the housing. This absorption causes the laminate to swell and expand, which generates hydrodynamic pressure in the system and forces the drug compartment to reduce the volume and induce the release of drug from a liquid formulation through the delivery orifice.

C. pH-independent release system

This system is designed for the release of acidic or basic drug in the gastrointestinal tract at a rate of independent of the variation in gastrointestinal pH. It is prepared by blending a drug with one or more buffering agents which help maintain a constant pH during the course of gastrointestinal transit, granulating to form small granules and then coating with gastrointestinal fluid permeable film-forming polymers (i.e. cellulose derivatives).

The pharmaceutical techniques involved in the preparation of above systems
are discussed in greater detail by Hui et al (1987) and Chien (1992b).

1.5 DESIGN OF LITHIUM SUSTAINED/CONTROLLED RELEASE SYSTEM

The effective drug delivery via oral route depends on the two determining factors: (1) the nature of the dosage forms in which the drug is presented and (2) the residence time in the gastrointestinal tract. All the oral controlled release systems discussed above are designed to control the rate of drug released from the system. Some of them may be able to minimize the influence of gastrointestinal (GI) environment such as pH changes in the GI tract. However, they are not able to control or to influence the GI dynamics such as gastric emptying and GI transit, although they control the nature of drug presented in the dosage form. The systems have therefore only limited utilization if the system can not remain in the vicinity of the absorption site for the time of drug release, since the system releases active drug at a slower rate compared to the conventional dosage forms. The GI environment and dynamics play a critical role in drug absorption. It is much more relevant for the design of a oral sustained/controlled release system to take GI physiology into consideration, with optimization of dosage form characteristics such as release rate of drug from the system. Nevertheless, all the pharmaceutical products for the oral route of administration and the design of dosage forms (either solid, dispersion or liquid) must be developed within the intrinsic characteristics of GI physiology, irrespective of the mode of drug delivery (immediate, sustained/controlled release).

1.5.1 Physiological Consideration

A. Gastrointestinal (GI) Tract

The gastrointestinal tract, illustrated in Fig. 1.3, consists mainly of three parts: the stomach, the small intestine (the duodenum, jejunum and ileum) and the large intestine. The major function of the stomach is to temporarily store food, to mix food and to finally empty it into the duodenum of the small intestine. Very little drug absorption occurs in the stomach as a physiological result of its limited surface area
Fig. 1.3 The gastrointestinal tract

pH

<table>
<thead>
<tr>
<th>Location</th>
<th>pH</th>
<th>Length</th>
<th>Surface Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.0-2.0</td>
<td>0.25 m</td>
<td>-</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4.0-5.5</td>
<td>1.9 m</td>
<td>462 m²</td>
</tr>
<tr>
<td>Jejunum</td>
<td>5.5-7.0</td>
<td>2.80 m</td>
<td>184 m²</td>
</tr>
<tr>
<td>Ileum</td>
<td>7.0</td>
<td>4.20 m</td>
<td>276 m²</td>
</tr>
<tr>
<td>Colon</td>
<td>7.2-8.4</td>
<td>1.50 m</td>
<td>-</td>
</tr>
<tr>
<td>Cecum</td>
<td>7.2-8.4</td>
<td>0.065 m</td>
<td>-</td>
</tr>
</tbody>
</table>

With the compliments of Capsugel Library
(0.1-0.2 m²) covered by a thick layer of mucous coating, the lack of villi the mucosal surface and the short residence time of most drug in the stomach. The residence time of the contents or dosage forms in the stomach depends on the dynamic patterns of the stomach, which are responsible for gastric emptying. The gastric emptying process is, however, influenced by many factors such as dietary intake, stress, exercise, sex, age, etc. It is variable and unpredictable within and between individuals. It has been recognized that the gastric emptying time is one of the most important physiological factors that may lead to erratic bioavailability of a drug from oral sustained/controlled release dosage form and to variations in pharmacological responses (Levine, 1970; Levy, 1972 and Wilson et al, 1989).

The small intestine has enormous number of villi on its mucosal surface that create a large surface area (4500 m²). These villi are minute fingerlike projections of the mucosa and are most numerous in the duodenum and proximal jejunum. There is a progressive decrease in surface area from the proximal to the distal region of the small intestine. Therefore, the proximal small intestine is the region with the most efficient absorption. For maximal systemic bioavailability, the drug should be targeted for delivery in the vicinity of this region.

The large intestine lacks villi, and its primary function is to store indigestible food residue. However, in some cases, it may play an important absorptive role (Staib et al, 1986; Godbillon et al, 1985 and Yuen et al, 1993).

B. Gastrointestinal (GI) Transit

The GI transit time of a oral dosage form along with the GI tract is known to vary from one individual to another. Some studies suggested that the maximum duration in the GI tract is approximately 24 hours for most human subjects, but it could vary from 8 to 62 hours (Hinton et al, 1969; Good et al, 1974 and Park et al, 1984). The total GI transit time takes into account the gastric emptying time, the transit times of the small and large intestines. Since most orally administrated drugs are absorbed in the upper portion of the small intestine, the transit time of a dosage form from stomach to the ileocecal junction is critically important to target drugs at the vicinity of absorption sites.
In the small intestine, the transit duration of the contents or dosage forms, regardless of their nature (i.e. shape, size and physical state), is about 3-4 hours in both the fasted and the fed states (Caride, 1984; Davis et al, 1986(a); Ollerenshaw et al, 1987 and Mundy et al, 1989). Because of the relative constancy in the small intestinal transit, the residence time of the dosage form in the stomach appears to be a major determining factor in the overall GI transit time. As the gastric emptying time may vary from 0.5 to 16 hours (Mojaverian et al , 1985), it could greatly affect the absorption of drug in the GI tract and produce the individual differences in bioavailability of drug.

In addition, each drug may have its own absorption site (absorption window) in the GI tract such as the proximal region in the small intestine. If a sustained/controlled release system releases its active drug after passage through these areas, the absorption of the drug may be seriously impaired and the bioavailability of the drug could be substantially reduced.

In summary, the drug absorption from oral dosage forms is constrained by the total residence time in the GI tract. To achieve reproducibility in drug release and absorption during the transfer course of dosage forms through the GI tract, oral sustained/controlled release system should be ideally transported to the target site of absorption and reside there for a prolonged period of time to release a drug dose at a controlled rate. Thus, delay in gastric emptying time could provide a possibility to extend the total GI retention time of dosage forms, therefore, to maximize the therapeutical benefits, to minimize the side effects related to the blood level fluctuation, to overcome the intrinsic disadvantage of the system (reduced drug absorption) and to achieve uniform clinical response.

1.5.2 Prolongation of GI Transit Time

A. Factors Influencing Gastric Emptying

There are two types of factors which potentially influence the gastric emptying process: (a) physiological factors and (b) pharmaceutical factors. The physiological factors are associated with human subjects. They are: food, diseases, age, sex,
exercise, etc., which are difficult to control and vary greatly from one to another individual. Extensive studies have shown that the gastric emptying process is influenced by these factors (O'Reilly et al, 1987; Bogentoft et al, 1978; Wald et al, 1981; Cammack et al, 1982; Mojaverian et al, 1987; Davis et al, 1986(b); Nimmo, 1976; Kraus et al, 1984; Moore et al, 1983 and Ramsbottom et al, 1974). However, the presence of food in the stomach has more important effect on the gastric emptying. Several studies have shown that the gastric residence time of a dosage form is significantly prolonged in the fed subjects (Davis et al, 1984 (a&b) & 1986(b&c); Sangekr et al, 1987; Khosla et al, 1989; Borin et al, 1990 and Sournac et al, 1991).

The pharmaceutical factors are these related to the physical properties of dosage forms such as shape, size, state (solid or liquid) and density of the dosage form. Among them, the size and density of the delivery system have been found to be more significant factors in influencing the gastric emptying time (Hinder et al, 1977; Bechgaard et al, 1984; Smith et al, 1986; Meyer et al, 1985 and Ehle et al, 1986).

B. Approaches to Prolongation of the GI Transit Time

Several approaches have been developed to prolong the residence time of drug delivery systems in the GI tract. They are discussed below.

B-1 Bioadhesive Approach

This approach is conceptualized on the basis of a GI self-protective mechanism. This self-protective mechanism is due to the fact that the specialized goblet cells located in the stomach and duodenum continuously secrete a large amount of mucus that remains closely applied to the surface epithelium. The mucus contains mucin, which is capable of neutralizing the hydrochloric acid and withstanding the action of pepsin and thus protects the epithelial cell membrane [Chien, 1992 (b)].

The concept of using mucoadhesive polymer (i.e. carboxymethylcellulose) to extend the gastric emptying time is shown in Fig. 1.4. The drug delivery system coated with the polymer binds to the mucin molecules in the mucus lining and is therefore retained on the surface epithelium for extended periods of time. The drug
Fig. 1.4 Interaction of a bioadhesive drug delivery system with the mucus layer on the gastrointestinal surface epithelium (Hui et al, 1987)

Fig. 1.5 Hydrodynamically balanced system before and after contact with gastric fluid (Hui et al, 1987)
molecules contained in the system are constantly released through the polymer for absorption (Park \textit{et al.}, 1984 & 1987; Dittgen \textit{et al.}, 1989 and Smart \textit{et al.}, 1984). Such adhesion may cause problems if the drug released is locally irritating to the mucosa in the stomach.

**B-2 Floating Approach**

The floating approach is based on the principle that the density of the dosage forms is lighter than the normal gastric contents (1.0-1.4), therefore, the system can float on the gastric contents to prolong gastric residence time.

One of the systems (hydrodynamically balanced system, HBS), in either capsule or tablet form, is designed to prolong residence time in the stomach by remaining buoyant in the gastric fluid (Sheth and Tossounian, 1978 & 1984). The formulations are prepared by using a high level (20-75\%) of one or more gel-forming hydrocolloids (i.e. hydroxyethylcellulose) to produce granules and then compressing these granules into a tablet (or encapsulating into capsules). On contact with gastric fluid, the tablet or granules forms a water-impermeable colloid gel barrier around its surface with thickness growing with time (see Fig. 1.5). The gel barrier controls the rate of the gastric fluid penetration into the system and the rate of drug release. It also maintains a bulk density of less than 1 and thus remains buoyant in the stomach for up to 6 hours (Park and Robinson, 1987). However, subsequent work established that low density dosage forms are unable to retain the system in the stomach unless water is present. This requires subjects to take a glass of water every hour, an unacceptable procedure under most circumstances (Hui and Robinson, 1987). Additionally, the increase in retention time may be due to adhesion to the gastric mucosa, rather than floating.

Another system was attempted by Ingarri \textit{et al.} (1987). The system is a bilayer compressed matrix floating tablet. One of the tablet layers contains a carbon dioxide generating blend and a hydrophilic polymer. The second layer is a hydrophilic matrix containing the active drug, which is released at a sustained/controlled way. On contact of the gastric fluid, the carbon dioxide entrapped in the gelified hydrocolloid is liberated to cause the floating of the tablet.
However, it has been suggested by many researchers that floating systems do not possess an inherent ability for gastric retention, but rely on the presence of a meal to retard their emptying (Muller-Lissner et al, 1981 and Mazer et al, 1988). The gastric emptying times for both floating and non-floating single units are short in fasted subjects (less than 2 hours), but are prolonged after a meal (around 4 hours) [Davis et al, 1984 (a and b) & 1986(b and c)]. There was no overall difference in gastric emptying or colon arrival times.

B-3 Controlling the size of dosage forms

As discussed before, the size of an administrated solid particles is one of the factors which affects the gastric emptying process. Because of the sieving mechanism of the stomach, solids of small particle size (< 2 mm) can be emptied with liquid into duodenum, and the large particles (> 2 mm) can not be emptied unless they have been ground to a particle size of 2 mm or less. Several studies have shown that the mean gastric emptying time increased by increasing the size of a dosage form (Jonsson et al, 1983 and Davis et al, 1990). In the fasted state, increase in the size of the dosage form may defy the emptying process or convert the stomach from the interdigestive to digestive pattern, at which state the large dosage form is retained for long periods of time in the stomach until the arrival of the time when they are emptied as a bolus (Hinder et al, 1977). In the fed state, the large dosage forms tend to reside in the stomach while grinding and mixing take place. However, the large size of dosage form may have pharmaceutical limitations such as obstruction of the dosage form in the GI tract (Davis et al, 1988; Khosla et al, 1989 and Course, 1991).

B-4 High density approach

The influence of the density of a oral dosage form on the gastric emptying time is increasingly recognized. Studies has suggested that the density must exceed a critical value which then could influence the gastric emptying (Devereux, 1987; Clarke, 1989 and Course, 1991). It has been found that the residence time of the dosage form in the stomach is prolonged if the density is greater than 2.8 g/cm³. The increase in residence time with increased density may due to an increased resistance of the dosage
form to the normal contractions of the stomach or a deeper settling of the dosage form into the folds of the stomach, particularly at its base.

The preparation of high density dosage forms is much simpler, compared to the other approaches. In preparing such formulations, drug can be coated onto a heavy core or mixed with heavy insert materials such as barium sulphate, titanium dioxide, ferric oxide or zinc oxide. The weighted pellets or tablets are then covered with a diffusion controlled membrane to control drug release at a certain rate from the system.

1.5.3 Design of novel oral lithium sustained/controlled release system

A. Lithium products available commercially

There are two types of lithium pharmaceutical products available on the market in terms of the mode of lithium delivery: (1) Immediate release products and (2) Controlled release products. Both are in a tablet form. As mentioned in Sections 1.2 and 1.3, lithium has very narrow therapeutic window, the side effects are usually due to rapidly rising lithium blood levels and high serum level peaks. Studies with lithium in human volunteers has shown that rapidly disintegrating tablets generally produce more side effects such as tremor, mild drowsiness, vomiting, etc., because of the fluctuation in serum lithium level (Amdisen, 1967; Brown, 1978 and Muller-Oerlinghausen et al, 1986).

The first type of product such as Camcolit-250 or Camcolit-400 is a conventional tablet formulation which disintegrates in the gastric fluid and releases lithium immediately (within a few minutes) when it arrives in the stomach. As discussed in section 1.4, the immediate release may create sharp serum peaks which could lead to levels in excess of the upper limits of the therapeutical window. The fluctuation in the serum lithium levels is usually produced by multiple dosing also gives a greater risk of toxicity, particularly for lithium with narrow serum levels.

To maintain serum lithium concentrations within the narrow therapeutic levels and to minimize the side effects caused by the sharp peaks and the fluctuation, several controlled release preparations have been developed and are commercially available.
in UK, such as Phasal®, Priadel®, Litarex® and Liskonum®. Although these products are all claimed as controlled release tablets, the single dose pharmacokinetic study of three controlled release formulations (Priadel®, Litarex® and Liskonum®) and a conventional formulation (Camcolit-400) has, however, shown that the three controlled release formulations differ greatly from one to another in their pharmacokinetic profiles, but the profile of Priadel® is similar to that of Camcolit as seen in Fig. 1.6 (Tyrer et al, 1982 and Shelley et al, 1986). No differences were found in the absorption and the bioavailability of lithium following administration of a controlled release preparation (Priadel) and a conventional preparation (Camcolit) (Tyrer and Birch, 1976; Wall et al, 1978). The in-vitro release of lithium from Priadel® in 0.1 N hydrochloride acid solution as medium was carried as described in Section 2.6, Chapter 2. The result was, however, not satisfactory either in terms of controlled release (see Fig. 1.7). As discussed in sections 1.5.1 & 1.5.2, a satisfactory sustained/controlled release system should ideally release its active content with reproducible or predictable kinetics or at a controlled rate and be independent of varying conditions in the GI tract, particularly in GI transit time.

B. Design of lithium sustained/controlled release system

The current controlled release formulations may have good control in the release rate of lithium from the tablets, but no control or no influence on the GI dynamics (i.e. gastric emptying and GI transit). This could be the reason why the variation occurs among these controlled release formulations and no significant clinical benefits were observed. To overcome the common disadvantage of sustained/controlled release system caused by the GI dynamics and to maximize the clinical advantages, a novel oral lithium delivery system was designed in this thesis on the basis of the following ideas: (1) With taking GI physiological characteristic (especially dynamic) into consideration, the principle of the high density approach is employed. To increase the density of the system (greater than 3.0 g/cm³), lithium titanate was prepared by employing a chemical reaction between a lithium compound and a heavy compound (i.e. titanium dioxide). Because of its high density, the system will stay in the stomach for a longer period of time, and hence extend the total GI transit time. (2) The system
Fig. 1.6 The pharmacokinetic profiles of three controlled release formulations (Priadel®, Litarex® and Liskonum®) and a conventional formulation (Camcolit-400) (Shelley et al, 1986)
Fig. 1.7 The *in-vitro* 12 hours dissolution profile of a controlled release formulation (Priadel®) in 0.1 N hydrochloride acid solution as medium
also releases lithium at a sustained or controlled rate during its delayed transit through the GI.

1.6 LITHIUM COMPOUNDS USED IN THERAPY

Different lithium compounds are used in lithium preparations. The salt, which is usually used, is lithium carbonate (see Table 1.1), although no solid evidence is available to show that one salt is clearly better than others. Other salts such as citrate, sulphate, glutamate and adipate are used in some lithium preparations. This may result from formulation design and the process used in the preparation of the dosage forms. Different formulations and preparing processes may require different properties of the compounds.

Lithium titanate prepared in this thesis, however, has never been used in lithium preparations for the lithium treatment. It is one of the compounds in the Li$_2$O-TiO$_2$ system and has been found to be useful in ion exchange and semiconductor materials (Onodera et al, 1989 and Massidda et al, 1988). The details about the compound are discussed in Chapter 2.

1.7 OBJECTIVES OF THE STUDY

The objectives of this study were as follows:
1. To prepare lithium titanate with different formation conditions and to determine the properties of lithium titanate produced.
2. To evaluate the physical characteristics of lithium titanate by using different analytical techniques
3. To investigate the release characteristic and mechanisms of lithium from lithium titanate powder.
4. To study the effects of the formation conditions and other factors on the characteristics of lithium titanate
5. To investigate the possibility of formulating lithium titanate into tablets and therefore to achieve a controlled release formulation.
6. To establish a specification of lithium titanate for a standard quality control.
### Table 1.1 Lithium compounds used in lithium preparations on the market in different countries

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Lithium Salt</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camcolit</td>
<td>C¹</td>
<td>carbonate</td>
<td>UK</td>
</tr>
<tr>
<td>Litarex</td>
<td>S/R²</td>
<td>citrate</td>
<td>UK</td>
</tr>
<tr>
<td>Phasar</td>
<td>S/R</td>
<td>carbonate</td>
<td>UK</td>
</tr>
<tr>
<td>Priadel</td>
<td>S/R</td>
<td>carbonate</td>
<td>UK</td>
</tr>
<tr>
<td>Eskalith</td>
<td>C</td>
<td>carbonate</td>
<td>USA</td>
</tr>
<tr>
<td>Lithane</td>
<td>C</td>
<td>carbonate</td>
<td>USA</td>
</tr>
<tr>
<td>Lithonate</td>
<td>C</td>
<td>carbonate</td>
<td>USA</td>
</tr>
<tr>
<td>Lithizine</td>
<td>C</td>
<td>carbonate</td>
<td>Canada</td>
</tr>
<tr>
<td>Licarb</td>
<td>C</td>
<td>carbonate</td>
<td>Canada</td>
</tr>
<tr>
<td>Lithium Scharffenberg</td>
<td>C</td>
<td>adipate</td>
<td>Germany</td>
</tr>
<tr>
<td>Hypnorex</td>
<td>S/R</td>
<td>carbonate</td>
<td>Germany</td>
</tr>
<tr>
<td>Litio ICI</td>
<td>C</td>
<td>carbonate</td>
<td>Italy</td>
</tr>
<tr>
<td>Lithium Negroni</td>
<td>C</td>
<td>glutamate</td>
<td>Italy</td>
</tr>
<tr>
<td>Lithium Duretter</td>
<td>S/R</td>
<td>sulphate</td>
<td>Sweden</td>
</tr>
</tbody>
</table>

¹ C = Conventional formulation  
² S/R = Sustained/Controlled release formulation  

(Adapted from Schou, M., 1973)
CHAPTER 2

MATERIALS AND METHODS
2.1 CHOICE OF STARTING MATERIALS

2.1.1 General consideration

The choice of starting materials for producing a product is of primary importance, as the product may be administrated to humans. Therefore, all the materials should be non toxic to man and provide no environmental hazards, in addition to the properties of the materials required for producing the product. As mentioned in section 1.5, the density of the materials is another major criterion in this study. Thus, the starting materials should be chosen in accordance with all these criteria: availability, toxicity and density.

There are two different methods of preparing a dense product: chemical reactions and physical mixing with heavy materials. Barium sulphate has been used to increase density of dosage forms in pharmaceutical research (Devereux et al, 1990). However, the application of chemical reactions to increase the density is limited (Poyner, 1992). There are different chemical compounds which can be used to produce dense products of lithium. Chemically, lithium compounds such as carbonate, nitrate, hydroxide or oxalate can react with metal oxide, nitrate and oxalate. If heavy metal compounds are chosen (e.g. ferric oxide, titanium dioxide), a dense lithium salt can be produced by simply sintering lithium compounds with them or immersing metal oxides in lithium hydroxide solution. Unfortunately, the nitrate, oxalate and hydroxide of lithium are not used in medications or other human uses. There is neither a BP or a USP grade of these materials available. The use of these as starting materials does not offer any benefit. Besides, nitrates produce a toxic gas, nitrogen dioxide or monoxide when they are heated at high temperatures.

It is clear that the materials, lithium carbonate, titanium dioxide and ferric oxide are quite promising as starting materials. Lithium carbonate has been used in psychiatric medication for a very long time (see section 1.2). A BP or USP grade of lithium carbonate is available on the market. Both titanium dioxide and ferric oxide are used in the pharmaceutical and food industries. The densities are 3.9 g/cm³ for titanium dioxide, 5.24 g/cm³ for ferric oxide. Ferric oxide is often used as a colouring agent. However, titanium dioxide is a preferable additive for pharmaceutical products.
First of all, it has been widely used in the pharmaceutical industry and in cosmetics and food products. Secondly it is a white powder, odourless and non-absorbable. Therefore lithium carbonate and titanium dioxide were chosen as starting materials for preparing a dense lithium product, lithium titanate ($\text{Li}_2\text{TiO}_3$) in this thesis.

2.1.2 Lithium carbonate and titanium dioxide

A. Lithium carbonate

Lithium carbonate was used as the source of lithium, it is soluble in diluted acid, practically insoluble in water and insoluble in alcohol. The density of the powder is 2.11 $\text{g/cm}^3$. It melts at temperature 720 °C and decomposes between 600 °C and 720°C (Castellanos et al, 1979 and Izquierdo et al, 1980). Three grades of lithium carbonate powders were used in this study, Table 2.1.

Table 2.1 Batch numbers, grades, purities and suppliers of lithium carbonate powders used in the study

<table>
<thead>
<tr>
<th>Batch No</th>
<th>Grades</th>
<th>Purity(%)</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>497OH</td>
<td>GPR</td>
<td>99.0</td>
<td>BDH</td>
</tr>
<tr>
<td>145K</td>
<td>GPR</td>
<td>99.0</td>
<td>BDH</td>
</tr>
<tr>
<td>392</td>
<td>BP/USP</td>
<td>99.5</td>
<td>CETEMA LTD</td>
</tr>
<tr>
<td>3490092M</td>
<td>AnalR*</td>
<td>99.5</td>
<td>BDH</td>
</tr>
</tbody>
</table>

* only used for preparation of lithium standard solution

B. Titanium dioxide

Titanium dioxide, the other reactant, increases the density of a final product and produces an effective core for a carrier of the lithium ion. It has not been used for such a purpose either in the pharmaceutical industry or in cosmetics. Titanium itself is completely non-toxic. The element was discovered in the bones and flesh of
Titanium dioxide is an extremely stable compound. It is insoluble in water, hydrochloric acid, nitric acid and dilute sulphuric acid. It is only soluble in hot concentrated sulphuric acid and hydrofluoric acid. It exists in three crystal forms: rutile, anatase and brookite with densities 4.23, 3.90 and 4.13 g/cm³ respectively. All three forms occur naturally, but the latter is rare and of little commercial interest. No commercial brookite is available.

The chemical structures of rutile and anatase are shown in Fig. 2.1. Rutile is the most stable form. It has a higher density and greater chemical stability than anatase. It melts at 1825°C. The possible insertion of lithium into rutile is limited, 1-2 atomic % (Murphy et al, 1983). Anatase has no specific melting point as it is irreversibly transformed to rutile before a melting point is reached. Anatase is the only titanium dioxide product available on the market with a BP or USP standard. The materials used in the study are detailed in Table 2.2.

**Table 2.2** Batch numbers, grades, purities and suppliers of titanium dioxide (anatase) used in the study

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Grades</th>
<th>Purity(%)</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>5014</td>
<td>BP</td>
<td>99.9</td>
<td>COLORCON</td>
</tr>
<tr>
<td>7247</td>
<td>BP</td>
<td>99.9</td>
<td>COLORCON</td>
</tr>
<tr>
<td>920644</td>
<td>BP</td>
<td>99.9</td>
<td>COLORCON</td>
</tr>
<tr>
<td>921163</td>
<td>BP</td>
<td>99.9</td>
<td>COLORCON</td>
</tr>
</tbody>
</table>

C. Particle sizes

It is well known that particle sizes of raw materials can play an important role in their physical properties, such as solubility, dissolution and flow properties. The particle size may affect both kinetics of reaction and properties of the final product produced from a solid-state reaction. In order to control the particle size effects of lithium carbonate and titanium dioxide, the particle size of each batch was analyzed by the following methods.
Fig. 2.1 Chemical structures of two crystal forms of lithium titanate dioxide  a: rutile crystal  b: anatase crystal
The particle sizes of lithium carbonate powders were determined by two methods, sieving and laser light diffraction (Model MALVERN 2600). Sieving is one of the simplest methods of size analysis. It is universally applicable. Three sizes of sieves (75 μm, 150 μm and 300 μm) were assembled together in a stack (largest sieve size at the top, smallest at the bottom). Twenty grams of lithium carbonate powders was added to the top sieve and placed on the sieve shaker (Endecott test sieve shaker, F.F.L. IMK II) for 15 minutes. The powders on each sieve were collected and reweighed. The data were converted to a percentage (weight of powders on each sieve divided by total weight of the powders added) and plotted against the size fraction. The size distribution of all batches of lithium carbonate are shown in Table 2.3.

### Table 2.3 Particle sizes of lithium carbonate powders (Batch No. 497OH, 145K and 392) measured by sieving method

<table>
<thead>
<tr>
<th>size ranges(μm)</th>
<th>497OH</th>
<th>145K</th>
<th>392</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤75</td>
<td>34.20%</td>
<td>97.73%</td>
<td>91.83%</td>
</tr>
<tr>
<td>75-150</td>
<td>51.30%</td>
<td>1.07%</td>
<td>6.37%</td>
</tr>
<tr>
<td>150-300</td>
<td>6.96%</td>
<td>0.94%</td>
<td>1.80%</td>
</tr>
<tr>
<td>≥300</td>
<td>7.54%</td>
<td>0.26%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

Laser light diffraction employed more sophisticated techniques. It is based on the Fraunhofer diffraction of a collimated and monochromatic beam of light by suspended particles. Light passes from the source through the sample cell window to a receiver lens. A detector consisting of thirty one concentric rings collects the scattered rays. According to the light intensity detected in each ring, a size distribution is produced. The machine calculates a volume of equivalent diameter and tabulates this in a variety of possible ways including the cumulative percentage under size and over size and frequency distribution.
The particle size of lithium carbonate powders was measured by adding a small quantity directly to the dispersant liquid (ethanol), stirring with a magnetic stirrer to obtain an homogenous suspension and transferring a suitable quantity of the suspension directly to the measuring cell (PSI cell, 14 ml) containing dispersant solvent. Because the measurement is carried out by volume distribution, which tends to be affected by a large particle and can produce an erroneously large mean size if aggregates are present, it is important to have a good presentation of the samples in the dispersant solvent. The particle size of lithium carbonate is tabulated in Table 2.4. The results are in good agreement with those obtained from the sieving method.

Table 2.4 Particle sizes of lithium carbonate powders (Batch No. 497OH, 145K and 392) measured by laser light diffraction

<table>
<thead>
<tr>
<th>Batch No</th>
<th>10% under(μm) (X±SD)</th>
<th>50% under(μm)* (X±SD)</th>
<th>90% under(μm) (X±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>497OH</td>
<td>10.00±3.29</td>
<td>39.13±4.60</td>
<td>102.43±1.80</td>
</tr>
<tr>
<td>145K</td>
<td>16.20±0.50</td>
<td>28.67±0.81</td>
<td>49.47±1.01</td>
</tr>
<tr>
<td>392</td>
<td>21.47±0.46</td>
<td>48.00±0.65</td>
<td>86.93±1.39</td>
</tr>
</tbody>
</table>

* 50% under size = D(v,0.5) which is defined as volume median diameters, equals to mass median diameters in the laser light diffraction method.

Titanium dioxide is a very fine powder. The average particle size is about 0.3 μm (Handbook of pharmaceutical excipients, 1986). Both methods described above are not sensitive enough for measuring such a small particle size. Therefore, a surface area measurement was taken to obtain an indirect answer of the particle size. The method is detailed in the section 2.4.6. Little variation from batch to batch was found (see Table 2.5).
Table 2.5 Specific surface areas of titanium dioxide powders used in the study

<table>
<thead>
<tr>
<th>Batch Number</th>
<th>Specific surface area (m²/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5014</td>
<td>9.613±0.026</td>
</tr>
<tr>
<td>7247</td>
<td>9.872±0.038</td>
</tr>
<tr>
<td>920644</td>
<td>10.457±0.009</td>
</tr>
<tr>
<td>921163</td>
<td>9.972±0.017</td>
</tr>
</tbody>
</table>

2.2 OTHER MATERIALS

Details of the other materials used for different studies in this thesis are shown in Table 2.6.

2.3 PREPARATION OF LITHIUM TITANATE SAMPLES

2.3.1 General

Many attempts have been made to synthesize selective inorganic ion adsorbents for the recovery of metallic materials. Particular attention has been paid to lithium by scientists because of the requirement of lithium in the blanket region of a controlled thermonuclear fusion reactor. The quantity has been estimated to be from 200 to 1000 tons per 1 GW generation of electric power (Ooi et al, 1986). Ways of obtaining sufficient lithium from sea water have been sought. The most favourable method is adsorption, using suitable adsorbents (ion exchange materials). Several studies have reported that the following compounds exhibit high selectivity for the lithium ion if they are treated with acid solution to become hydrous metal oxide: Li₂SnO₃ and LiRhO₂ (Lang, 1966), LiMn₂O₄ (Ooi, 1986), Li₂TiO₃ (Onodera et al, 1988) and Li₂SbO₃ (Onodera et al, 1989).

The need for inorganic ion exchange materials, for lithium conducting solid electrolytes (Kolotykin et al, 1985) and new ceramic composition materials (Johnson
Table 2.6 Other materials used in the study

<table>
<thead>
<tr>
<th>Name</th>
<th>Batch No</th>
<th>Grade</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinpyrolidone</td>
<td>9883130F</td>
<td>LR</td>
<td>BDH</td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>57182</td>
<td>LR</td>
<td>HERCULES</td>
</tr>
<tr>
<td>Klucel</td>
<td>1622</td>
<td>BP</td>
<td>FMC</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>618535</td>
<td>GPR</td>
<td>HOECHEST</td>
</tr>
<tr>
<td>PEG 10000</td>
<td>620770</td>
<td>GPR</td>
<td>HOECHEST</td>
</tr>
<tr>
<td>Glucose</td>
<td>9584970K3</td>
<td>GPR</td>
<td>BDH</td>
</tr>
<tr>
<td>EMDEX</td>
<td>R-2X</td>
<td>BP</td>
<td>MENDELL</td>
</tr>
<tr>
<td>Tabletose</td>
<td>790</td>
<td>BP</td>
<td>FORUM LTD</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>10241</td>
<td>AnalaR</td>
<td>BDH</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>793</td>
<td>BP</td>
<td>FMC</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1559700</td>
<td>Technical</td>
<td>BDH</td>
</tr>
<tr>
<td>Potassium bromide</td>
<td>5319520</td>
<td>IR spectroscopy</td>
<td>BDH</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>4519730M</td>
<td>AnalaR</td>
<td>BDH</td>
</tr>
</tbody>
</table>
et al, 1987), has led to the preparation of lithium titanate (Lang, 1954 and 1966; Jonke, 1957; Dorrian et al, 1969 and West et al, 1979). The kinetics and enthalpy of formation of the \( \text{Li}_2\text{O}-\text{TiO}_2 \) system have been investigated by Annopol’skii in 1971 and Dorrian et al in 1969. There is general agreement that the \( \text{Li}_2\text{O}-\text{TiO}_2 \) system contains four stable phases: \( \text{Li}_4\text{TiO}_4 \), \( \text{Li}_2\text{TiO}_3 \), \( \text{Li}_4\text{Ti}_2\text{O}_{12} \) and \( \text{Li}_2\text{Ti}_3\text{O}_7 \). The phase equilibrium among these four compounds was established by Izquierdo in 1980. The phase diagrams of \( \text{Li}_2\text{O}-\text{TiO}_2 \) system are shown in Fig.2.2. In the system, the molar ratio of lithium oxide and titanium dioxide and the heating temperatures are extremely important. The formation of the four compounds can be controlled by varying the molar ratio and the heating temperatures. Lithium Titanate (\( \text{Li}_2\text{TiO}_3 \)), as one of the four compounds in the system, can be only prepared by heating the mixture of lithium oxide and titanium dioxide at 50% mole composition at heating temperatures ranging from 600°C to 1200°C.

The preparation of the lithium titanate is described below. It can be prepared by either heating the mixture of lithium carbonate and titanium dioxide initially at a low temperature (e.g. 600 to 750°C) for a few hours to drive off carbon dioxide and finally at a higher temperature (e.g. 900 to 1200°C) for a few days, or by directly heating the mixture at a high temperature for a reasonable period (Onodera et al, 1988 and Annopol’skii et al, 1971). The time for completion of the reaction between lithium carbonate and titanium dioxide is variable, depending on the temperature. Which compound will be formed is controlled by the molar ratio of lithium oxide or lithium carbonate and titanium dioxide.

The preparation of the mixture of lithium carbonate and titanium dioxide powders can be performed in two ways, wet mixing and dry mixing. The wet mixing involves using organic solvents, such as acetone, as a contacting medium between both powders. Both powders are mixed with acetone to form a paste and the mixing is continued until all the acetone evaporates. The dry mixing is much simpler. The mixture is directly prepared by simply mixing both powders together. Organic solvents are not used, which may be preferable for production in the pharmaceutical industry. As the product (\( \text{Li}_2\text{TiO}_3 \)) may be introduced for pharmaceutical use, the dry mixing was chosen to prepare the mixture of lithium carbonate and titanium dioxide in this
Fig. 2.2 The phase diagram of a Li$_2$O-TiO$_2$ system  

a: mole of TiO$_2$ from 0 to 100%
b: mole of TiO$_2$ from 50 to 100% (Izquierdo and West, 1980)
2.3.2 Preparation of lithium titanate (Li$_2$TiO$_3$) samples

A. Mixture of lithium carbonate and titanium dioxide

A stoichiometric amount of lithium carbonate powder and titanium dioxide powder were accurately weighed to give a total weight of 200 g. The powders were mixed with a TURBULA shaker-mixer (Model: T2C) for 30 minutes. The TURBULA unit is based on the introduction of a new type of kinematic principle to create a third motion of inversion besides the traditional principal motions of rotation and translation. Therefore the mixing is the action of a three dimensional motion (see Fig. 2.3). After mixing with the TURBULA mixer, the mixture was passed through a 355μm sieve and mixed again with the mixer for 10 minutes. The mixing process (mixing with TURBULA for 10 minutes and a sieve) was repeated three times for each batch of the mixture to ensure that a uniform mixture was obtained. The mixing time can be varied depending on the quantity of the mixture prepared.

B. Li$_2$TiO$_3$ samples

The lithium titanate samples were initially prepared by heating the mixtures of lithium carbonate and titanium dioxide in a crucible at different temperatures, ranging from 680°C to 920°C for 24 hours in a electric muffle furnace (I) (Model: Gallenhamp, Pyromaxim Electronic controller, SIFAM ELECT. INST. CO. LTD.) whose temperature was not able to be controlled accurately. The temperature was maintained within ±15°C of the set temperature. Samples were also prepared at the same heating temperature ranges for 24 hours in another electric muffle furnace (II) (Model: BCF GENERAL PURPOSE FURNACE, LENTON THERMOL DESIGNS) whose temperature was controlled by a programme thermal controller (Model: ECF12/30). Before the mixture was placed inside of the furnace, the furnace had been balanced at a desired temperature for 24 hours and calibrated with a validated thermometer (Model: Thermocouple TYPE K2003, temperature ranges from -75°C to 1200°C) each time. The temperature was maintained within ±1°C of the set
Fig. 2.3  The mixing movement of TURBULA unit
temperature. The process of preparation of the lithium titanate samples is shown in Fig. 2.4. After heating, the samples were taken out and allowed to cool down at room temperature.

2.4 CHARACTERIZATION OF $\text{Li}_2\text{TiO}_3$ SAMPLES

2.4.1 General

The $\text{Li}_2\text{O}-\text{TiO}_2$ system has not been used for pharmaceutical purposes. Less attention has been therefore paid to those physical and chemical properties, which play an essential role in therapeutical effects. The formation of lithium titanate, ion exchange property and crystal growth (Mikkelsen, 1979) have been studied, but the physical and chemical properties of lithium titanate are unknown apart from the density which was reported to be 3.417 g/cm$^3$ (Kordes, 1935). Several methods were employed in this thesis to characterize the lithium titanate samples produced.

Completion of a chemical reaction between lithium carbonate and titanium dioxide is important to ensure that pure product lithium titanate is obtained. Infra-red (IR) spectroscopy was used to check the completion of the reaction, as the carbon dioxide group in lithium carbonate molecule gives a clear peak in the IR spectrum (see Fig. 2.5).

The density of lithium titanate product was measured by an Air Comparison Pycnometer (Beckman 930).

Loss of weight on heating was determined to give information on the completion of the reaction between lithium carbonate and titanium dioxide powders. The lithium content in the product and purity of the product were calculated based on the value of loss of weight on heating.

Both particle size and surface area are relevant to the release of lithium ion from the product and its preparations. Different particle size distribution and surface area may result in different release rates of the lithium ion. The particle size was analyzed by the laser light diffraction (Model: MALVERN 2600). The surface area was determined by a BET surface area analyzer (MODEL: Quantasorb).

Dissolution studies of the powder produced and its preparations were carried
Fig. 2.4 Flow diagram of preparation of lithium titanate (Li₂TiO₃) (* mixing with TURBULA mixer and a sieve)
Fig. 2.5 IR spectrum of lithium carbonate
out by USP method II to characterize the release profile of lithium ion for the samples and to evaluate if the controlled/sustained release profile can be achieved in vitro.

Ion equilibrium of the product in diluted hydrochloride acid solutions was carried out to understand the release mechanism of lithium ion for the product. The affinity of lithium ion with hydrogen ion was also calculated.

Other methods were also employed to characterize the product. X-ray diffraction was used to identify the crystal form of the product. Scanning electron microscopy (SEM) was also introduced to observe the surface structure of the product particle. Dielectric measurement and magic angle spinning (MAS) were undertaken to differentiate the products prepared under different chemical conditions.

2.4.2 Infra-red (IR) spectroscopy

IR spectrometry involves examination of the twisting, bending, rotating and vibrational motions of atoms in a molecule. The infrared region includes radiation at wavelength between 0.7 and 500 μm or in wavenumbers, between 14,000 cm\(^{-1}\) and 20 cm\(^{-1}\). The spectral range used most is the mid-infrared region, which covers wavenumbers from 4000 cm\(^{-1}\) to 400 cm\(^{-1}\) (2.5 to 25 μm in wavelength).

The chemical reaction between lithium carbonate and titanium dioxide can be explained by the following formula. The carbon dioxide group in the lithium carbonate molecule has special IR absorption at wavenumber between 1600 and 1800 cm\(^{-1}\). Before the mixture is heated, the peak can be seen in the spectrum. However, the peak will disappear as the carbon dioxide is driven off after the completion of the reaction.

The IR spectrum scanning of the mixture of lithium carbonate and titanium dioxide before and after the chemical reaction was carried out at wavenumber ranges from 4000 cm\(^{-1}\) to 400 cm\(^{-1}\) using an IR spectroscopy (Model: PERKIN ELMR 841). A KBr disc was used for the scanning.

The KBr disc containing the sample was prepared by the following method. About 200 mg of pre-dried KBr powder was mixed with 1 to 2 mg of the sample and ground into a fine powder, which was pressed in an evacuable die at sufficient
pressure to produce a transparent disc at about 1 mm thickness.

2.4.3 Loss of weight on heating

When the mixture of lithium carbonate and titanium dioxide is heated at 680°C, the carbon dioxide was driven off. Theoretically, 28.62% of total weight of the mixture will be lost if the chemical reaction is complete according to formulae 1. Therefore, the loss of weight on heating will give the information of the completion of the reaction and purity or lithium content of the product. The weight loss was obtained by weighing the mixture before heating ($W_1$, the weight of the mixture used) and subtracting the weight of the mixture after heating ($W_2$). The percentage of weight loss ($L$, representing loss of weight on heating) was calculated by the equation 1. The lithium content in the product and the purity of the product were also calculated by the equations 2 and 3.

$$L = \frac{W_1 - W_2}{W_1} \times 100\% \quad [1]$$

$$C_{Li} = \frac{Q_{Li}}{Q_p} \times 100\% \quad [2]$$

where:

- $C_{Li}$ = lithium content in the product ( % )
- $Q_{Li}$ = amount of lithium added
- $Q_p$ = weight of final product obtained

$$P (\%) = \frac{C_{Li}}{C_t} \times 100\% \quad [3]$$

Where:

- $P =$ purity of the product
- $C_t =$ theoretic value of lithium content of lithium titanate ($\text{Li}_2\text{TiO}_3$, 12.62 % )
2.4.4 Density measurements

The densities of the initial reactive mixtures and the lithium titanate products were measured using an Air Comparison Pycnometer (Model: Beckman 930, High Wycombe, Bucks) which is specifically designed to measure the density of solids including powders, granules, pellets, tablets or porous-irregular-shaped solids. The true volume of the sample was measured and hence the true density can be calculated by the following equation.

\[ d = \frac{w}{v} \]  \[4\]

Where \( d \) is density of the sample, \( v \) is the true volume and \( w \) the weight of the sample.

2.4.5 Particle size

The particle size of the product was determined using a laser light diffractor (Model: MALVERN 2600) by adding the product powder directly into the measuring cell containing ethanol as a dispersant solvent, then stirring with a magnetic stirrer for 20 minutes. The distribution of the particle size and the 10, 50 and 90% under size were obtained.

2.4.6 Surface area

The surface area of the product powder was measured by a single point BET method, using BET surface area analyzer (Model: QUANTASORB, QUANTACHROME). A pre-mixed gases of nitrogen and helium were used as an adsorbate (N2) and a carrier (He). An adequate quantity of the sample powder, which was obtained by preliminary experiments, was added to the sample cell and degassed with pure nitrogen to clean the surface of the sample powder. The degassed sample was then moved to the cell holder for measuring. The quantity of nitrogen absorbed on the sample was read in integrator counts, which can be converted into the weight of nitrogen absorbed on the sample by the following equation 5.

\[ X = \frac{A}{A_{cal}} \times V_{cal} \times \frac{P_{M}}{RT} \]  \[5\]
Where:
X = weight of adsorbate (nitrogen) adsorbed on the sample
A = sample integrator counts
A_{cal} = calibration integrator counts
V_{cal} = calibration volume (cm^3)
P_\text{a} = ambient pressure (atm)
M_n = nitrogen molecular weight (28)
T = temperature in K
R = gas constant (82.1 ml/atmdy.mol)

The theory of BET is discussed in modern texts on surface chemistry (Gregg, 1961; Young et al, 1962 and Lowell et al, 1984). The basic theory of BET (Brunauer, Emmet, Teller) is explained by the equation 6.

\[
\frac{1}{X[(P/P_\text{a}) - 1]} = \frac{C' - 1}{X_mC'} \times \frac{P'}{P_\text{a}} + \frac{1}{X_mC'} \tag{6}
\]

Where:
X = weight of nitrogen adsorbed on the surface at relative pressure P/P_\text{a}
P = partial pressure of nitrogen
P_\text{a} = saturated vapour pressure of nitrogen
X_m = weight of nitrogen adsorbed at a coverage of one monolayer
C' = constant which is a function of the heat of the nitrogen condensation and heat of adsorption

Equation 6 yields a straight line when 1/X[(P/P_\text{a}) - 1] is plotted versus P/P_\text{a}. Therefore, the value of the weight of the nitrogen adsorbed at the monolayer (X_m) can be calculated from the slope and the intercept values. Because of the assumption in the equation 6, the linear relationship between 1/X[(P/P_\text{a}) - 1] and P/P_\text{a} is usually found to be in the range P/P_\text{a} from 0.05 to 0.35 (Gregg, 1961). Thus, data points outside of this range should be avoided for accurate surface area measurements. The total surface area of the sample, S_t, is determined from equation 7. The specific surface area of the sample is given by equation 8.
\[ S_i = \frac{X_m N A_{cs}}{M_i} \]  

where:

- \( M_i \) = nitrogen molecular weight (28)
- \( N \) = Avogadro's number \( (6.023 \times 10^{23}) \)
- \( A_{cs} \) = cross section area of nitrogen molecule \( (16.2 \times 10^{-2} \text{ m}^2) \)
- \( S_i = S / \text{weight of sample} \)  

The single point BET method is based on the fact that the intercept of a BET plot is generally small when compared to the slope and can be ignored. If the intercept is assumed to be zero, the BET equation 6 can be simplified to equation 9.

\[ X_m = X \left[ 1 - (P/P_o) \right] \]  

Thus, by measuring the amount of gas adsorbed at one value of \( P/P_o \), preferably near \( P/P_o \) being 0.3, the monolayer capacity \( X_m \) can be calculated by combining equation 5 and 9, given in equation 10.

\[ X_m = \frac{A_i}{A_{cal}} \times V_{cal} \times \frac{P_s M_i}{RT} \times \left[ 1 - (P/P_o) \right] \]  

Therefore, the total surface area of the sample is given in equation 11.

\[ S_t = \frac{A_i}{A_{cal}} \times V_{cal} \times A_{cs} \times \frac{P_s N_i}{RT} \times \left[ 1 - (P/P_o) \right] \]  

2.4.6 In-vitro dissolution

A. Determination of lithium ion

Flame emission spectroscopy and atomic absorption spectroscopy methods are usually used for lithium ion determination. Both have been well established and are about equally good for the measurement (Bybus et al, 1970). The lithium ion contents in all studies were determined by a flame emission spectrophotometry at wavelength 670.8 nm, using an atomic absorption spectrophotometer (Model: PERKIN-ELMER
The sample in the form of solution is introduced into the air-acetylene flame as a fine spray using a nebuliser. The high temperature of the flame vaporise the sample and provides thermal energy to excite the ground state neutral atoms. When the excited atoms return to the ground state, they emit light of wavelengths characteristic of the lithium. The intensity of this emitted light is directly proportional to the concentration of the lithium ion in the flame.

It has been established that the working range for lithium by flame emission spectroscopy is linear up to a concentration of about 0.3 mmol/l. Therefore, the concentration of the standard solution used was less than 0.3 mmol/l and a linear calibration curve was obtained by plotting the mean emission reading of each standard solution against concentrations of lithium in the standard solution. A calibration curve was obtained before each determination of the samples.

B. In-vitro dissolution

The amount of lithium released from the lithium titanate powder and the tablets in vitro was determined by USP method II (paddle method), using a PHARMA dissolution tester (Model: PTWS, W. Germany), in 1000 ml of dissolution medium (0.1N hydrochloric acid solution) for 6 hours or 8 hours or 12 hours at 37°C with paddle rotation speed of 100 rpm. Three or six replicates of samples containing 6 mmol of lithium were used in each test. A 1.5 ml of sample was collected by an automated sampler at various pre-determined time intervals. The lithium concentrations in the sample solutions were directly determined by measurement of the flame emission at 670.8 nm after appropriate dilution.

2.4.8 Ion equilibrium

A. Time course

A knowledge of when the equilibrium between lithium ion and hydrogen ion can be reached is an important characteristic of solution behaviour of lithium salts. The experiment was carried out as follows. Five samples were prepared by adding
0.3 g of the product powder to 10 ml of 0.2 N hydrochloric acid solution. The samples were kept in a water bath at 37°C with continuing horizontal rotation for pre-designed time interval. A 0.1 ml of filtered solution was diluted to 100 ml with distilled water. The lithium ion was determined in each sample. The quantity of lithium ion in the solution was plotted against time. If the equilibrium is reached, the lithium ion contents in the solution will be independent of time.

B. Affinity of lithium ion

The chemical equilibrium of the product in acid solutions can be described as follows. The amount of lithium ion can be exchanged by hydrogen ion at molar ratio

\[ \text{Li}_2\text{TiO}_3(S) + 2\text{H}^+ \leftrightarrow 2\text{Li}^+ + \text{H}_2\text{TiO}_3(S) \]

1:1. It means that one mole hydrogen ion can only exchange with one mole of lithium ion. The exchange ratio between lithium ion (Li⁺) and hydrogen ion (H⁺) is expressed as F, defined here as affinity. Therefore, the F value can be given in equation 12. Theoretically, the value of F should be 1 ( [Li⁺] = [H⁺] ).

\[ F = \frac{[\text{Li}^+]^2}{[\text{H}^+]^2} \quad [12] \]

B-1 Effect of amount of the product

The effect of the amount of the product was investigated by adding different amounts of the product powders to 10 ml of 0.1 N hydrochloric acid solutions and keeping them in a water bath at 37°C with continuous horizontal rotation for a period time which was found above. The lithium ion content which had exchanged with hydrogen ion in the solution was analyzed and the F value was calculated. The amount of lithium ion in the solution was plotted as a function of the amount of the powders added.

B-2 Effect of amount of hydrogen ion

The effect of the amount of hydrogen ions was studied by adding the same amount of the powder to 10 ml of different concentrations of hydrochloric acid solutions and keeping the sample in a water bath at 37°C for the period time which was found above. The lithium ion replaced by hydrogen in the solutions was
determined and the F value was calculated. The amount of lithium ion in the solution was plotted as a function of the amount of hydrogen ion in the solution.

2.4.9 Other methods

A. Scanning electron microscopy (SEM)

Scanning electron microscopy is often used to provide information on particle size and shape, texture and surface details. The particles of starting materials and the products were coated with gold on the plate, using a coater (Model: EMITECH K550) to prevent the build-up of charge on the surface of the sample. The coated samples were examined using SEM (Model: PHILIPS XL20) to identify their surface structures.

B. Powder X-ray diffraction

The samples were investigated by X-ray powder technique using an X-ray diffractometer (Model: PHILIPS PW 1390 CHANG CONTROL & SIETRONICS XRD automated system), which is used to measure the scattered intensity of X-ray diffraction as a function of angle (see Fig.2.6). The samples were prepared for the diffractometry by pressing the sample powder into a sample holding window with a glass slide on the back, then sealing the front of the window with adhesive paper, reversing the holder and removing the glass slide to reveal the surface of the powder. The holder was placed at a stage inside of the diffractometer for scanning at the angle ranges (2θ) from 4° to 100°.

C. Dielectric measurement

Low frequency dielectric spectroscopy (LFDS) has been found to be considerable useful in providing the information on the structure and behaviour of pharmaceutical materials (Craig, 1989 and Baker et al., 1990). The technique involves the measurement of the electric properties of a material, here expressed by three measurable parameters, capacitance (C), dielectric loss (G/ω, where G is the conductances and ω is the frequency of the measurement) and a loss factor (tanδ). All of them are related to the
Fig. 2.6 Schematic diagram of a simple X-ray powder diffractometer
permittivities of the material, given in Equations 13-15. The permittivity is an intrinsic
dielectric property of the material and also quite characteristic.

\[
C = \frac{A \times \varepsilon}{l} \quad [13]
\]

and

\[
\frac{G}{\omega} = \frac{\varepsilon'' \varepsilon_0 A}{l} \quad [14]
\]

and

\[
tan\delta = \frac{\varepsilon''}{\varepsilon'} \quad [15]
\]

where :
\( A = \) area of two metal electrodes
\( \varepsilon = \) permittivity of the material
\( l = \) distance between two metal electrodes
\( \varepsilon_0 = \) permittivity of free space \([(1/36) \times 10^{-9}]\)
\( \varepsilon_r'' = \) part of relative permittivity representing the "leakage" or "loss"
\( \varepsilon_r' = \) part of relative permittivity representing the capacitance decreasing

The relationship between these permittivity are given in following equations.

\[
\varepsilon = \varepsilon_r \times \varepsilon_0 + \varepsilon_\infty \quad [16]
\]

\[
\varepsilon_r = \varepsilon'_r - i\varepsilon''_r \quad [17]
\]

Here \( \varepsilon_r \) is the relative permittivity. It has exactly the same value as the dielectric
constant, \( K. \) \( \varepsilon_\infty \) is the permittivity at infinite frequencies. \( i \) is i-notation, the square
root of -1.

The dielectric measurement involves the application of a small alternating
voltage \((1 \text{ V rms or } 0.1 \text{ V rms})\) to a sample and the subsequent measurement of the
charge stored \((\text{as capacitance, } C)\) and lost \((\text{as dielectric loss, } G/\omega)\) over a large
range of frequencies from \(10^6 \text{ Hz to } 10^4 \text{ Hz.}\) The resulting spectrum was plotted with
logarithm \( C \) and \( G/\omega \) as \( Y \)-axis and logarithm frequency as \( X \)-axis.

The sample tablets were prepared as follows. Three hundred milligrams of
sample powders were compressed to form discs of diameter 8.5 mm, using a single
flat faced punch tableting machine (Model: MANESTY F3) with application of a constant displacement setting of the upper punch.

The disc was directly placed between two round metal plates (aluminium, diameter of 9 mm) inside of the sample holder. Two electrical wires (acted as electrodes) were connected to each side of the plates. The electrodes were mounted to a perspex dielectric cell (measuring box), using insulating materials. The dielectric responses of the samples were measured at 25°C and 30-40% of relative humidity over the frequency range of $10^5$ and $10^2$ Hz, using a dielectric analyzer (Model: Chelsea Dielectric Group, London). Before the measurement, the sample was kept for 24 hours in an environmental cabinet (Fison Environment Equipment) where the temperature and the relative humidity were maintained at 25°C and 30-40% respectively. Three replicates of each sample were measured.

D. Solid state NMR-Magic angle spinning (MAS)

High resolution solid state NMR is a recently developed technique to provide additional information for elucidation of molecular structures. There are several techniques available for solid NMR measurement. The details of these techniques were reviewed by Fyfe and Mehring in 1983.

The ordinary NMR techniques and spectrometers employed routinely for liquid samples will not even provide a detectable spectrum of a solid sample, because of the following failures: the dipolar broadening, chemical shift anisotropy and long spinning relaxation times. The new techniques, dipolar decoupling, cross polarisation and magic angle spinning (MAS), can overcome these difficulties.

The sample for the NMR measurement was prepared as described below. The sample powder examined was pressed into a 2 cm long special rotor tube (a sample holder) which can be put inside of the spin unit (Model: MAS-DB, PNEUMATIC UNIT). The sample spinning was driven by a filtered and dried compressed air supply. The NMR measurements of the samples were carried out by MAS decoupling technique using NMR spectrometer (Model: MSL-300, Bruker multinuclear spectrometer) at rotor spinning speed 9750 Hz and spectrometer frequency 116.84 MHz ($^7$Li)
2.5 SPECIFICATIONS

Quality control plays a very important role in assuring the integrity of a drug product with regard to safety, potency and biological availability. It is even more relevant for lithium titanate (Li₂TiO₃) which has never been used as a drug product. From the BP specification of lithium carbonate and titanium dioxide plus some special properties of lithium titanate, which have been found in this thesis, a draft specification of lithium titanate has been proposed to provide basic criteria for its standardization and quality control. All the tests in the specification were carried out to see if it is adequate for the product. Since lithium titanate may also be used as a novel controlled release system, an additional specification was also proposed to provide a standard process of the formation of the product and other characteristics such as dissolution profile, density, particle size and surface area, etc.

2.6 DESIGN OF ORAL LITHIUM DOSAGE FORMS

Lithium is usually taken orally as an antidepressant. It is easily absorbed in the gastric-intestinal region. Among the oral dosage forms, the tablet is the most common one. Therefore, it was chosen for the lithium titanate preparations. By making tablets, there two aims were desired to be achieved: keeping a tablet intact to provide high density of the preparation which may delay gastric emptying time, and establishing a controlled release profile of lithium (a zero or first order release at suitable rate). Different formulations were designed by application of different binding agents and channelling agents to alter the release profile of lithium ion in vitro for the preparations.

The tablets were prepared by a wet granulation process. A definite amount of lithium titanate powder was mixed with an adequate amount of binder solution to produce a wet mass, which was forced through a sieve size 1.5 mm to form wet granules. The granules were dried at 85°C and mixed with 1% of magnesium stearate as a lubricant prior to compression. The tablets were compressed on a single-punch tablet machine (Model: MANESTY F3), at a tablet weight about 350 mg containing 6 mmol of lithium, using a flat faced punch of 8.5 mm diameter.

The density of the tablets was determined to see if the density can be achieved
to greater than 3.0 g/cm$^3$. The method is described in section 2.4.4.

The dissolution test of the tablets was carried out in 1000 ml of 0.1N hydrochloride acid solution for 12 hours to characterize the release of lithium \textit{in vitro}. Six tablets were used for each test.

The dissolution of a commercial lithium product (Priadel®) was also studied \textit{in vitro} to be used as a reference. The method was the same as described above, section 2.4.6.
CHAPTER 3

PREPARATION AND EVALUATION OF LITHIUM TITANATE
3.1 INTRODUCTION

3.1.1 Solid state reaction

Solid state reactions are often used for the preparation of polycrystalline solids such as powders. The method used most often is the direct reaction of a mixture of solid starting materials. The reaction occurs between relatively inert crystallite, which any motion is restricted and it depends on the presence of the lattice defects, consequently solids do not usually react together at room temperature.

The general principles of solid state reactions were reviewed by Welch in 1955; West in 1984 and Corbott in 1988. Two main processes are involved in a solid reaction: (1) nucleation and (2) growth of the nuclei to form product layer. Nucleation is the reorganization of the structure to form the product. Only at very high temperature do the reacting phase have sufficient thermal energy to enable them to move within the crystal. The subsequent stage is the counter diffusion of the reacting units to build up the product layer at the initial point of contact between the reacting phase.

Three of the important kinetic factors that influence the reaction rate are (1) the surface area of the reacting solids, (2) the nucleation and (3) the diffusion of reacting unit through the product layer. Factors (2) and (3) are dependent on the nature of starting materials. The factor (1) controls the area of contact between reacting grains in a mixture (West, 1984 and Garner, 1955). Increasing the total surface area by decreasing the particle size of the reacting solids can often facilitate the reaction. The surface area can vary enormously, depending on whether the reacting solids are in the form of a fine powder, coarse powder or a single crystal. Therefore, the surface areas of the starting materials (or particle sizes) have a great influence on solid state reactions.

In summary, thermodynamic and kinetic factors such as heating temperatures and particle size of starting materials play an important role in the formation of the desired product by the solid state reaction.
3.1.2 Application of techniques to solid characterization

Several analytic techniques which can be applied to characterization of inorganic solids were discussed by Cheetham et al in 1987. Three of main physical techniques are (a) X-ray diffractions, (b) microscopic techniques and (c) spectroscopic methods. X-ray diffraction gives straightforward phase identification for all crystalline solids. Microscopic techniques (optical and electron microscopy) are often used as a first step in examining a solid. Spectroscopic methods such as NMR and IR are mainly used to provide as a mean of elucidating molecular structures. However, their usages for inorganic solids are limited. For example, carbonate has a characteristic IR absorption spectrum; solid NMR techniques are applied to limited inorganic solids containing elements that have a non-zero nuclear spin. $^7$Li NMR spectrum has been developed and was used for the study of Li ion migration in LiAlSiO$_4$ solid (West, 1984) and for the study of mechanism of lithium action in vivo (Renshaw et al, 1985, 1986 and 1988 and Riddell et al, 1993).

3.2 EXPERIMENTAL

3.2.1 Preparation and characterization of samples

Four 25 g specimens of the same mixture of lithium carbonate (Batch No. 392) and titanium dioxide (Batch No.920644) were heated individually at the following temperatures: 680°C, 720°C, 820° and 920°C for 24 hours in the furnace (II) (see Chapter 2, section 2.3.2). The samples produced were coded as follows: $D_1$(680°C), $D_2$(720°C), $D_3$(820°C) and $D_4$(920°C).

The initial mixture and the samples were examined by IR spectroscopy. The samples $D_1$, $D_2$, $D_3$ and $D_4$ were characterized by using all of the methods described in section 2.4 (see Chapter 2).

3.2.2 Particle size of lithium carbonate

Two starting materials (lithium carbonate and titanium dioxide) were used in preparation of lithium titanate. The particle size of titanium dioxide was found to be quite uniform from batch to batch (see Table 2.5), however, it is a very fine powder and the particles easily aggregate to form large agglomerates. Different degrees of
aggregation cause a variation in the particle size, deaggregation can be achieved by sieving. The particle size for lithium carbonate was found to vary from batch to batch (see Fig. 3.1, Tables 2.3 and 2.4). The following experiments were carried out to observe the effects of this variable.

A. Batch variation of lithium carbonate

The particle size distributions of three batches of lithium carbonate (4970H, 145K and 392) are shown in Fig.3.1(a,b and c). Three batches of the mixtures were prepared by mixing these three batches of lithium carbonate separately with the same batch of titanium dioxide (Batch No. 7247). The mixture 200 g of each was heated individually in the furnace(II) at 820°C for 24 hours. The properties, the particle sizes and the surface areas of the resulting samples were determined. Their surface structures were examined by SEM. The dissolution tests of the samples were carried out.

B. Effect of particle size of lithium carbonate

B-1 Separation of the particle size

Three ranges of the particle sizes (< 75 μm, 75-150 μm, 150-300 μm) were separated by adding lithium carbonate powder to a set of sieves at sizes of 75 μm, 150 μm and 300 μm (largest on the top, smallest at the bottom) and shaking with a shaker (Model: Endecott, FFL. IMK II). The fraction on each sieve was collected to give 30 g of powder, coded as A-75 (particle size less than 75 μm), A-150 (particle size between 75 μm and 150 μm) and A-300 (particle size between 150 μm and 300 μm).

B-2 Effect of the particle sizes

Three batches of the reactive mixtures (50 g each) were prepared by mixing these lithium carbonate powders separately with aliquot from a same batch of titanium dioxide (B/N 920644). Thirty grams of each mixture was individually heated at 820°C for 24 hours in the furnace(II). The samples produced (A-75, A-150 and A-300) were evaluated by measuring their densities, surface areas and other properties. Their crystal
Fig. 3.1 Particle size distributions of three batches of lithium carbonate (percentage of under size, over size and frequency as function of particle size) a: 497-OH b: 145K c: 392
forms were examined by SEM and X-ray diffraction. The release of lithium \textit{in vitro}
was studied by undertaking the dissolution test. The ion equilibrium of the samples
was also carried out.

3.2.3 Heating time

A 200 g of the mixture of lithium carbonate (B/N 145K) and titanium dioxide
(B/N 920644) was prepared as described in Chapter 2, section 2.3.2.

Four 25 g specimens of the above mixture were individually heated at 820 °C
for the following time: 4, 8, 16 and 24 hours. The samples produced were examined
by IR spectroscopy and SEM. Other properties such as the density, loss of weight on
heating (lithium content and purity) and surface area were determined. Dissolution
studies of the samples were also carried out.

3.2.4 Furnace variation

Three 25 g of the mixtures of lithium carbonate (B/N 497OH) and titanium
dioxide (B/N 5014) powders were prepared by the method described in Chapter 2, but
without the sieving process. The mixtures were individually heated at set temperatures:
680°C, 820°C and 920°C for 24 hours in the furnace(I) (see Chapter 2, section 2.3.2)
in which the temperature was maintained within ± 15°C. The samples produced were
examined by IR, SEM and X-ray diffraction. The densities of the samples were
measured and the dissolution study of the powders was carried out. All the results
obtained were compared with those for the samples made in the furnace(II) at the
same set temperatures above.

3.2.5 Loading size of the mixture

A batch of 400 g of the mixture (lithium carbonate, B/N 145K; Titanium
dioxide, B/N 7247) was prepared by mixing two batches of 200 g of the mixtures
together with the TURBULA mixer for 40 minutes. The preparation of 200 g of the
mixture was detailed in Chapter 2 (see section 2.3).

Four different quantities of the mixture: 25 g, 50 g, 100 g and 200 g were
individually heated at 820°C for 24 hours in the furnace(II). The resulting samples
(A-25, A-50, A-100 and A-200 respectively) were examined by IR spectroscopy and SEM. The properties of the samples such as loss of weight on heating, lithium content, purity and density were determined. The in vitro release characteristics of lithium for the products were studied.

3.2.6 Reproducibility

Fifteen batches of the reactive mixtures at a batch size of 200 g of each were prepared by the method described in section 2.3.3, using aliquot from the same batch of lithium carbonate (Batch No. 392) and the same batch of titanium dioxide (Batch No. 921163). They were grouped into three sets (I, II and III). Five batches of the mixtures were individually heated at 750°C for 24 hours (coded as Group I), five at 820°C (coded as Group II) and five at 920°C (coded as Group III). After heating, each batch of the product was examined by IR spectroscopy and SEM. The density, loss of weight on heating, lithium content, purity and surface area of all products produced were determined. The release profiles of lithium for the samples were studied in vitro by carrying out a dissolution test.

The five sub-batches of lithium titanate produced at the same heating temperature were mixed together with the TURBULA mixer to give a sample of about 1 kg. They were coded as 720-5, 820-5 and 920-5. The results of the surface areas and dissolution studies of these samples were compared with those of the samples D\textsubscript{2}, D\textsubscript{3} and D\textsubscript{4} (which were made at 720, 820 and 920°C at an initial mixture size of 25 g).

3.3 RESULTS AND DISCUSSIONS

3.3.1 Preparation and characterization

A. IR spectra

The titanium dioxide (TiO\textsubscript{2}, anatase) spectrum had few clear features [see Fig.3.2(a)]. The lithium carbonate spectrum had six peaks at the following wavenumbers: 1500 cm\textsuperscript{-1} (peak 1), 1440 cm\textsuperscript{-1} (peak 2), 1080 cm\textsuperscript{-1} (peak 3), 860 cm\textsuperscript{-1} (peak 4), 600 cm\textsuperscript{-1} (peak 5) and 400 cm\textsuperscript{-1} (peak 6). The four peaks (1, 2, 3 and 4) are
Fig. 3.2 IR spectra of titanium dioxide (anatas), lithium carbonate and the initial reactive mixture  

a: Titanium dioxide (TiO$_2$)  
b: Lithium carbonate (Li$_2$CO$_3$)  
c: the initial mixture of Li$_2$CO$_3$ and TiO$_2$ at molar ratio 1:1
specifically related to the carbonate group, which were also present in the spectrum of the mixture [see Fig. 3.2(c)]. The peaks 5 & 6 are usually associated with metal-oxygen bond. After the samples were heated, the peaks 1 & 2 can still be seen in the sample D1 spectrum, but with much lower intensity and the peaks 3, 4, 5 & 6 became a broader peak [see Fig. 3.3(a)]. However, the four peaks have disappeared in the spectra of the samples D2, D3, and D4 [see Fig. 3.3(b-d)]. This clearly indicated that the chemical reaction between lithium carbonate and titanium dioxide was complete at the heating temperatures 720, 820 and 920°C for 24 hours, but not at 680°C.

B. Loss of weight on heating

The loss of weight on heating (L%), lithium content (C_L%), and the purity (P%) of the samples produced are tabulated in Table 3.1. With increasing the temperature, the values of L%, C_L%, and P% gradually increased. The sample D1 has the lowest values [see Fig. 3.4(a,b and c)], which may be the result of incomplete reaction. The values (C_L%, and P%) of the samples D2, D3 and D4 were close to the theoretical values, but the loss of weight on heating were slightly higher than theoretical. Moisture and/or impurity present in the starting materials (as the materials were not preheated before they were used) may explain the observation [see Fig. 3.4(a)]. The results suggest that at higher temperatures, the product is purer. For samples prepared at temperature above 720°C, there is no significant difference in the value of the loss of weight on heating.

C. Density

The densities of the samples are also shown in the Table 3.1 and Fig. 3.4(d). They are all greater than 3.0 g/cm³. The density of the sample D1 is slightly lower than these of others. However, the values are in good agreement with the literature value (3.42 g/cm³).

D. Particle size

The particle sizes of the samples at 10%, 50% and 90% under size were tabulated in Table 3.2. The size distribution was plotted in percentage of under size,
Fig. 3.3 IR spectra of the lithium titanate samples a: D₁ (680°C)  b: D₂ (720°C)  
c: D₃ (820°C)  and d: D₄ (920°C)
Table 3.1  Loss of weight on heating (L%), lithium content (C_{Li}%), purity (P%) and density (d) for samples of lithium titanate made at different temperatures

<table>
<thead>
<tr>
<th>samples</th>
<th>D_1</th>
<th>D_2</th>
<th>D_3</th>
<th>D_4</th>
<th>theoretical</th>
</tr>
</thead>
<tbody>
<tr>
<td>t°C</td>
<td>680</td>
<td>720</td>
<td>820</td>
<td>920</td>
<td>NA</td>
</tr>
<tr>
<td>L%</td>
<td>27.61</td>
<td>28.72</td>
<td>28.80</td>
<td>28.86</td>
<td>28.62</td>
</tr>
<tr>
<td>C_{Li}%</td>
<td>12.37</td>
<td>12.60</td>
<td>12.62</td>
<td>12.63</td>
<td>12.65</td>
</tr>
<tr>
<td>P%</td>
<td>97.79</td>
<td>99.63</td>
<td>99.76</td>
<td>99.84</td>
<td>100.00</td>
</tr>
<tr>
<td>d(g/cm^3)</td>
<td>3.40</td>
<td>3.46</td>
<td>3.46</td>
<td>3.42</td>
<td>3.42*</td>
</tr>
</tbody>
</table>

* from the reference by Kordes, 1935.
NA: not applicable
Fig. 3.4 Properties of lithium titanate made at different temperatures  

- a: loss of weight on heating (L%)  
- b: lithium content (C_{Li}%)  
- c: purity (P%)  
- d: density (g/cm³)
over size and frequency as function of particle size (see Fig.3.5). No difference was found at the median diameter of particle size (50% under size). The 10% and 90% under size values of the sample $D_4$ are larger, which also can be seen in Fig.3.5(d) as the curve was slightly shifted to the right side. The 10% under size values of $D_3$ and $D_4$ were similar, but larger than these of $D_1$ and $D_2$. In summary, there is no great difference in the particle size distribution.

Table 3.2 Particle size at 10%, 50% and 90% under size (X±SD, n=3) for lithium titanate samples made at different heating temperatures

<table>
<thead>
<tr>
<th>sample name</th>
<th>10% (µm)</th>
<th>50% (µm)*</th>
<th>90% (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_1$</td>
<td>10.83±1.48</td>
<td>38.83±1.20</td>
<td>81.72±3.90</td>
</tr>
<tr>
<td>$D_2$</td>
<td>11.10±0.70</td>
<td>36.43±0.33</td>
<td>69.70±0.69</td>
</tr>
<tr>
<td>$D_3$</td>
<td>17.27±0.95</td>
<td>39.83±0.82</td>
<td>82.23±5.40</td>
</tr>
<tr>
<td>$D_4$</td>
<td>17.60±0.61</td>
<td>39.40±1.14</td>
<td>90.87±3.90</td>
</tr>
</tbody>
</table>

* 50% under size was defined as mass median diameter of particles

E. Surface areas

Significant differences were found in the surface areas of the samples. Samples prepared at higher temperatures had large surface areas (see Table 3.3), but the particle sizes are similar for all samples. This is not the common relationship between the particle size and the surface area. It indicates that the surface structure of lithium titanate particles is controlled by the crystallization at the surface of the particles. Although the particle size of the samples are similar, the degree of the crystallization is different, and may be controlled by the heating temperature. The higher the temperature used, the more crystallization occurs, the smaller the surface area.

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Fig. 3.5 Particle size distributions of lithium titanate samples made at (a) 680°C (D₁), (b) 720°C (D₂), (c) 820°C (D₃) and (d) 920°C (D₄)(% under size, % over size and % frequency as function of particle sizes)
Table 3.3 Surface areas \((S_i, X\pm SD)\) of lithium titanate samples made at different heating temperatures

<table>
<thead>
<tr>
<th>Samples</th>
<th>(D_1)</th>
<th>(D_2)</th>
<th>(D_3)</th>
<th>(D_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T^\circ C)</td>
<td>680</td>
<td>720</td>
<td>820</td>
<td>920</td>
</tr>
<tr>
<td>(S_i (m^2/g))</td>
<td>4.3738±0.012</td>
<td>2.3307±0.020</td>
<td>1.3740±0.016</td>
<td>0.7805±0.023</td>
</tr>
</tbody>
</table>

F. Dissolution of powders

The *in vitro* dissolution results for the samples \((D_1, D_2, D_3\) and \(D_4\)) are shown in Fig.3.6(a). The amount of lithium released from the sample \(D_1\) was much greater than that for the sample \(D_4\). With increasing the temperature from 680 to 920\(^\circ C\), the quantity of lithium released from the samples decreased in the order of \(D_1 > D_2 > D_3 > D_4\) respectively, which agrees well with the surface areas \((D_1 > D_2 > D_3 > D_4)\). The smaller the surface area of the sample, the lower the amount of lithium released. The decrease in the quantity of lithium released from the sample prepared at the high temperature is, therefore, a consequent of the lower surface area and the higher crystallinity of the sample made at higher temperature. The release rate of lithium (here defined as percentage of lithium released per hour, \%/hr) decreased in the order of \(D_1 > D_2 > D_3 > D_4\). It was, however, found to be greatly different within 2 hours [see Fig. 3.6(b)]. After 2 hours, the release rate was similar, and independent of the temperature. The initial release of lithium within 1 hour \((r_1, \%/hr)\), the initial "burst", decreased for the sample prepared at high temperature, which results in the overall differences in the amounts of lithium released from the powders. The initial release rate \(r_1\) is characteristic for each sample. The results suggested that the heating temperature affects the initial release rate more potentially.

The percentages of lithium released at 2 hours, 6 hours and 12 hours are tabulated in Table 3.4. As the reaction for the preparation of the sample \(D_1\) was not complete, it is not considered as a pure sample of lithium titanate product. Therefore, three different release patterns were obtained *in vitro*: fast\((D_2)\), intermediate\((D_3)\) and slow\((D_4)\).
Fig. 3.6 a: Percentage of lithium released *in vitro* from the samples made at different temperatures as function of time in 0.1 N of hydrochloride acid solution  

b: The release rate of lithium for the samples made at different temperatures as function of time
Table 3.4 Percentages of lithium released *in vitro* at 2, 6 and 12 hours from lithium titanate samples made at different heating temperatures

<table>
<thead>
<tr>
<th>samples</th>
<th>T°C</th>
<th>2 hrs</th>
<th>6 hrs</th>
<th>12 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D_2)</td>
<td>720</td>
<td>71.38±0.78</td>
<td>92.46±0.63</td>
<td>104.57±0.12</td>
</tr>
<tr>
<td>(D_3)</td>
<td>820</td>
<td>45.08±0.98</td>
<td>69.68±0.47</td>
<td>88.25±1.13</td>
</tr>
<tr>
<td>(D_4)</td>
<td>920</td>
<td>23.16±0.34</td>
<td>39.78±0.55</td>
<td>50.88±0.23</td>
</tr>
</tbody>
</table>

G. Ion equilibrium

G-1 Time course

The time for the equilibrium to be established for a lithium titanate sample \((D_3, 820^\circ C)\) in hydrochloride acid solution was measured. The result is shown in Fig.3.7(a). The time to reach an equilibrium is 6 hours. After 6 hours, the lithium concentration in the solution was independent of the time. In order to ensure that equilibrium for all the samples reached, 24 hours was chosen as the time for the equilibrium study.

G-2 Effect of the amount of the sample

The amount of lithium ion exchanged with 1 mmol of hydrogen ion (10 ml of 0.1N hydrochloride acid solution) is shown in Fig.3.7(b). The amount of lithium ion released into the solution with increasing sample weight eventually becomes independent of the amount of powder added. The affinity (F value) was calculated and is also shown in Fig.3.7(b). The maximum F value obtained is 1.14, which agrees the theoretical value (F=1). When the F value reached 1, the amount of lithium ion exchanged with hydrogen ion was independent of the quantity of the sample used. It suggested that the amount of lithium released from lithium titanate powder can be limited by the quantity of hydrogen ion available in the solution. When the exchange ratio is less than 1, the increase of the quantity of the samples (lithium content) can increase the release of lithium. When the F value reaches 1, the ion exchange between lithium ion and hydrogen ion will be at maximum level.
Fig. 3.7 Ion equilibrium profiles  

a: Time course  

b: The effect of the amount of the samples added 

c: The exchange ratio of lithium and hydrogen ions  

d: The effect of the quantity of sample added on the equilibrium

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G-3 Effect of the amount of hydrogen ion

The results of the ion equilibrium experiments for the samples D_1, D_2, D_3 and D_4 in 10 ml of the following concentrations of hydrochloride acid solutions: 0.01N, 0.02N, 0.04N, 0.08N, 0.10N and 0.20N are shown in Fig.3.7(c). The quantity of lithium ion exchanged with hydrogen ion increased with increasing the concentrations of the acid solutions (the amount of hydrogen ion in the solution). A linear relationship between hydrogen ion added and lithium ion released was obtained for all samples. The F values of the samples (or the slope of the regression line) increased from 0.878 to 1.002 with increasing the formation temperature of the sample lithium titanate from 680 to 920°C respectively, Table 3.5. D_3 and D_4 have similar values for F which are close to the theoretical value (F=1). This suggests that the samples D_3 and D_4 (prepared at 820 and 920°C) are similarly formed as Li_2TiO_3 products. The value of intercepter at Y axis for all lines, however, decreased form 0.448 to 0.009 with increasing the temperature of formation from 680 to 920°C, which may indicated some differences in the intermediate process of the reaction for preparation of Li_2TiO_3 and the release mechanism of lithium ion. The sample prepared at the lowest temperature (i.e. D_1, 680°C) has the lowest value of F and the highest value of the intercept and vice versa. Theoretically, if the product (Li_2TiO_3) is pure and well formed, the F value (the affinity between lithium ion and hydrogen ion) should be 1 and the intercept zero. Therefore, the samples D_3 and D_4 are purer than D_1 and D_2. The intermediate, lithium oxide (Li_2O), may not be completely converted into lithium titanate (Li_2TiO_3) at a low temperature. It may be present in the final product, but to a different extent. The higher the temperature, the less the Li_2O in the final product, which explains the observation obtained from the dissolution study (the initial release rate, r_1, is much slower for the sample made at high formation temperature. The release mechanism is suggested to be mainly a ion exchanged mechanism in the dilute acid solution.

To observe the effects of the quantity of the sample and the hydrogen ion added on the equilibrium, the lithium ion released in the solution was plotted against the amount of the hydrogen ion as function of the quantity of the lithium titanate powder used [see Fig. 3.7 (d)]. When the amount of lithium titanate powder (sample
Table 3.5 The F values (the slope), the intercepter at Y axis and the correlation coefficient (R) from the equilibrium curves for samples $D_1$, $D_2$, $D_3$ and $D_4$

<table>
<thead>
<tr>
<th>samples</th>
<th>T°C</th>
<th>F value</th>
<th>Y intercepter</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_1$</td>
<td>680</td>
<td>0.87798</td>
<td>0.448182</td>
<td>0.9983</td>
</tr>
<tr>
<td>$D_2$</td>
<td>720</td>
<td>0.90141</td>
<td>0.283939</td>
<td>0.9990</td>
</tr>
<tr>
<td>$D_3$</td>
<td>820</td>
<td>0.97111</td>
<td>0.063333</td>
<td>0.9990</td>
</tr>
<tr>
<td>$D_4$</td>
<td>920</td>
<td>1.00160</td>
<td>0.008788</td>
<td>0.9989</td>
</tr>
</tbody>
</table>

$D_3$ was increased to 0.6 g (equivalent to 10.883 mmol), a non-linear relationship was obtained between the amount of hydrogen ion from 0.1 mmol ($F=3.9$) and 0.4 mmol ($F=2.4$) (see line III). Obviously, the ion exchange ratio ($F$) is much greater than the theoretical value of 1, which suggests the following facts: (1) the release of lithium into a dilute acid solution is not only by ion exchange mechanism. (2) the amount of lithium released from the powder could be increased, to a certain extent, by increasing the quantity of the powder, but it is quite limited. In contrast, when the amount of the powder was reduced to about 0.1 g (equivalent to about 1.794 mmol of lithium), a non-linear relationship was seen between the amount of hydrogen ion from 1 mmol ($F=1.08$) to 2 mmol ($F=0.82$) (see line I). As shown in Fig.3.7(d)(line I), most of the lithium ion contained (1.794 mmol) in the powder was released to the solution (1.644 mmol) when 2 mmol hydrogen ion is present. A linear relationship was obtained when 0.3 g of the lithium titanate powder (equivalent to 5.441 mmol of lithium) was used. Except for the non-linear part of line I and line III, the linear relationship obtained from the three quantities of samples (line I, II and III) is similar. The nature of this phenomena is unknown. It may be related to the properties of the powder, the presences of $\text{Li}_2\text{O}$ and the release mechanism of lithium.

H. SEM

The electron microscopy photos of the samples formed at different temperatures show that no significant differences in their particle sizes and shapes (see
photos 3.1 & 3.2), which agrees the results from the laser light diffraction. The surface structure of the particles, however, varied. The crystallinity increased in the order of $D_1 << D_2 < D_3 < D_4$. Sample $D_4$ showed much clearer outline of the crystal form than the others. Therefore, increasing the heating temperature causes the surface of the particles to become more crystalline, which agrees with the results obtained from other above studies. As seen above, the crystallinity on the surface of the particle leads to the differences in the surface area, rather than the particle size itself.

I. X-ray powder diffraction

The X-ray diffraction data of the initial mixture before heating is shown in Fig.3.8(a). Compared to the traces of the samples ($D_1$, $D_2$, $D_3$ and $D_4$) [see Fig.3.8(b-e)], the trace of the sample mixture differs completely from those of the samples, which indicated that a new crystal form was produced on heating. No significant differences were found in the main features of the diffraction pattern of the samples formed at different temperatures. All the results agree well with those reported by Annopirskill in 1971 [see Fig.3.8(f) and Table 3.6]. However, there were four overlapping peaks in the range from $20^\circ$ to $25^\circ$ in the trace of the sample $D_1$ (made at $680^\circ$C). At higher formation temperatures, the numbers of peaks in the range is gradually reduced, as shown in Fig.3.8 (c-e). The results suggest that lithium titanate can be formed at $680^\circ$C, but with low crystallinity. An increase in the formation temperature of lithium titanate, the product becomes purer and more crystallized. The degree of crystallinity is related to the temperature of formation.

J. Dielectric measurement

The dielectric responses of the samples $D_1$, $D_2$, $D_3$ and $D_4$ are shown in Fig. 3.9. The samples $D_1$ and $D_2$ show similar responses with a crossing point (at about $3 \log F, Hz$) on the two curves ($\log C$ and $\log G/\omega$) as seen Fig. 3.9 (a and b). The sample $D_3$ had much higher responses as both curves were shifted [see Fig. 3.9(c)]. The crossing point of both curves was also shifted to a higher frequency ($4 \log F, Hz$). The sample $D_4$ showed the highest response with a crossing point at $5 \log F$ (Hz) [see Fig. 3.9 (d)]. Increasing the formation temperature results in a change in the dielectric
Photos 3.1  SEM of lithium titanate samples  

**Left:** Sample $D_1$ ($680^\circ$C)  
**Right:** Sample $D_2$ ($720^\circ$C)
Photos 3.2 SEM of lithium titanate samples  **Left:** Sample D₃ (820°C)  **Right:** Sample D₄ (920°C)
Fig. 3.8 X-ray diffraction patterns of the initial mixture and lithium titanate samples

a: Mixture of Li$_2$CO$_3$ and TiO$_2$ at molar ratio 1:1  
b: Sample D$_1$ (680°C)  
c: Sample D$_2$ (720°C)
Fig. 3.8 X-ray diffraction patterns of lithium titanate samples  

- d: Sample D₃ (820°C)  
- e: Sample D₄ (920°C)  
- f: Li₂TiO₃ (reference from Annopol’skii, 1971)
Table 3.6 X-ray powder diffraction data of the lithium titanate samples made at different formation temperatures and the reference

<table>
<thead>
<tr>
<th></th>
<th>D₁(680°C)</th>
<th>D₂(720°C)</th>
<th>D₃(820°C)</th>
<th>D₄(920°C)</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>θ°</td>
<td>d(Å)</td>
<td>θ°</td>
<td>d(Å)</td>
<td>θ°</td>
<td>d(Å)</td>
</tr>
<tr>
<td>18.6</td>
<td>4.770</td>
<td>18.6</td>
<td>4.770</td>
<td>18.6</td>
<td>4.770</td>
</tr>
<tr>
<td>36.0</td>
<td>2.495</td>
<td>36.1</td>
<td>2.488</td>
<td>36.1</td>
<td>2.488</td>
</tr>
<tr>
<td>43.8</td>
<td>2.067</td>
<td>43.8</td>
<td>2.067</td>
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<td>2.067</td>
</tr>
<tr>
<td>47.9</td>
<td>1.899</td>
<td>47.9</td>
<td>1.903</td>
<td>47.9</td>
<td>1.899</td>
</tr>
<tr>
<td>58.0</td>
<td>1.595</td>
<td>57.8</td>
<td>1.595</td>
<td>57.8</td>
<td>1.595</td>
</tr>
<tr>
<td>63.6</td>
<td>1.463</td>
<td>63.6</td>
<td>1.463</td>
<td>63.6</td>
<td>1.463</td>
</tr>
</tbody>
</table>
Fig. 3.9 Dielectric spectra of lithium titanate samples  

- **a:** Sample D₁ (680°C)  
- **b:** Sample D₂ (720°C)  
- **c:** Sample D₃ (820°C)  
- **d:** Sample D₄ (920°C)
response (increasing the capacitance and the conductance of the sample).

The dielectric response is usually produced by the polarization of the dielectric materials when an electric field is applied. The processes of the polarization can arise from four different mechanisms (Anderson, 1984): (1) a slight displacement of the negatively charged electron cloud in an atom relative to the positively charged nucleus; (2) a slight relative distortion or separation of anions and cations within the molecule; (3) a reorientation of the molecule containing permanent electric dipoles; (4) the migration of lattice vacancies, impurity ions together with free electrons. Therefore, the nature of molecule structure of the material produces an effect on the dielectric response. The difference in the response indicates the changes of contributions of bonding force between atoms in the molecule. The heating temperature resulted in the differences of crystallization, which is reflected by the dielectric response. In addition, it demonstrated the possibility of using this technique to identify the samples prepared at different heating temperatures.

K. NMR (MAS) measurement

The $^7$Li NMR spectra of the lithium titanate samples ($D_1$, $D_2$, $D_3$ and $D_4$) showed no differences as seen in Fig. 3.10. The main Li$^+$ peak appeared at an identical chemical shift in the spectra of samples $D_1$, $D_2$, $D_3$ and $D_4$, which shows that the lithium environment in all of the samples is similar and symmetrical (reflecting the simple (NaCl) structure of Li$_2$TiO$_3$. Compared to the spectrum of the mixture of lithium carbonate and titanium dioxide (see Fig.3.11), the side peaks of the lithium titanate samples have much lower intensity. The mixture has much more side peaks than the samples. The chemical shift ($\delta$) of Li$^+$ in the mixture ($\delta$=0.0493 ppm) differs from that in the samples ($\delta$=0.186). It indicates that the chemical environment of lithium in both the mixture and the samples is different. After heating, the samples were formed as one identical compound, lithium titanate (Li$_2$TiO$_3$), thus confirming that the heating temperature dose not affect the chemical composition and structure of lithium titanate formed.

3.3.2 Particle size of lithium carbonate
Fig. 3.10  NMR spectra of lithium titanate samples  a: Sample D₁ (680°C)  b: Sample D₂ (720°C)  c: Sample D₃ (820°C)  and d: Sample D₄ (920°C)
Fig. 3.11 NMR spectra of the initial mixture of Li$_2$TiO$_3$ and TiO$_2$ (a) and lithium titanate sample D$_3$ (b)
A. Batch variation

As mentioned in chapter 2, the particle size of lithium carbonate powder was found to vary from batch to batch. The SEM photos of these batches show that the particle size was decreased in the order of the batch 392, 497OH and 145K (see photos 3.3, 3.4 and 3.5), which agrees well with the results obtained from the laser light diffraction measurement. This was also confirmed by the surface areas of these batches: 392, 0.4630 m²/g; 497OH, 0.7346 m²/g; 145K, 0.9983 m²/g. As seen in the scanning electron micrographs, the crystals of these batches differed greatly, which was also demonstrated by X-ray diffraction of these lithium carbonate powders (see Fig. 3.12, the peaks marked as I, II & III).

The loss of weight on heating, lithium content, purity and density of the samples produced (coded as A-497OH, A-145K and A-392 respectively) were found not to differ appreciably (see Table 3.7). The nature of the samples as reflected in their surface area and size range were, however, different, Tables 3.7 and 3.8. The particle size decreased in the order of A-497OH > A-392 > A-145K, which is also demonstrated in their SEM images (see photos 3.6). The surface areas of the samples A-497OH and A-392 were similar, but the sample A-145K had slightly larger surface area (see Table 3.7).

Table 3.7 The loss of weight on heating (L%), lithium contents (C_Li%), purities (P%), densities (d) and surface areas (S_i) of the lithium titanate samples prepared with different batches of lithium carbonate powders (A-497OH, A-145K and A-392)

<table>
<thead>
<tr>
<th>samples</th>
<th>A-497OH</th>
<th>A-392</th>
<th>A-145K</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/N Li_2CO_3</td>
<td>497OH</td>
<td>392</td>
<td>145K</td>
</tr>
<tr>
<td>L%</td>
<td>28.92</td>
<td>28.82</td>
<td>28.80</td>
</tr>
<tr>
<td>C_Li,%</td>
<td>12.57</td>
<td>12.56</td>
<td>12.62</td>
</tr>
<tr>
<td>P%</td>
<td>99.37</td>
<td>99.29</td>
<td>99.76</td>
</tr>
<tr>
<td>d(g/cm^3)</td>
<td>3.43</td>
<td>3.46</td>
<td>3.46</td>
</tr>
<tr>
<td>S_i(m²/g)</td>
<td>1.4287</td>
<td>1.4094</td>
<td>1.6712</td>
</tr>
</tbody>
</table>
Photos 3.3  SEM of lithium carbonate, Batch No. 392
Photos 3.4 SEM of lithium carbonate, Batch No. 497OH
Photos 3.5  SEM of lithium carbonate, Batch No. 145K
Fig. 3.12 X-ray diffraction patterns of three batches of lithium carbonate

a: 392
b: 497OH
c: 145K

Fig. 3.12 X-ray diffraction patterns of three batches of lithium carbonate  a: 392
b: 497OH  and c: 145K
Photos 3.6  SEM of lithium titanate samples made with three different batches of lithium carbonate  **Top:** Sample A-497OH  **Middle:** Sample A-392  and **Bottom:** Sample A-145K
Table 3.8 The particle size of the lithium titanate samples (A-497OH, A-392 and A-145K) (10%, 50% and 90% under size; X±SD, n=3)

<table>
<thead>
<tr>
<th>samples</th>
<th>10% under(μm)</th>
<th>50% under(μm)</th>
<th>90% under(μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-497OH</td>
<td>13.33±3.14</td>
<td>62.00±2.91</td>
<td>104.60±3.19</td>
</tr>
<tr>
<td>A-392</td>
<td>14.30±0.35</td>
<td>35.88±0.55</td>
<td>63.60±1.67</td>
</tr>
<tr>
<td>A-145K</td>
<td>10.37±1.39</td>
<td>20.90±0.29</td>
<td>45.33±2.15</td>
</tr>
</tbody>
</table>

The percentage of lithium released from the samples in the dissolution test decreased in the order of A-392 > A-145K > A-497OH [see Fig.3.13(a)]. A significant decrease in amount of lithium released was observed between the samples A-392 and A-497OH. Although the sample A-145K had larger surface area and smaller particle size, the amount of lithium released after 4 hours was less than that of the sample A-392. The initial release rate of the sample A-497OH (r_i, %/hr) was much slower than these of the samples A-392 and A-145K [see Fig.3.13(b)]. These results suggest that the batch variation in particle size of lithium carbonate powder does not affect the loss of weight on heating, lithium content, purity and density, but influences the particle size, surface area and dissolution profile of the lithium titanate samples formed. No clear trend was found to correlate the particle sizes or surface areas of the samples to their dissolution rate.

B. Effect of the initial particle size of lithium carbonate

The properties of the lithium titanate samples prepared with three different size ranges of lithium carbonate from the same bulk batch (A-75, A-150 and A-300) are tabulated in the Table 3.9. No significant difference was found. The surface areas of the samples, however, decreased greatly in the order of A-75, A-150 and A-300 with increasing their particle size, Table 3.9. The sample A-300 has the largest particle size, therefore, it has the smallest surface area and vice versa. In this case, the surface area correlated well with the particle size.
Fig. 3.13 a: The *in vitro* release profile of lithium for the samples A-497OH, A-145K and A-392 and b: The release rate of lithium of A-497OH, A-392 and A-145K.
Table 3.9 The loss of weight on heating (L%), lithium content (C_{Li}%), purity (P%), density (d) and surface area of the lithium titanate samples (A-75, A-150 and A-300)

<table>
<thead>
<tr>
<th>samples</th>
<th>A-75</th>
<th>A-150</th>
<th>A-300</th>
</tr>
</thead>
<tbody>
<tr>
<td>L%</td>
<td>28.68</td>
<td>28.90</td>
<td>28.95</td>
</tr>
<tr>
<td>C_{Li}%</td>
<td>12.60</td>
<td>12.64</td>
<td>12.64</td>
</tr>
<tr>
<td>P%</td>
<td>99.60</td>
<td>99.92</td>
<td>99.92</td>
</tr>
<tr>
<td>d(g/cm^3)</td>
<td>3.40</td>
<td>3.42</td>
<td>3.40</td>
</tr>
<tr>
<td>S, (m^2/g)</td>
<td>2.3380</td>
<td>1.2117</td>
<td>0.7619</td>
</tr>
</tbody>
</table>

The X-ray diffraction patterns of the samples show that all the samples have the same crystal form, Fig. 3.14. The initial particle size of lithium carbonate does not affect the formation of the crystal of lithium titanate. From the SEM photos 3.7, 3.8 and 3.9, it can be seen that the particle sizes of the samples A-75, A-150 and A-300 differed greatly. The crystals on the particle surface of the sample A-75 were smaller than those of the samples A-150 and A-300. Both samples A-150 and A-300 have more regular shape and smoother surface.

The percentage of lithium released from the samples in vitro decreased in the order of A-75 > A-150 > A-300 [see Fig. 3.15(a)]. Compared to the sample A-150, the sample A-300 had a more significant decrease in the amount of lithium released. The initial release rates (r_i, %/hr) of the samples are shown in the Fig. 3.15(b). A substantial difference was found between the samples A-75 and A-300. However, A-75 and A-150 had similar initial release rate (r_i).

No difference was found in the ion equilibrium of the samples, Fig.3.15(c). The ion exchange ratio (F value) and the linear regression coefficient (R) are shown in Table 3.10. The equilibrium lines for A-75, A-100 and A-300 between lithium ion and hydrogen ion are identical, which suggested that a lithium titanate was formed with similar crystallinity.

In summary, the particle size of lithium carbonate has a potential effect on
Fig. 3.14 X-ray diffraction patterns of the lithium titanate samples (a) A-75, (b) A-150 and (c) A-300
Photos 3.7  SEM of lithium titanate sample A-75 at different magnifications
Photos 3.8 SEM of lithium titanate sample A-150 at different magnifications
Photos 3.9  SEM of lithium titanate sample A-300 at different magnifications
Fig. 3.15 a: The in vitro release profiles for samples A-75, A-150 and A-300 b: The release rate of lithium of the samples A-75, A-150 and A-300 and c: The ion equilibrium for the samples A-75, A-150 and A-300
the particle size of the product and thus, affects the release rate of lithium. However, the density, loss of weight on heating, lithium content, purity and the formation of lithium titanate are independent of the particle size of lithium carbonate.

Table 3.10 The ion exchange ratio (F) and linear regression coefficient (R) of the lithium titanate samples (A-75, A-150 and A-300)

<table>
<thead>
<tr>
<th>samples</th>
<th>A-75</th>
<th>A-150</th>
<th>A-300</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0.9301</td>
<td>0.9697</td>
<td>0.9479</td>
</tr>
<tr>
<td>R</td>
<td>0.9985</td>
<td>0.9996</td>
<td>0.9961</td>
</tr>
</tbody>
</table>

3.3.3 Heating time

The IR spectra of the samples (C₁, C₂, C₃ and C₄) heated for 4, 8, 16 and 24 hours respectively showed that the carbonate group peaks have disappeared. The reaction for all the samples was complete. It indicates that the reaction between lithium carbonate and titanium dioxide can be complete at 820°C within 4 hours (see Fig. 3.16). No major differences were found in the properties of the samples except that the purity of C₁ was slightly lower than those of others, Table 3.11, and the surface area of the sample C₄ was lower.

Table 3.11 The loss of weight on heating (L%), lithium contents (C₃%), purities (P%), densities (d) and surface areas (Sₐ) of the lithium titanate samples (C₁, C₂, C₃ and C₄)

<table>
<thead>
<tr>
<th>samples</th>
<th>C₁</th>
<th>C₂</th>
<th>C₃</th>
<th>C₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>heating time</td>
<td>4 hrs</td>
<td>8 hrs</td>
<td>16 hrs</td>
<td>24 hrs</td>
</tr>
<tr>
<td>L%</td>
<td>28.62</td>
<td>28.64</td>
<td>28.70</td>
<td>28.82</td>
</tr>
<tr>
<td>C₃%</td>
<td>12.52</td>
<td>12.53</td>
<td>12.60</td>
<td>12.56</td>
</tr>
<tr>
<td>P%</td>
<td>98.97</td>
<td>99.05</td>
<td>99.60</td>
<td>99.29</td>
</tr>
<tr>
<td>d(g/cm³)</td>
<td>3.46</td>
<td>3.47</td>
<td>3.47</td>
<td>3.46</td>
</tr>
<tr>
<td>Sₐ(m²/g)</td>
<td>1.8334</td>
<td>1.8696</td>
<td>1.8322</td>
<td>1.6721</td>
</tr>
</tbody>
</table>
Fig. 3.16 IR spectra of the lithium titanate samples heated for different time  

- a: $C_1$ (4 hours)  
- b: $C_2$ (8 hours)  
- c: $C_3$ (16 hours)  
- d: $C_4$ (24 hours)
The SEM photos of the samples are shown in photos 3.10 and 3.11. The mass was fused together when the sample (C1) was heated for 4 hours. No clear crystal outline can be seen (photos 3.10, left). On increasing the heating time, the outline becomes visible on the surface of the particles (see photos 3.11), and the definition of the crystallites also becomes larger (C1 < C2 < C3 ≤ C4). No significant differences were observed in the particle appearances and sizes of these powders.

The dissolution results of the samples show that the amount of lithium released from the sample heated for longer times decreased, Fig.3.17(a). A significant difference was found in the initial release rate (r1) between the samples C1, C2 and C3 [see Fig.3.17(b)], but no difference between the samples C3 and C4.

The results implied that the crystallization of lithium titanate needs considerable time, probably over 16 hours, to be complete, although the reaction can be complete at 820°C within 4 hours. Heating for 24 hours is probably sufficient to allow crystallization to be complete. The crystallization has important influence on the release profile of lithium, and may be the reason why the heating time has less effect on the properties of the final product.

3.3.4 Furnace variation

The samples produced at 680, 720 and 820°C in the furnace (I) were coded as A-680, B-820 and C-920 respectively. The IR spectra of the samples are shown in Fig. 3.18. The carbonate group peaks disappeared in the spectra of the samples B-820 and C-920, but not in the sample A-680. The reaction was not complete at 680°C, which agrees well with that of D1 prepared at 680°C in the furnace (II).

The SEM photos (3.12) show that the crystals of lithium titanate become more regular at the high temperature, but the surface structure of the particles differed greatly. The samples A-680 and B-820 had irregular particle shapes and sizes. The outline of crystal forms of A-680 and B-820 were not clear. The sample C-920 showed much clearer outline of the crystal form, which is also in good agreement with the results of the samples made in the furnace (II).

The X-ray diffraction data of the samples show that the crystal of lithium titanate was well formed in the samples A-820 and C-920 [see Fig. 3.19 (b,c)].
Photos 3.10 SEM of lithium titanate samples heated for 4 and 8 hours. **Left:** Sample C₁ (4 hours)  **Right:** Sample C₂ (8 hours)
Photos 3.11  SEM of lithium titanate samples heated for 16 and 24 hours  
Left: Sample C₃ (16 hours)  
Right: Sample C₄ (24 hours)
Fig. 3.17  a: The *in vitro* release profile of lithium for the samples $C_1$ (4 hours), $C_2$ (8 hours), $C_3$ (16 hours) and $C_4$ (24 hours)  b: The release rate of lithium of samples $C_1$, $C_2$, $C_3$ and $C_4$
Fig. 3.18 IR spectra of the initial reactive mixture (a) and the samples prepared in the furnace (I) after heating at (b) 680°C (A-680), (c) 820°C (B-820) and (d) 920°C (C-920) for 24 hours.
Photos 3.12  SEM of lithium titanate samples made in the furnace (I) at (Top) 680°C (A-680), (Middle) 820°C (B-820) and (Bottom) 920°C (C-920)
Fig. 3.19 X-ray diffraction patterns of the lithium titanate samples made in the furnace (I) after heating at (a) 680°C (A-680), (b) 820°C (B-820) and (c) 920°C (C-920)
However, the pattern for the sample A-680 was different from those of samples B-820 and C-920 [see Fig. 3.19(a)]. A trace of the initial reaction mixture can still be seen in the pattern of A-680. The reaction for the sample A-680 was not complete and the lithium titanate was not well formed, agreeing well with the IR results.

The above results were compared with those of samples (D₁, D₃ and D₄) produced at 680, 820 and 920°C respectively in the furnace (II) [see Fig.3.3(a,c and d), Fig.3.8(b,d,e)], no significant differences were observed for the samples produced at 820 and 920°C (D₃ and B-820; D₄ and C-920). More peaks were present in the X-ray diffraction trace of the sample A-680 than in the sample D₁, which implies that the degree of the formation of the titanate and the extent crystallization were different between these two samples.

The densities of all the samples made in the furnaces (I) & (II) are shown in Table 3.12. The density of the sample A-680 was the lowest and much lower than the reference value(3.42 g/cm³). No noticeable difference was found between the samples D₃ and B-820 , or D₄ and C-920.

<table>
<thead>
<tr>
<th>furnace</th>
<th>I</th>
<th>II</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>samples</td>
<td>A-680</td>
<td>B-820</td>
<td>C-920</td>
<td>D₁</td>
<td>D₃</td>
</tr>
<tr>
<td>set t°C</td>
<td>680</td>
<td>820</td>
<td>920</td>
<td>680</td>
<td>820</td>
</tr>
<tr>
<td>measured t°C</td>
<td>675±17</td>
<td>791±17</td>
<td>901±15</td>
<td>680</td>
<td>820</td>
</tr>
<tr>
<td>d(g/cm³)</td>
<td>3.36</td>
<td>3.44</td>
<td>3.45</td>
<td>3.40</td>
<td>3.46</td>
</tr>
</tbody>
</table>

The dissolution results of the samples (A-680, B-820 and C-920) show that the percentage of lithium released from the samples decreased with increase in the temperature of formation [see Fig. 3.20 (a)], which agrees with the result obtained with the samples made in furnace (II). However, the amount of lithium released was different between the samples made at a same temperature, but in the furnace (I) and
Fig. 3.20 The *in vitro* release profiles of lithium for the samples prepared in the furnaces (I) and (II)  

a: Samples prepared in the furnace (I) at 680°C (A-680), 820°C (B-820) and 920°C (C-920)  
b: Samples prepared at 680°C in the furnaces (I) (A-680) and (II) (D1)  
c: Samples prepared at 820°C in the furnaces (I) (B-820) and (II) (D2)  
d: Samples prepared at 920°C in the furnaces (I) (C-920) and (II) (D4)
(II) (B-820 and D₃ or C-920 and D₄) [see Fig. 3.20 (c and d)], except the samples A-680 and D₁, Fig. 3.20 (b). The quantities of lithium released from B-820 and C-920 were greater than those from D₃ and D₄. The release rate of lithium from samples made in the furnace (II) was slower than that from the samples made in the furnace (I) after heating at a same temperature, Fig. 3.21. It suggests that a variation of the temperature maintained during the heating process for preparation of the product may also affect the crystallization of lithium titanate, and therefore influence the release profile of lithium.

### 3.3.5 Loading size of the mixture

The IR spectra of the samples prepared with different loads of the initial reactive mixtures in furnace II (A-25, A-50, A-100 and A-200) showed no difference, as seen in Fig. 3.22. The carbonate group peaks disappeared in all the spectra. The reactions of the samples were all complete.

From the SEM photos 3.13 and 3.14, no great difference was found in the particle shape and the surface structure. The crystal form was similar in all case. The size of the crystal was the same for the samples A-25, A-50 and A-100. The sample A-200 (largest loading size), however, had a larger crystal size and more regular shape at the particle surface.

The properties of the samples are tabulated in Table 3.13. No changes were found with increasing the loading size of the mixture.

**Table 3.13** The loss of weight on heating (L%), lithium content (C_{Li}%), purity (P) and density (d) of the lithium titanate samples (A-25, A-50, A-100 and A-200)

<table>
<thead>
<tr>
<th>samples</th>
<th>A-25</th>
<th>A-50</th>
<th>A-100</th>
<th>A-200</th>
</tr>
</thead>
<tbody>
<tr>
<td>L%</td>
<td>28.80</td>
<td>28.82</td>
<td>28.78</td>
<td>28.61</td>
</tr>
<tr>
<td>C_{Li}%</td>
<td>12.55</td>
<td>12.55</td>
<td>12.62</td>
<td>12.52</td>
</tr>
<tr>
<td>P%</td>
<td>99.21</td>
<td>99.21</td>
<td>99.76</td>
<td>99.17</td>
</tr>
<tr>
<td>d(g/cm³)</td>
<td>3.45</td>
<td>3.45</td>
<td>3.46</td>
<td>3.46</td>
</tr>
</tbody>
</table>
Fig. 3.21  The *in vitro* release rate of lithium at different dissolution time for the lithium titanate samples prepared at (a) 680°C in the furnaces (I) (A-680) and (II) (D1), (b) 820°C in the furnaces (I) (B-820) and (II) (D3) and (c) 920°C in the furnaces (I) (C-920) and (II) (D4)
Fig. 3.22 IR spectra of the lithium titanate samples A-25, A-50, A-100 and A-200
Photos 3.13 SEM of lithium titanate samples  

**Left:** Sample A-25  

**Right:** Sample A-50
Photos 3.14  SEM of lithium titanate samples  Left: A-100  Right: A-200
The amount of lithium released from the sample A-200 was less than that for the sample A-25, A-50 and A-100, Fig. 3.23(a). However, there was no significant difference observed between the samples A-25 and A-50. In general, the percentage of lithium released from the sample powders tended to decrease with increase in the load size. The initial release rate of lithium \( r_i \) showed no difference between A-25 and A-50, but decreased in the order of A-25 \( r_i \) > A-100 \( r_i \) > A-200. The reason was unknown and it could be caused by several factors which may affect the reaction process and crystallization. When the load size was increased to 200 g, the thickness of the mixture with load size of 200 g was much greater than that with the size of 25 g, which may affect the micro-thermal condition and kinetic factors during the heating process.

3.3.6 Reproducibility

The IR spectra of three groups of lithium titanate produced by heating 200 g of the mixture at 720, 820 and 920°C for 24 hours are shown in Fig.3.24, 3.25 and 3.26. All the peaks related to the carbonate group are absent in the spectra of all the products. The reactions between lithium carbonate and titanium dioxide were all complete. No difference was found in any of the samples, within the groups or between the groups.

The SEM results show that there was no difference in the particle size and crystal form within the five sub-batches of lithium titanate at each heating temperature (see photos 3.15, 3.16, 3.17, 3.18, 3.19 and 3.20). However, there were appreciably differences between the groups. The product (lithium titanate) becomes more crystalline at a higher formation temperature, as demonstrated in previous studies.

The properties of the three groups of lithium titanate are shown in Table 3.14, 3.15 and 3.16. No differences were found within each group. The values of L%, C_Li%, P% increased slightly with increasing the temperature from 720 to 920°C, as seen in the Tables (the mean value), which is in a good agreement with the results obtained in section 3.3.1. In terms of these properties, lithium titanate can be prepared reproducibly.

The percentage of lithium released from the samples was not noticeably
Fig. 3.23  a: The *in vitro* release profile of lithium for samples A-25, A-50, A-100 and A-300  b: The release rate of lithium of the samples A-25, A-50, A-100 and A-300

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Fig. 3.24 IR spectra of lithium titanate samples, Group I (720°C)  

- a: Sample No.1  
- b: Sample No.2  
- c: Sample No.3  
- d: Sample No.4  
- e: Sample No.5
Fig. 3.25 IR spectra of lithium titanate samples, Group II (820°C)  a: Sample No.1  
  b: Sample No.2  c: Sample No.3  d: Sample No.4  and e: Sample No.5
Fig. 3.26 IR spectra of lithium titanate samples, Group III (920°C)  

a: Sample No.1  
b: Sample No.2  
c: Sample No.3  
d: Sample No.4  
e: Sample No.5
Photos 3.15  SEM of lithium titanate samples, Group I (720°C)  **Top:** Sample No.1  
**Middle:** Sample No.2  and **Bottom:** Sample No.3
Photos 3.16  SEM of lithium titanate samples, Group I (720°C)  
Top: Sample No.4  
Bottom: Sample No.5
Photos 3.17 SEM of lithium titanate samples, Group II (820°C)  Top: Sample No.1  Middle: Sample No.2  and Bottom: Sample No.3
Photos 3.18  SEM of lithium titanate samples, Group II(820°C)  **Top:** Sample No.4  **Bottom:** Sample No.5
Photos 3.19 SEM of lithium titanate samples, Group III (920°C)  Top: Sample No.1 
Middle: Sample No.2  and Bottom: Sample No.3
Photos 3.20  SEM of lithium titanate samples, Group III(920°C)  Top: Sample No.4  Bottom: Sample No.5
different within the group I, or group II, or group III [see Fig.3.27 (a, b and c)]. The release pattern of lithium for the samples in each group is the same. The initial release rate ($r_i$, %/hr) of lithium also showed no difference among the five sub-batches of each group [see Fig.3.28 (a, d and c)]. When the mean percentage of lithium released from the five sub-batches was plotted as function of time, it can be seen that the release profile of lithium was also reproducible for the samples prepared at 720°C or 820°C or 920°C (see Fig.3.29).

Table 3.14  The loss weight on heating (L%), lithium content ($C_{Li}$%), purity (P%), density (d) and surface area ($S_i$) of lithium titanate samples made at 720°C (Group I) (mean value, X±SD)

<table>
<thead>
<tr>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>L%</td>
<td>28.71</td>
<td>28.69</td>
<td>28.71</td>
<td>28.81</td>
<td>28.67</td>
<td>28.71±0.05</td>
</tr>
<tr>
<td>$C_{Li}$%</td>
<td>12.60</td>
<td>12.60</td>
<td>12.60</td>
<td>12.62</td>
<td>12.60</td>
<td>12.60±0.01</td>
</tr>
<tr>
<td>P%</td>
<td>99.60</td>
<td>99.60</td>
<td>99.60</td>
<td>99.76</td>
<td>99.60</td>
<td>99.63±0.06</td>
</tr>
<tr>
<td>d(g/cm³)</td>
<td>3.47</td>
<td>3.47</td>
<td>3.45</td>
<td>3.47</td>
<td>3.44</td>
<td>3.46±0.01</td>
</tr>
<tr>
<td>$S_i$(m²/g)</td>
<td>2.2253</td>
<td>2.3584</td>
<td>2.4092</td>
<td>2.3156</td>
<td>2.3521</td>
<td>2.3321±0.06</td>
</tr>
</tbody>
</table>
### Table 3.15 The loss of weight on heating (L%), lithium content (C_Li%), purity (P%), density (d) and surface area (S_i) of lithium titanate samples made at 820°C (Group II) (mean value, X±SD)

<table>
<thead>
<tr>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>L%</td>
<td>28.79</td>
<td>28.81</td>
<td>28.77</td>
<td>28.81</td>
<td>28.82</td>
<td>28.80 ± 0.02</td>
</tr>
<tr>
<td>C_Li%</td>
<td>12.62</td>
<td>12.62</td>
<td>12.62</td>
<td>12.62</td>
<td>12.62</td>
<td>12.62 ± 0.00</td>
</tr>
<tr>
<td>P%</td>
<td>99.76</td>
<td>99.76</td>
<td>99.76</td>
<td>99.76</td>
<td>99.76</td>
<td>99.76 ± 0.00</td>
</tr>
<tr>
<td>d(g/cm³)</td>
<td>3.47</td>
<td>3.47</td>
<td>3.45</td>
<td>3.47</td>
<td>3.44</td>
<td>3.45 ± 0.01</td>
</tr>
<tr>
<td>S_i(m²/g)</td>
<td>1.3966</td>
<td>1.4249</td>
<td>1.4458</td>
<td>1.4055</td>
<td>1.3740</td>
<td>1.4094 ± 0.02</td>
</tr>
</tbody>
</table>

### Table 3.16 The loss of weight on heating (L%), lithium content (C_Li%), purity (P%), density (d) and surface area (S_i) of lithium titanate samples made at 920°C (Group III) (mean value, X±SD)

<table>
<thead>
<tr>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>L%</td>
<td>28.91</td>
<td>28.85</td>
<td>28.86</td>
<td>28.84</td>
<td>28.86</td>
<td>28.86 ± 0.02</td>
</tr>
<tr>
<td>C_Li%</td>
<td>12.64</td>
<td>12.63</td>
<td>12.63</td>
<td>12.62</td>
<td>12.63</td>
<td>12.63 ± 0.01</td>
</tr>
<tr>
<td>P%</td>
<td>99.92</td>
<td>99.84</td>
<td>99.84</td>
<td>99.76</td>
<td>99.84</td>
<td>99.84 ± 0.01</td>
</tr>
<tr>
<td>d(g/cm³)</td>
<td>3.42</td>
<td>3.42</td>
<td>3.42</td>
<td>3.43</td>
<td>3.43</td>
<td>3.42 ± 0.01</td>
</tr>
<tr>
<td>S_i(m²/g)</td>
<td>0.7848</td>
<td>0.7515</td>
<td>0.8144</td>
<td>0.8089</td>
<td>0.7814</td>
<td>0.7882 ± 0.02</td>
</tr>
</tbody>
</table>
Fig. 3.27 The *in vitro* release profile of lithium for lithium titanate samples made at (a) 720°C, Group I, (b) 820°C, Group II and (c) 920°C, Group III
Fig. 3.28 The *in vitro* release rate of lithium of lithium titanate samples made at (line a) 720°C, Group I; (line b) 820°C, Group II and (line c) 920°C, Group III
Fig. 3.29 The mean percentage of lithium released *in vitro* from lithium titanate samples made at 720°C (Group I), 820°C (Group II) and 920°C (Group III)
3.4 CONCLUSIONS

The completion of the reaction between lithium carbonate and titanium dioxide for preparation of lithium titanate can be achieved at the temperature 720°C or higher with a 24 hour heating period. In general, the higher the temperature, the purer the lithium titanate product.

The heating period has little effect on the properties of the final product such as density, loss of weight on heating, lithium content and purity. However, different heating duration causes differences in the in vitro release rate of lithium, especially the initial release rate ($r_i$). To allow the crystallization of lithium titanate to be complete, a heating time of 24 hours is required.

The chemical structure of lithium titanate formed is independent of the heating temperature and the duration of heating. It depends only on the molar ratio of the starting materials (lithium carbonate and titanium dioxide) contained in the initial reactive mixture. As long as the ratio is kept at 1:1, lithium titanate ($Li_2TiO_3$) is formed on the completion of the reaction.

The formation temperature has little effect on the density, loss of weight on heating, lithium content and purity which are however influenced by the extent of the overall reaction. All the products made at different temperatures have densities that were greater than 3.0 g/cm$^3$, agreeing well with the literature value (3.42 g/cm$^3$).

The particle size of the product is not associated with the heating temperature and time, but the particle size of lithium carbonate. Different particle size distributions of lithium carbonate produce variations in the particle size, the surface area and the in vitro release profile of lithium from the final product. The crystal form of lithium carbonate also has an effect on the final product. Other properties such as purity of the product, lithium content, loss of weight on heating are less influenced by variation in particle size of lithium carbonate. It is important and necessary to control the particle size and crystal form of lithium carbonate (and titanium dioxide) used in order to obtain a standard lithium titanate product and reproducible in vitro release profile of lithium.

The heating temperature has a potential influence on the completion of the reaction and crystallization. By changing the temperature, the extent of crystallization
of lithium titanate can vary and thereby change the surface area of the powder, even though the powders have similar particle size distributions. Consequently, the in-vitro release pattern of lithium can be altered. By controlling the formation temperature, three basic release patterns of lithium can be obtained: fast, intermediate and slow.

The release mechanism of lithium ion in diluted acid solution is mainly by ion exchange. Differences in the initial release rate \( r_1 \) for the products made at different temperatures are caused by differences in (1) the degree of the crystallization and (2) the presences of the water soluble intermediate, \( \text{Li}_2\text{O} \), in the final product.

The dielectric property of lithium titanate reflects the nature of its formation. The dielectric response of lithium titanate provided specific information on the crystallization, which identifies the difference between the products made at different formation temperatures and the degree of the crystallization.

Changing the equipment (furnace) has a limited effect on the properties of lithium titanate. The higher the temperature, the less the effects. The mixing process employed in preparation of the mixture can also affect the crystallization of lithium titanate and therefore, altering the dissolution profile of lithium in vitro.

The loading size of the initial reactive mixture can affect the dissolution characteristics of lithium from the product, but not the other properties of lithium titanate. The initial release rate of lithium \( r_1 \) tended to decrease for the product prepared with a larger load size. The reason is unknown. It may be related to the changes of the depth of the initial reactive mixture as a same container was used for the preparation.

The reproducibility of the method of preparing lithium titanate is satisfactory in terms of the properties and dissolution characteristics of lithium in vitro. To obtain a standard lithium titanate product and a reproducible release profile of lithium in vitro, the following things must be controlled: the particle sizes and the crystal forms of lithium carbonate and titanium dioxide powders, the process of the initial reactive mixture preparation, the loading size of the mixture for the preparation, the formation temperature and the heating duration.
CHAPTER 4

DESIGN OF ORAL LITHIUM TITANATE DOSAGE FORMS
4.1 INTRODUCTION

4.1.1 General

To achieve a therapeutical effect, any active drug needs to be delivered into the site of its action inside of the body and produces a biological response. Various pharmaceutical dosage forms are available for delivering active drugs to the body by different routes, for example, tablets, capsules, pellets, injections, etc. The choice of the dosage forms is dependent on the physical-chemical properties of the drugs, the way in which the body treats the drug and the diseases.

The oral route is considered the most natural, uncomplicated, convenient and safe means of administering drugs. Lithium has been used orally as anti-depressant for decades. The therapeutic effect and the problems of the bioavailability of lithium products have been demonstrated and increasingly recognized. Tablets are the dosage form available in the marketplace.

As mentioned in Chapter 1, for the oral controlled release dosage forms, it is important to overcome the potential problems associated with the GI environment and dynamics. The design of oral controlled release system by optimization of dosage form characteristics in relation to GI anatomy and physiology could provide a opportunity to maximize their therapeutic benefits. A novel approach was explored in this thesis to produce a distinct heavy material lithium titanate (3.42 g/cm³) with three different slow release patterns. Because of its high density, it may provide some influences on the total GI transit time.

A lithium controlled-release dosage form (tablets) is designed on the basis of the following idea: (1) high density (GI consideration), as discussed in Chapter 1. (2) The tablets should release enough lithium at a constant rate. As suggested in Chapter 3, lithium titanate powder releases lithium in-vitro at a first order rate (the release rate decreases with time). Therefore, different tablets formulations are designed to keep a intact tablet for maintaining a constant density through the GI tract and to alter the release character of lithium.
4.1.2 Methods of preparing tablets

A Excipients

Tablets usually consist of several other materials (excipients) in addition to the main active drugs. The excipients have different functions. They are usually classified into the following types according to their principal functions in the tablets:

1. Diluents and Absorbents, which are often used in very low dose tablets (i.e. active ingredients less than 0.1 g) to make up the major portion of the tablet.  
2. Moistenng agents and Binders, which are like "glue" powders to add the cohesive strength for forming granules.  
3. Disintegrants, which are used for the purpose of causing the tablets to break apart (disintegrate) when placed in aqueous environment.  
4. Lubricants, which act between powder and metal surfaces in relative motion to prevent friction and wear.  
5. Glidants, which are the materials that improve the flow characteristics of granulations.  

In a tablet formulation, the excipients mentioned above are not always necessary. The choice of the excipients depends on the properties of active ingredients and the types of tablets intended. All the excipient contributes the characteristics of the final tablets.

B. Preparation of tablets

There are three main methods used for the preparation of compressed tablets: a wet granulation method, a dry granulation method and a direct compression method. The wet granulation is widely employed method for the production of compressed tablets. It involves the following steps:  
1. weighing and blending the ingredients together,  
2. preparing the wet granulation mass with a binder solution,  
3. screening the damp mass through a sieve to produce wet granules,  
4. drying to obtain dry granules,  
5. dry screening,  
6. lubrication and blending and  
7. tableting by compression.

The dry granulation and the direct compression methods require some special properties of both active substances and excipients, which are well discussed by Gunsel et al (1970) and Ansel et al (1990).
4.2 EXPERIMENTAL

4.2.1 Preparation of capsules as references

Capsules of lithium titanate were used as references to be compared with the tablets formulations. Therefore, the capsules should be identical with the powders in terms of the release characters of lithium in-vitro. The equivalent 6 mmol of lithium amount of lithium titanate powder was accurately weighed and filled into a capsule shell (No.1) by hand. Three batches of lithium titanate powders made at different formation temperatures (720, 820 and 920 °C) were used to produce three batches of capsules at 15 capsules each (designated as C-720, C-820 and C-920 respectively). The dissolution test of these capsules was carried out. In addition, one batch of lithium carbonate capsules (CLi-1) containing 6 mmol of lithium was also prepared by filling lithium carbonate powder (USP/BP grade) into the shell. The dissolution test of the capsule was also studied. The method of the dissolution test is detailed in Chapter 2.

4.2.2 Choices of the binders

A. Different binders

Five different binders and one combined binder were used in the formulations, which are detailed in Table 4.1. One batch of lithium titanate powder made at 820°C for 24 hours was used as a model of active ingredient. The tablets were prepared by the method described in Chapter 2 and summarized in Fig.4.1 according to the formula in Table 4.1. The tablet weight of the resulting tablets was determined and the release of lithium from the tablets was studied by carrying out dissolution test in 0.1 N hydrochloric acid solution for 6 hours. The method of dissolution test is given in Chapter 2.

B. Different concentrations of PVP solutions

Three different concentrations of PVP aqueous solutions (5%, 10% and 15%) were used, which are shown in Table 4.2. The preparation of the tablets (containing 6 mmol of lithium) was the same as described above (see Chapter 2 and Fig.4.1). The dissolution tests of these tablets were carried out in 0.1 N hydrochloric acid solution for 6 hours.
Table 4.1 The formula of lithium titanate tablets prepared by using different binders (batch sizes: 30 tablets each)

<table>
<thead>
<tr>
<th>Formula</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% PVP aqueous solution (ml)</td>
<td>3.27</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5% PEG 4000 aqueous solution(ml)</td>
<td>-</td>
<td>3.47</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5% PEG10000 aqueous solution(ml)</td>
<td>-</td>
<td>-</td>
<td>3.38</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5% KluceI aqueous solution(ml)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.57</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.5%EC+2.5%PVP ethanol solution(ml)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.13</td>
<td>-</td>
</tr>
<tr>
<td>5% EC ethanol solution(ml)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.21</td>
</tr>
<tr>
<td>magnesium stearate(^2)(post-granulation)</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

\(^1\)The amount of lithium powder (B/N A-200) was calculated to be equivalent 6 mmol of lithium in each tablet according to the lithium content \((C_u\%)\) and the purity \((P\%)\) of the batch, for example, for this batch (A-200), the \(C_u\%\) and \(P\%\) are 12.54\% and 99.13\% respectively. The amount of lithium titanate powder was weighed within ±15\% of the actual weight.

\(^2\)The percentage of magnesium stearate was a per cent of total dry granules weight and was added prior to compression.
Lithium titanate powder

---add a binder solution

Wet mass

---through a sieve (1.5mm)

Wet granules

---dry at 80°C for 30 min.

Dry granules

---through a sieve (1.5mm)
---add 1% of magnesium stearate
---mixing

Mixture

---compressing with a set of flat faced punch and die at 8.5 mm diameter

Tablets

Fig. 4.1 Flow diagram of preparation of lithium titanate tablets with different binders solutions
C. Preparation of lithium titanate tablets

Three batches of lithium titanate tablets were made by introducing 5% of PVP solution as a binder and using the method described in Section 2.6, Chapter 2 and Fig. 4.1 with three different batches of lithium titanate powders prepared at 720, 820 and
Table 4.2 The formula of lithium titanate tablets prepared by using different concentrations of PVP aqueous solutions (batch size: 30 tablets each)

<table>
<thead>
<tr>
<th>Formula</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>lithium titanate (A-200)(g)</td>
<td>9.961</td>
<td>9.994</td>
<td>9.992</td>
</tr>
<tr>
<td>% PVP aqueous solution</td>
<td>5%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>amounts of PVP used</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* 920°C for 24 hours. The tablets prepared with these powders were designated as T-720, T-820 and T-920. The tablet weight and density of the tablets were measured. The mechanical strength of the tablets was determined by a tablet strength tester (CT40 Engineering systems, NOTTINGHAM). The dissolution test of the tablets were carried out and the results were compared with the capsules.

4.2.3 Effects of channelling agents

Seven water soluble pharmaceutical materials (see Table 4.3) were chosen in this study and used as channelling agents to increase the release of lithium from the tablets. The tablets containing 6 mmol of lithium were prepared by the method described in Fig.4.2, using 5% of PVP aqueous solution as a binder. The total dry granules were then divided into eight identical batches. One of them was tableted directly by adding 1% magnesium stearate (as Rq). The other batches were mixed with 10% of channelling agents (10% of dry granule weight) and 1% of magnesium stearate prior to compression. The formula are shown in Table 4.3. The dissolution study of the tablets in-vitro was preformed for 6 hours.

4.2.4 Effects of tablets weights

Lithium titanate tablets with three different strengths (equivalent 2 mmol, 4 mmol and 6 mmol of lithium) were prepared by using 5% of PVP aqueous solution as a binder and by adjusting the tablet weight, as described in Fig.4.3. The quantities of the ingredients used in the tablets are tabulated in Table 4.4. The tablet weight for
Table 4.3 The formula of lithium titanate tablets prepared by adding different channelling agents (Batch size: 15 tablets approximately)

<table>
<thead>
<tr>
<th>Formula</th>
<th>R₀</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
<th>R₇</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium titanate (A-200)</td>
<td>5.950</td>
<td>5.953</td>
<td>5.950</td>
<td>5.951</td>
<td>5.950</td>
<td>5.952</td>
<td>5.953</td>
<td>5.950</td>
</tr>
<tr>
<td>dry granules (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% PEG 4000 (g)</td>
<td>_</td>
<td>0.595</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>10% Sorbitol (g)</td>
<td>_</td>
<td>_</td>
<td>0.595</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>10% Glucose (g)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>0.595</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>10% Avicel PH102 (g)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>0.595</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>10% Emdex (g)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>0.595</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>10% Tabbletose (g)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>0.595</td>
<td>_</td>
</tr>
<tr>
<td>10% Citric acid (g)</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>0.595</td>
</tr>
<tr>
<td>Magnesium stearate (1% w/w )</td>
<td>0.060</td>
<td>0.060</td>
<td>0.060</td>
<td>0.060</td>
<td>0.060</td>
<td>0.060</td>
<td>0.060</td>
<td>0.060</td>
</tr>
</tbody>
</table>
Lithium titanate powder  
(A-200)  

\[ \rightarrow \text{add 5\% PVP solution} \]

Wet mass  

\[ \rightarrow \text{through a sieve (1.5mm)} \]

Wet granules  

\[ \rightarrow \text{dry at 80\textdegree C for 60 min.} \]

Dry granules  

\[ \rightarrow \text{divided equally into eight batches} \]

\[
\begin{array}{cccccccc}
R^0 & R^1 & R^2 & R^3 & R^4 & R^5 & R^6 & R^7 \\
\end{array}
\]

\[ \rightarrow \text{add channelling agents} \]

\[ \rightarrow \text{add 1\% of magnesium stearate} \]

\[ \rightarrow \text{mixing} \]

Mixtures  

\[ \rightarrow \text{compressing into tablets} \]

Eight batches of tablets

---

**Fig. 4.2** Flow diagram of the preparation of lithium titanate tablets with different channelling agents
Lithium titanate powder (A-200)

$\xrightarrow{\text{add 5\% PVP aqueous solution}}$

Wet mass

$\xrightarrow{\text{through a sieve (1.5 mm)}}$

Wet granules

$\xrightarrow{\text{dry at 80\degree C for 40 min.}}$

Dry granules

$\xrightarrow{\text{add 1\% of magnesium stearate}}$
$\xrightarrow{\text{mixing}}$

Mixture

$\xrightarrow{\text{compressing with a set of punch and die at diameter 8.5 mm}}$
$\xrightarrow{\text{adjusting tablet weight}}$

Tablets

$T_a (2\text{mmol Li}) \quad T_b (4\text{mmol Li}) \quad T_c (6\text{mmol Li})$

**Fig. 4.3** Flow diagram of the preparation of lithium titanate tablets at different weights
each strength was determined and the dissolution of the tablets was undertaken to investigate the influence of the tablet weight and the strength on the release of lithium in-vitro.

**Table 4.4** The quantities of the ingredients used in the preparation of the tablets with different strengths (Batch size: 25 tablets each strength)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium titanate (A-200) (g)</td>
<td>20.109</td>
</tr>
<tr>
<td>5% PVP aqueous solution</td>
<td>q.s</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1% (w/w)</td>
</tr>
</tbody>
</table>

**4.2.5 Effects of tablets sizes**

Three different sizes of non-disintegrating lithium titanate tablets of diameters 3, 5 and 8.5 mm were prepared by using 5% ethyl cellulose ethanol solution for granulation and employing three sets of flat-faced punches and dies at diameters of 3 mm, 5 mm and 8.5 mm. The process of the preparation is described in Fig. 4.4. The amounts of the ingredients used in the formulation are shown in Table 4.5. The dissolution test of all tablets (equivalent 6 mmol of lithium as a single dose for each size of tablets) was carried out as described in Chapter 2.

**Table 4.5** The formula used in the preparation of dry granules of lithium titanate for the different sizes tablets (batch size: equivalent 90 tablets, containing 6 mmol of lithium each)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium titanate (A-200) (g)</td>
<td>30.152 (540 mmol Li)</td>
</tr>
<tr>
<td>5% EC ethanol solution</td>
<td>q.s</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1% (w/w)</td>
</tr>
</tbody>
</table>

**4.3 RESULTS AND DISCUSSIONS**

**4.3.1 Capsules**
Lithium titanate powder
(A-200)

$\downarrow$

$\text{add 5\% EC ethanol solution}$

Wet mass

$\downarrow$

$\text{through a sieve (1.5 mm)}$

Wet granules

$\downarrow$

$\text{dry at 80°C for 50 min.}$

Dry granules

$\downarrow$

$\text{add 1\% of magnesium stearate}$

$\downarrow$

$\text{mixing}$

Mixture

$\downarrow$

$\text{compressing with three sets of punches}$

$\text{and dies at diameters 3, 5 and 8.5 mm}$

Tablets

$\downarrow$

S-3(3 mm) S-5(5 mm) S-8.5(8.5 mm)

Fig. 4.4 Flow diagram of the preparation of the lithium titanate tablets at different diameters
The dissolution profiles of the capsules prepared with lithium titanate powders made at different formation temperatures (720, 820 and 920°C) and lithium carbonate (USP/BP grade) are shown in Fig.4.5(a). The amount of lithium released in-vitro form the lithium titanate capsules (C-720, C-820 and C-920) is very different from the lithium carbonate capsules (CLi-1). Lithium is released more slowly from the capsules containing lithium titanate than those containing lithium carbonate. Within 1 hour of the dissolution test in-vitro, 100% of lithium released form the CLi-1 capsules, 61.74%, 26.19% and 15.86% released form the capsules C-720, C-820 and C-920 respectively. It is clearly shown that the lithium titanate capsules have slow release characteristics in-vitro. Compared to the results obtained with the powder forms, there was no difference observed, as shown in Fig.4.5(b,c and d) when the powder was placed in a capsule. In terms of the release pattern of lithium, the lithium titanate capsules are identical with the powder form.

4.3.2 Choices of the binders

The tablet weight of the lithium titanate tablets prepared by using different binders and the equivalent amount of lithium are shown in Table 4.6. Each tablet contains approximately 6 mmol of lithium in all formulations. The calculation of both tablet weight and lithium content is described in footnotes 1 and 2 of Table 4.6.

The results of the dissolution of tablets made with different binders are shown in Fig.4.6. The amounts of lithium released form the tablets F2, F3 and F4 (binders: 5% PEG4000, 5%PEG10000 and 3% Klucel solutions respectively) are similar [see Fig.4.6(a)]. These tablets release lithium much faster than the tablets of F1, F5 and F6 (binders: 5%PVP, 2.5%EC & 2.5%PVP and 5%EC solutions respectively), as seen in Fig.4.6(b). The amount of lithium released from the tablets of F1 and F5 showed no difference, but decreased slightly from the tablets of F6 [see Fig.4.6(b)]. Because the binders used in the tablets F2, F3 and F4 are readily soluble in water, the tablets made with these binders disintegrate when the tablets are exposed in the dilute acid environment and release lithium. During the 6 hours of dissolution test, the tablets of F1 gradually eroded and the tablets of F5 and F6 did not disintegrate. That is the
Table 4.6 The tablet weight of lithium titanate tablets and its equivalent amount of lithium

<table>
<thead>
<tr>
<th>Formula</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binders</td>
<td>5%PVP</td>
<td>5%PEG4000</td>
<td>5%PEG10000</td>
<td>3%Klucel</td>
<td>2.5%EC</td>
<td>2.5%PVP</td>
</tr>
<tr>
<td>Tablet weight (g)$^1$</td>
<td>0.355</td>
<td>0.353</td>
<td>0.345</td>
<td>0.336</td>
<td>0.372</td>
<td>0.368</td>
</tr>
<tr>
<td>Equivalent lithium(mmol)$^2$</td>
<td>5.981</td>
<td>5.971</td>
<td>5.976</td>
<td>5.969</td>
<td>5.964</td>
<td>5.967</td>
</tr>
</tbody>
</table>

Tablet weight ($W_T$) = \[
\frac{\text{Total weight of the mixture prior to compression}}{\text{Batch size of tablets}}
\]

The equivalent lithium = \[
W_T \times \text{Li}_2\text{TiO}_3\% \times P\% \times C_{Li}\%
\]

in each tablet (mmol) lithium atom weight(6.941)

where

- \(\text{Li}_2\text{TiO}_3\%\) = the percentage of lithium titanate powder in the tablet
- \(P\%\) = purity of the lithium titanate powder used in the tablet
- \(C_{Li}\%\) = lithium content in the lithium titanate powder used in the tablet
- \(W_T\) = the tablet weight
Fig. 4.5 The *in vitro* release profiles of lithium for lithium titanate capsules and powders during 12 hours dissolution test  

a: Capsules (CLi-1, C-720, C-820 and C-920)  
b: Capsules (C-720) and powder (made at 720°C)  
c: Capsules (C-820) and powder (made at 820°C)  
d: Capsules (C-920) and powder (made at 920°C)
Fig. 4.6 The percentage of lithium released from the tablets made with different binders during 6 hours dissolution test. 

a: Tablets F2 (5% PEG 4000 solution), F3 (5% PEG 10000 solution) and F4 (3% Klucel solution) 

b: Tablets F1 (5% PVP solution), F5 (2.5% EC and 2.5% PVP ethanol solution) and F6 (5% EC ethanol solution) with zero order of release.
reason why less lithium ion was released from the tablets F6. Because PVP (water soluble) was used in the tablets of F5, the amount of lithium released was similar to that from the tablets F1, although it did not disintegrate. In addition, the tablets made with the following binders: 5%PVP, 2.5%EC and 2.5%PVP mixture and 5% EC showed zero order of release over the 6 hours in-vitro [see Fig.4.6(b)].

In summary, non-disintegrating tablets were obtained by using 5%EC or a mixture of 2.5%EC and 2.5%PVP as the binders. A zero order of release was achieved by using PVP solution or EC solution or the mixture of both as the binder, but the quantity of lithium released form these tablets was about 30% or less within 6 hours.

B. Different concentrations of PVP solutions

The amount of lithium released in-vitro from the tablets prepared with 5%, 10% and 15%PVP solutions are similar form one to another, as shown in Fig.4.7. The concentration of PVP solution had no influence on the release characteristics of lithium when the concentration was increased from 5% to 15% during 6 hours dissolution test in the dilute acid solution.

C. Preparation of lithium titanate tablets

The tablet weight, the density and the hardness of lithium titanate tablets are tabulated in Table 4.7. The densities of the tablets (T-720, T-820 and T-920) containing lithium titanate powder made at 720, 820 and 920°C respectively are all greater than 3.0 g/cm³. The hardness of the tablets, however, decreased in the order of T-720 > T-820 > T-920, which was caused by the compressing pressure units applied (see Table 4.7). The higher the pressure, the harder the tablets.

The amount of lithium released form the tablets of T-720, T-820 and T-920 decreased greatly, as seen in Fig.4.8(a). The tablets of T-820 and T-920 released lithium at zero order rates. The tablets of T-720, however, did not release lithium at a zero order rate. Compared to the results obtained with the capsules containing the same lithium titanate powder as the tablets, much less amount of lithium (about 20% to 30% less) released form the tablets preparations [see Fig.4.8(b, c & d)]. The tablets preparations reduce the surface area and hence prevent the dissolution media from
Fig. 4.7 The *in vitro* release profiles of lithium for the lithium titanate tablets prepared with different concentrations of PVP solutions.
Fig. 4.8 The in vitro release profiles of lithium for the lithium titanate tablets and capsules containing lithium titanate powders made at different formation temperatures
a: Tablets (T-720, T-820 and T-920)  b: Tablets (T-720) and capsules (C-720)  c: Tablets (T-820) and capsules (C-820)  and d: Tablets (T-920) and capsules (C-920)
contacting the lithium titanate powder.

Table 4.7 The tablet weight, the density and the hardness of lithium titanate tablets prepared with lithium titanate powders made at different formation temperatures

<table>
<thead>
<tr>
<th>Tablets</th>
<th>T-720</th>
<th>T-820</th>
<th>T-920</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet weight(g)</td>
<td>0.352</td>
<td>0.345</td>
<td>0.348</td>
</tr>
<tr>
<td>equivalent Li(mmol)</td>
<td>6.170</td>
<td>6.078</td>
<td>6.176</td>
</tr>
<tr>
<td>Density(g/cm³)</td>
<td>3.31</td>
<td>3.48</td>
<td>3.48</td>
</tr>
<tr>
<td>Mechanical strength(kg)</td>
<td>5.75</td>
<td>3.91</td>
<td>2.64</td>
</tr>
<tr>
<td>CP* units</td>
<td>43</td>
<td>37</td>
<td>30</td>
</tr>
</tbody>
</table>

*CP- machine setting units displayed on the tableting machine.

4.3.3 Effects of the channelling agents

The tablet weight and its equivalent amount of lithium of tablets prepared with different channelling agents are tabulated in Table 4.8.

The results of the dissolution test of the tablets are shown in Fig.4.9(a). Tablets of R⁴, R⁵, R⁶ and R⁷ (channelling agents: Avicel PH102, Emdex, Tabletose and Citric acid respectively) disintegrated, but R⁰ (without the channelling agents), R¹, R² and R³ (channelling agents: PEG4000, Sorbitol and Glucose respectively) eroded during the 12 hours dissolution test. Formulations of R⁴, R⁵ and R⁷ have similar release rate of lithium, but faster than the others (R⁰, R¹, R², R³ and R⁶) whose release rate of lithium are also similar [see Table 4.9 and Fig.4.9 (b)]. The amount of lithium released from these disintegrated tablets R⁷ is not greatly different from lithium titanate capsules (or the powder)[see Fig.4.9(c)]. The tablets of R⁷, R⁴, R⁵ and R⁶ released lithium in a decreasing order: R⁷ > R⁴ > R⁵ > R⁶. Although the tablets R⁶ disintegrated, the amount of lithium released is similar to these of eroded tablets (R⁰, R¹, R² and R³). Above all, it is suggested that the disintegrating process affects the release rate more than the channelling agents. In these disintegrating tablets, the channelling agents, in fact, acted as disintegrants. The release rate of lithium is not improved by using water soluble materials as channelling agents or disintegrants, since the amount of lithium released from the disintegrating tablets is either similar to that from the eroding tablets or much
Table 4.8 The tablet weight ($W_T$) of lithium titanate tablets made with different channelling agents and its equivalent amount of lithium ($E_{Li}$)

<table>
<thead>
<tr>
<th>Formulations</th>
<th>$R^0$</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$R^4$</th>
<th>$R^5$</th>
<th>$R^6$</th>
<th>$R^7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$W_T$ (g)</td>
<td>0.318</td>
<td>0.381</td>
<td>0.381</td>
<td>0.350</td>
<td>0.351</td>
<td>0.350</td>
<td>0.352</td>
<td>0.350</td>
</tr>
<tr>
<td>$E_{Li}$ (mmol)</td>
<td>5.373</td>
<td>5.964</td>
<td>5.964</td>
<td>5.380</td>
<td>5.395</td>
<td>5.380</td>
<td>5.411</td>
<td>5.375</td>
</tr>
</tbody>
</table>

Table 4.9 Percentages of lithium released at 1, 6 and 12 hours from the tablets made with different channelling agents

<table>
<thead>
<tr>
<th>Time(hrs)</th>
<th>$R^0$</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$R^4$</th>
<th>$R^5$</th>
<th>$R^6$</th>
<th>$R^7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.32±0.70</td>
<td>8.65±0.20</td>
<td>8.38±0.38</td>
<td>13.80±1.62</td>
<td>19.39±1.07</td>
<td>17.72±0.02</td>
<td>14.00±0.15</td>
<td>26.19±1.18</td>
</tr>
<tr>
<td>6</td>
<td>37.49±0.68</td>
<td>40.25±1.39</td>
<td>34.75±0.08</td>
<td>42.45±4.16</td>
<td>54.46±2.62</td>
<td>50.80±0.74</td>
<td>38.30±0.27</td>
<td>53.59±2.37</td>
</tr>
<tr>
<td>12</td>
<td>56.11±1.12</td>
<td>58.58±1.92</td>
<td>53.28±1.04</td>
<td>61.07±3.14</td>
<td>72.79±1.86</td>
<td>70.52±0.72</td>
<td>56.64±2.64</td>
<td>76.54±5.31</td>
</tr>
<tr>
<td>DIG*</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>

* = Disintegration
E = Eroded
D = Disintegrated
Fig. 4.9 The percentage of lithium released in vitro from the lithium titanate tablets prepared with different channelling agents. a: Tablets R4, R5, and R7. b: Tablets R0, R1, R2, R3, and R6. c: Tablets R4, R5, R6, and R7; Capsules (C-820).
4.3.4 Effect of the tablet weights

The tablet weight of lithium titanate tablets containing different amounts of lithium is shown in Table 4.10.

Table 4.10 Three different tablet weights of lithium titanate tablets at a constant diameter

<table>
<thead>
<tr>
<th>Tablets Names</th>
<th>T_a</th>
<th>T_b</th>
<th>T_c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet weight(g)</td>
<td>0.117</td>
<td>0.234</td>
<td>0.352</td>
</tr>
<tr>
<td>Strengths</td>
<td>2 mmol Li</td>
<td>4 mmol Li</td>
<td>6 mmol Li</td>
</tr>
</tbody>
</table>

The percentage of lithium released from the tablets decreased in the order of $T_a > T_b > T_c$ with increasing the strength or tablet weight (2 mmol > 4 mmol > 6 mmol respectively), as shown in Fig.4.10 (a). All the tablets eroded during the 12 hours dissolution test. The lower the strength, the faster the release rate [see Fig.4.10(b)], although the surface areas of the tablets increased with increasing the tablet weight. This might indicate that the mechanism of lithium released from tablets is not as simple as conventional dissolution. As demonstrated in chapter 3, the lithium ion released by mainly exchanging hydrogen ion in the dissolution medium (0.1 N HCL solution). The exposure of the surface areas of the tablets, therefore, may have a great influence on the release rate. As the tablet dimensions decreased with reducing the weight, the thickness of the tablets decreased. The dissolution medium can penetrate more easily into the lower weight tablets and exchange lithium into the solution. This may be the reason why the lower weight tablets released lithium faster than the higher weight tablets at 1 hour dissolution, but not exceeding the first hour release rate of lithium titanate capsules or powders [see Fig.4.10 (b)]. After 1 hour, the release rate of lithium seems not to differ from one type to another.

4.3.5 Effect of the tablets sizes

The tablet weight, size and the numbers of tablets equivalent to 6 mmol of
Fig. 4.10  a: The *in vitro* release profiles of lithium for the lithium titanate tablets at different tablet weights  

b: The *in vitro* release rate of lithium of the tablets and the capsules (C-820)
lithium are shown in Table 4.11.

**Table 4.11** The tablet sizes, the tablet weight, the equivalent amount of lithium and the numbers of tablets equivalent to 6 mmol of lithium

<table>
<thead>
<tr>
<th>Tablets Names</th>
<th>S-3</th>
<th>S-5</th>
<th>S-8.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter(mm)</td>
<td>3</td>
<td>5</td>
<td>8.5</td>
</tr>
<tr>
<td>Tablet weight</td>
<td>46 mg</td>
<td>123 mg</td>
<td>368 mg</td>
</tr>
<tr>
<td>Lithium (mmol)</td>
<td>0.75</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Numbers of tablets</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

The tablets did not disintegrate during the 12 hours dissolution test. As seen in Fig.4.11(a), the amount of lithium released from the tablets decreased in the order of S-3 > S-5 > S-8.5 with an increase in the diameter of the tablets. The release rate of lithium at first hour dissolution was found to differ from one to another (S-3, 10.56%/hr; S-5, 7.25%/hr and S-8.5, 6.26%/hr). During the next 11 hours of dissolution test, the release rate of the tablets S-5 and S-8.5 appeared similar [see Fig.4.11(b)], but tablets S-3 generally have a faster release rate of lithium with more fluctuation. All the tablets showed an apparent zero order of release during the first 6 hours and released lithium at the following rates: S-3, 4.99±1.02%/hr; S-5, 3.95±0.61%/hr and S-8.5, 3.54±0.51%/hr [see Fig.4.11(c)]. During the next 6 hours dissolution, they also released lithium at constant rates, but slightly slower (S-3, 3.63±0.70%/hr; S-5, 2.47±0.30%/hr; S-8.5, 2.67±0.59%/hr)[see Fig.4.11(b)]. Therefore, the smaller the tablets, the faster the release rate when non-disintegrating tablets are employed, because the smaller tablets have a bigger surface area per unit mass exposed to the dissolution medium.

4.4 CONCLUSIONS

The lithium titanate capsules have the same release characteristics of lithium as the powders. The amount of lithium released from the capsules is also similar to that of the powder. Therefore, the capsules may provide a opportunity to be used as a oral
Fig. 4.11  a: The percentage of lithium released in vitro from non-disintegrating lithium titanate tablets at different diameters (S-3, 3 mm; S-5, 5 mm and S-8.5, 8.5 mm)  b: The in vitro release rate of lithium of the tablets (S-3, S-5 and S-8.5)  c: The zero order of release profile of lithium in vitro for the tablets (S-3, S-5 and S-8.5) during 6 hours dissolution test
dosage form of lithium titanate, since the powder itself has the slow-release characteristic. By controlling the formation condition of lithium titanate, the release pattern of lithium from the capsules could be controlled.

Non-disintegrating tablets were obtained by introducing 5% ethylcellulose ethanol solution or the mixture of 2.5% EC and 2.5% PVP ethanol solution as a binder for granulation. The erodible tablets were prepared by using 5% PVP aqueous solution as a binder. Both types of the tablets provided a zero order of release during 6 hours dissolution in-vitro, but at very low release rate (only about 30% or less of lithium released within 6 hours).

The tablets containing lithium titanate powders made at different formation temperatures (720, 820 and 920°C) released much less lithium than their capsules and powders. It suggested that the tablets formulations provided no additional advantages in terms of the quantity of lithium released, which is important in reaching therapeutical blood level, although the zero order of release was achieved when the tablets can be kept intact.

The channelling agents used in the tablets formulations did not provide a satisfactory improvement in the release rate of lithium. The amount of lithium released from these tablets only increased when the tablets disintegrated, but did not exceed the amount released from the capsules or powders. The disintegrating process, however, affects the release pattern of lithium from the tablet formulation.

The weight of the tablets for a constant diameter influences the release of lithium in-vitro. An increase in the weight led to a decrease in the amount of lithium released from the tablets formulations. The improvement of the release rate of lithium by reducing the tablets weight is possible, but did not exceed the rate of capsules or powder.

An decrease in tablet size provided an increase in the release rate of lithium form the non-disintegrating tablets. However, it involves more difficulties in technical aspects to make small tablets such as 3 mm diameter. Even though the 3 mm tablets were used, the amount of lithium released was about 50% within 12 hours in-vitro, which was far less than from the capsules (80% approximately).

In summary, the release rate of lithium was not changed easily by the tablet
formulation, because of the nature of the lithium titanate powder. A zero order of release could be achieved *in-vitro* during 6 hours by formulating lithium titanate powder into non-disintegrating or erodible tablets, but at very low release rate. A first order of release by formulating lithium titanate into disintegrating tablets at faster release rate can also be achieved, but which did not exceed the release rate from lithium titanate capsules.
CHAPTER 5

SPECIFICATIONS OF LITHIUM TITANATE
5.1 INTRODUCTION

5.1.1 General

Safety, potency and bioavailability are the main requirements for any drug product. To ensure these requirements is of primary important. In general, the qualities of pharmaceutical products are firmly assessed against their specifications in a BP or a USP (or pharmacopoeia of other countries, or other sources), if available, to ensure the therapeutical effects and safety. If this is not available, then standards must be produced.

Each product or compound has its own specific physical and chemical properties. The specifications of the product must define all the properties of the product such as purity, the characteristics and limits of related substances which may cause undesirable effect.

There is no unique method of governing the requirement for sustained release system (or modified release preparation) in terms of the release characteristic of the active drug. Since the sustained release or controlled release system has its own specific release profile in vitro, it is necessary to define the release characteristic which may affect the bioavailability of the drug. The BP or USP requires the dissolution profile for sustained or controlled release system, but there is no standard definitions, regulation and data requirements for such preparation.

A novel heavy compound, lithium titanate, with sustained release character, has its potential to be used in the treatment of mania and depression. Defining the properties of lithium titanate produced is therefore relevant. A draft of general specification of lithium titanate was proposed according to the BP specifications of lithium carbonate and titanium dioxide to provide basic criteria for a general assurance of its physical chemical characteristics.

5.1.2 Special considerations

According to the studies in previous chapters, lithium titanate has very specific characteristics. The in vitro release pattern of lithium for the powder can be altered by changing the formation temperature, heating time, the initial particle size of starting
materials (lithium carbonate or titanium dioxide) and the process of preparation. To produce a standard lithium titanate product with a reproducible \textit{in vitro} release profile of lithium, these characteristics mentioned above must be defined. Therefore an additional specification of lithium titanate was proposed to provide the specific criteria for controlling both the chemical formation of lithium titanate and the release characteristic of lithium \textit{in vitro} for the preparation.

5.2 SPECIFICATIONS OF LITHIUM TITANATE

5.2.1 General specification

The general specification of lithium titanate is detailed in Appendix I and summarized in Table 5.1. All the tests were carried out to see if the specification is suitable for lithium titanate.

5.2.2 Additional specification

Part A. Preparation of Lithium Titanate

A-1 Preparation of mixture of lithium carbonate and titanium dioxide

The preparation of the mixture of lithium carbonate and titanium dioxide is the same as described in Chapter 2. The process of mixing may have an effects on the uniformity of the mixture (the contacting area of both reactants). Therefore, the process needs to be controlled accordingly.

A-2 Preparation of Lithium Titanate (Batch size 700 g)

Five batches of the mixtures of lithium carbonate and titanium dioxide at 200g of each should be prepared as above and heated individually at the desired temperature\textsuperscript{1} (820°C) for 24 hours in a electric muffle furnace (Model: BCF General purpose furnace, LENTON THERMOL DESIGNS) where the temperature can be controlled by a programmed thermal controller (Model: ECF12/30). Before the mixture

\textsuperscript{1} The heating temperature can be chosen according to the requirement of the \textit{in-vitro} release profile of lithium.
**Table 5.1** The general specification of lithium titanate

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>white or almost white powder</td>
</tr>
<tr>
<td>Solubility</td>
<td>slowly soluble in hot sulphuric acid, practically insoluble in water, dilute mineral acids and 96% ethanol</td>
</tr>
<tr>
<td>Identification</td>
<td>A: red colour to a non-luminous flame, B: orange-red colour, C: violet-blue colour</td>
</tr>
<tr>
<td>Clarity and colour</td>
<td>BP Appendix IV A and B</td>
</tr>
<tr>
<td>Alkalinity or acidity</td>
<td>less than 2 ml of 0.1 M HCL or NaOH</td>
</tr>
<tr>
<td>Water soluble matter</td>
<td>less than 250 mg</td>
</tr>
<tr>
<td>Antimony</td>
<td>any colour not more intense than that of a reference solution</td>
</tr>
<tr>
<td>Arsenic</td>
<td>limit test, BP Appendix VII</td>
</tr>
<tr>
<td>Barium</td>
<td>opalescence not more than that of a reference solution</td>
</tr>
<tr>
<td>Heavy metal</td>
<td>limit test, BP Appendix VII</td>
</tr>
<tr>
<td>Iron</td>
<td>colour not more intense than that of a standard solution</td>
</tr>
<tr>
<td>Calcium</td>
<td>limit test, BP Appendix VII</td>
</tr>
<tr>
<td>Magnesium</td>
<td>limit test, BP Appendix VII</td>
</tr>
<tr>
<td>Potassium</td>
<td>less than 300 ppm</td>
</tr>
<tr>
<td>Sodium</td>
<td>less than 300 ppm</td>
</tr>
<tr>
<td>Chloride</td>
<td>limit test, BP Appendix VII</td>
</tr>
<tr>
<td>Sulphate</td>
<td>limit test, BP Appendix VII</td>
</tr>
<tr>
<td>Assay of lithium</td>
<td>not less than 12.55%</td>
</tr>
<tr>
<td>Purity(Li₂TiO₃)</td>
<td>98.0% to 100.5%</td>
</tr>
</tbody>
</table>
is placed inside of the furnace, the furnace should be balanced at the desired
temperature for 24 hours and calibrated with a validated thermometer (Model:
Thermocouple TYPE K2003) on each occasion prior to the inclusion of the sample.
After heating, the sample is taken out and allowed to cool down at room temperature.

COMMENTS: If the batch size is much greater than 700 g, the preparation is the
same as described above. However, only the numbers of batches of the mixture need
to be increased to meet the quantity as required.

Part B. The other characteristics of lithium titanate

The characteristics of lithium titanate is detailed in Table 5.2. They are
discussed below.

B-1 IR spectra of the mixture before and after heating

As demonstrated in chapter 3, an IR spectrum can be used for identification
of the reaction between lithium carbonate powder and titanium dioxide powder. The
method is detailed in chapter 2. No clear peaks should be seen at the following
wavenumbers: 1500 cm⁻¹, 1440 cm⁻¹, 1080 cm⁻¹ and 860 cm⁻¹ [see Fig. 5.1(c)].

B-2 Loss of weight on heating

The method of measuring the loss of weight on heating is detailed in Chapter
2. The value indicates the completion of the reaction between lithium carbonate and
titanium dioxide, which should not be less than the theoretical value (28.62%) to
ensure the potency of lithium and the purity of the product.

B-3 Lithium content

The lithium content of the product should be not less than 12.55%. The
content can be estimated by calculation ( see Chapter 2 ) or analyzed by the method
described in the general specification.

B-4 Purity of lithium titanate
Table 5.2 Additional specification (Part B) of lithium titanate

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR spectrum</td>
<td>no -CO₂ peaks appeared [Fig. 5.1(c)]</td>
</tr>
<tr>
<td>Loss of weight on heating</td>
<td>not less than 28.6% (w/w)</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>not less than 3.4</td>
</tr>
<tr>
<td>Particle size (μm)¹</td>
<td>35 to 40</td>
</tr>
<tr>
<td>Surface area (m²/g)</td>
<td>1.2 to 1.8</td>
</tr>
</tbody>
</table>
| Dissolution (USP method II, 100 rpm, at 37°C in 1000 ml of 0.1 N HCL solution) | 2 hrs: 40 to 50%  
6 hrs: 60 to 75%  
12 hrs: 80 to 100%  |
| SEM image                           | see Photos 5.1 (Middle)            |

¹ The particle size of lithium titanate was analyzed by laser light diffraction. The data showed in the Table is 50% under size which is defined as mass median diameter of the particle.
Fig. 5.1 IR spectra of (a) the initial reactive mixture and lithium titanate powder made at 720°C (b), 820°C(c) and 920°C(d)
The purity of the product should be not less than 99.00 %, which can also be calculated by the method detailed in Chapter 2 or analyzed by the method described in the general specification.

**B-5 Density**

The measurement of the density is described in Chapter 2. The density should not be less than 3.40 g/cm³.

**B-6 Particle size**

The measurement of the particle size is presented in Chapter 2. The particle size of lithium titanate is dependent on the particle size of starting material (lithium carbonate), which should be controlled within defined limits as it will affect the release characteristic of lithium. By controlling the particle size of lithium carbonate, the release profile of lithium *in vitro* can be controlled. The particle size distribution of lithium carbonate (BP) is shown in Fig.5.2 (a) and Table 5.3. All particles are less than 100 μm (preferable size: 50% below 50 μm).

**Table 5.3 Particle size range of lithium carbonate (Li₂CO₃, BP Batch No. 392)**

<table>
<thead>
<tr>
<th>Particle size</th>
<th>10% under(μm)</th>
<th>50% under(μm)</th>
<th>90% under(μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li₂CO₃</td>
<td>15-25</td>
<td>45-55</td>
<td>80-100</td>
</tr>
</tbody>
</table>

The particle size of lithium titanate powder is tabulated in Table 5.4 and Fig. 5.2 (b). All the particle size should be less than 100 μm (preferable size: 50% under size 40-50 μm)

**Table 5.4 The particle size range of lithium titanate at 10%, 50% and 90% under size**

<table>
<thead>
<tr>
<th>Particle size</th>
<th>10% (μm)</th>
<th>50% (μm)</th>
<th>90% (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium titanate</td>
<td>10-20</td>
<td>40-50</td>
<td>80-100</td>
</tr>
</tbody>
</table>
Fig. 5.2 The particle size distributions of (a) lithium carbonate (BP) and (b) lithium titanate powders
B-7 Surface area

The method is detailed in Chapter 2. The surface area is related to the formation condition of lithium titanate and the initial particle size of lithium carbonate. Different formation temperatures result in the different degree of crystallization which plays an essential role in the release characteristic of lithium ion for lithium titanium powder. The difference in the crystallization of lithium titanate is, however, explained by the surface area, even though the identical particle size of lithium carbonate is used. Different initial particle sizes of lithium carbonate were found to cause different particle size distributions of lithium titanate produced, which can be reflected by the surface area as well. It is therefore an important characteristic of lithium titanate and needs to be controlled to ensure the reproducibility of the product. The surface area of the lithium titanate powder is tabulated in Table 5.5.

Table 5.5 The surface area ($S_0$, m$^2$/g) of lithium titanate powder

<table>
<thead>
<tr>
<th>Temperature ($^\circ$C)</th>
<th>820</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area (m$^2$/g)</td>
<td>1.2 to 1.8</td>
</tr>
</tbody>
</table>

B-8 Dissolution

The dissolution test is carried out by USP method II at 37°C in 1000 ml of 0.1 N hydrochloride acid solution with agitation speed 100 rpm. The dissolution of the samples made at different temperatures has their own patterns as shown in Fig. 5.3. The release of lithium in-vitro is an important quality criterion for the product, specifically for controlled release systems, which may give a first indication of bioavailability. The method is detailed in Chapter 2.

B-9 Scanning of electron microscopy (SEM)

The method is described in Chapter 2. The SEM photos can clearly show the crystallization of lithium titanate, the particle size shape and the surface structure. The degree of the crystal growth is one of the main factors which contributes the release characteristic of lithium. The samples made at the same formation condition should show an identical surface crystal structure and a particle size distribution.
Fig. 5.3 The release profile of lithium in vitro for lithium titanate powder
Different formation conditions can result in different crystal growth as shown in Photos 5.1. Thus, the SEM photos can also be used as a tool to ensure the crystal growth on the particle surface and to indirectly ensure the release of lithium at required rate.

5.3 RESULTS AND DISCUSSIONS

5.3.1 The General Specification

Description
The appearance of lithium titanate powder is one of the primary physical characteristics. It is an easy and simple way to identify the foreign matters at early stage. If there is any changes in the appearance, it may indicate some problems with the quality of the powder. Lithium titanate is a white or almost white powder. The products made at 720, 820 and 920°C all comply.

Solubility
Solubility is characteristic for each chemical compound. It plays an important role in many aspects, such as quality, bioavailability of drug and formulation in particular, if the compound is used as a drug in medical treatment. This test of solubility provides qualitative information for identification of the compound.

Identification
The tests are performed to identify the presence of an active ingredient or main compositions. The test A is used to identify lithium ion and the tests B & C are for identification of titanium dioxide.

Clarity and colour of solution
This test is to control the foreign matters which give impurities. The method is detailed in BP, Appendix IV A and B. No foreign matter should be present in the solution which containing the samples examined.
Photos 5.1  SEM images of lithium titanate made at 720°C (Top), 820°C (Middle) and 920°C (Bottom)
Acidity or alkalinity

The test is also used to control the impurity which may be due to process of preparation of lithium titanate or manufacture of lithium carbonate and titanium dioxide used in the preparation. In the preparation of lithium titanate, lithium carbonate was decomposed into lithium oxide which may possibly remain in the finished product. Lithium oxide is strong alkali oxide, which gives alkalinity in the solution. It is therefore necessary to carry out the test to ensure the purity of the product, lithium titanate.

Water soluble matters

The test is to control the impurity of water soluble matters, which may due to the process of preparation of lithium titanate (i.e. lithium oxide) and the manufacture of the starting materials used (lithium carbonate and titanium dioxide).

Antimony, Arsenic, Barium and Heavy metals

These metal elements may present in the starting materials, lithium carbonate and titanium dioxide, which were used in preparation of lithium titanate. These tests are to control the elements within the limits which are detailed in BP, Appendix VII.

Iron, Calcium, Magnesium, Potassium and Sodium

These elements may potentially present in the starting materials used for producing lithium titanate, since they may be involved in manufacture of lithium carbonate and titanium dioxide. These tests are to control the impurities produced within the limits which detailed in BP, Appendix VII.

Chloride and Sulphate

Chloride and sulphate are the chemical reagents which are usually used in preparation of lithium carbonate and titanium dioxide. To control them within definite range will ensure the purity of lithium titanate.

Assay
(1) Titanium dioxide

The assay of titanium dioxide is not critical important. It can be used as a reference for the assurance of the purity and the composition of lithium titanate.

(2) Lithium

The assay of lithium is crucial for ensuring the accurate potency of the active composition, as lithium ion is pharmacological active element for the treatment of psychiatric disorders.

Note: The purity of lithium titanate can also be calculated by the following equation.

\[ \text{P\%} = \frac{C_L}{C_i} \times 100\% \] (see Chapter 2, equation 3)

Three batches of lithium titanate powders made at 720, 820 and 920°C were tested according to the general specification. The results are shown in Tables 5.6, 5.7 and 5.8. All three batches have passed the tests. The results suggested that the general specification could be used as a standard for the general control of the quality of lithium titanate. They provide the type of specification that would probably be appropriate for an official monograph.

5.3.2 The Additional Specification

The results of tests of three batches of lithium titanate powders (made at different temperatures) against the additional specification are detailed in Tables 5.9, 5.10 and 5.11. The powders made at 720 and 920°C does not comply the specification provided for the powder made at 820°C, which is satisfactory in term of the \textit{in vitro} release profile of lithium. The specification is appropriate to define the product and to identify from other products made at different formation conditions.

5.4 CONCLUSIONS

Both specifications are of primary important for producing a standard lithium titanate product. They are adequate in terms of the nature of the product and cover the aspects of the characteristics of the product. By assessing lithium titanate against these
specifications, the product (lithium titanate) can be ensured to be the one as required in terms of its physical-chemical properties and release profile *in-vitro*.
### Table 5.6: The results of the tests (General Specification) for lithium titanate made at 720°C for 24 hours (Batch No. 720-6, Batch size: 1 kg)

<table>
<thead>
<tr>
<th>TEST</th>
<th>SPECIFICATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>white or almost white</td>
<td>complies</td>
</tr>
<tr>
<td>Solubility</td>
<td>slowly soluble in hot sulphuric acid, practically insoluble in water, dilute mineral acids and 96% ethanol</td>
<td>complies</td>
</tr>
<tr>
<td>Identification</td>
<td>A: red colour to a non-luminous flame, B: orange-red colour, C: violet-blue colour</td>
<td>A: complies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: complies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: complies</td>
</tr>
<tr>
<td>Clarity and colour</td>
<td>BP appendix IV A and B</td>
<td>complies</td>
</tr>
<tr>
<td>Alkalinity or acidity</td>
<td>&lt; 2 ml 0.1 M HCL or 0.1 M NaOH</td>
<td>1.75 ml</td>
</tr>
<tr>
<td>Water soluble matter</td>
<td>&lt; 250 mg</td>
<td>192 mg</td>
</tr>
<tr>
<td>Antimony</td>
<td>any colour not more intense than that of a reference solution</td>
<td>complies</td>
</tr>
<tr>
<td>Arsenic</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Barium</td>
<td>opalescence not more than that of a reference solution</td>
<td>complies</td>
</tr>
<tr>
<td>Heavy metal</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Iron</td>
<td>colour not more intense than that of a standard solution</td>
<td>complies</td>
</tr>
<tr>
<td>Calcium</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Magnesium</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Potassium</td>
<td>&lt; 300 ppm</td>
<td>221 ppm</td>
</tr>
<tr>
<td>Sodium</td>
<td>&lt; 300 ppm</td>
<td>248 ppm</td>
</tr>
<tr>
<td>Chloride</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Sulphate</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Assay of lithium</td>
<td>not less than 12.55%</td>
<td>12.60%</td>
</tr>
<tr>
<td>Purity (Li$_2$TiO$_3$)</td>
<td>98.0% to 100.5%</td>
<td>99.63%</td>
</tr>
</tbody>
</table>
Table 5.7 The results of the tests (General Specification) for lithium titanate made at 820°C for 24 hours (Batch NO. 820-5, Batch size 1 kg)

<table>
<thead>
<tr>
<th>TEST</th>
<th>SPECIFICATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>white or almost white</td>
<td>complies</td>
</tr>
<tr>
<td>Solubility</td>
<td>slowly soluble in hot sulphuric acid, practically insoluble in water, dilute mineral acids and 96% ethanol</td>
<td>complies</td>
</tr>
<tr>
<td>Identification</td>
<td>A: red colour to a non-luminous flame, B: orange-red colour, C: violet-blue colour</td>
<td>A:complies B:complies C:complies</td>
</tr>
<tr>
<td>Clarity and colour</td>
<td>BP appendix IV A and B</td>
<td>complies</td>
</tr>
<tr>
<td>Alkalinity or acidity</td>
<td>$&lt; 2$ ml of 0.1M HCL or 0.1M NaOH</td>
<td>1.53 ml</td>
</tr>
<tr>
<td>Water soluble matter</td>
<td>$&lt;$250 mg</td>
<td>210 mg</td>
</tr>
<tr>
<td>Antimony</td>
<td>any colour not more than a reference solution</td>
<td>complies</td>
</tr>
<tr>
<td>Arsenic</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Barium</td>
<td>opalescence not more than that of a reference solution</td>
<td>complies</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Iron</td>
<td>colour not more intense than that of a standard solution</td>
<td>complies</td>
</tr>
<tr>
<td>Calcium</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Magnesium</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Potassium</td>
<td>$&lt; 300$ ppm</td>
<td>241 ppm</td>
</tr>
<tr>
<td>Sodium</td>
<td>$&lt; 300$ ppm</td>
<td>237 ppm</td>
</tr>
<tr>
<td>Chloride</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Sulphate</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Assay of lithium</td>
<td>not less than 12.55%</td>
<td>12.62%</td>
</tr>
<tr>
<td>Purity($\text{Li}_2\text{TiO}_3$)</td>
<td>$98.0%$ to 100.5%</td>
<td>99.76%</td>
</tr>
</tbody>
</table>
Table 5.8 The results of the tests (General Specification) for lithium titanate made at 920°C for 24 hours (Batch No.920-5, Batch size 1 kg)

<table>
<thead>
<tr>
<th>TEST</th>
<th>SPECIFICATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>white or almost white</td>
<td>complies</td>
</tr>
<tr>
<td>Solubility</td>
<td>slowly soluble in hot sulphuric acid, practically insoluble in water, dilute mineral acid and 96% ethanol</td>
<td>complies</td>
</tr>
<tr>
<td>Identification</td>
<td>A: red colour to a non-luminous flame, B: orange-red colour, C: violet-blue colour</td>
<td>A:complies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B:complies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C:complies</td>
</tr>
<tr>
<td>Clarity and colour</td>
<td>BP appendix IV A and B</td>
<td>complies</td>
</tr>
<tr>
<td>Alkalinity</td>
<td>&lt; 2 ml of 0.1M HCL or 0.1M NaOH</td>
<td>1.49 ml</td>
</tr>
<tr>
<td>Water soluble matter</td>
<td>&lt; 250 mg</td>
<td>199 mg</td>
</tr>
<tr>
<td>Antimony</td>
<td>any colour not more intense than that of a reference solution</td>
<td>complies</td>
</tr>
<tr>
<td>Arsenic</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Barium</td>
<td>opalescence not more than that of a reference solution</td>
<td>complies</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Iron</td>
<td>colour not more intense than that of a standard solution</td>
<td>complies</td>
</tr>
<tr>
<td>Calcium</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Magnesium</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Potassium</td>
<td>&lt; 300 ppm</td>
<td>256 ppm</td>
</tr>
<tr>
<td>Sodium</td>
<td>&lt; 300 ppm</td>
<td>249 ppm</td>
</tr>
<tr>
<td>Chloride</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Sulphate</td>
<td>limit test, BP appendix VII</td>
<td>complies</td>
</tr>
<tr>
<td>Assay of lithium</td>
<td>not less than 12.55%</td>
<td>12.63%</td>
</tr>
<tr>
<td>Purity(Li$_2$TiO$_3$)</td>
<td>98.0% to 100.5%</td>
<td>99.84%</td>
</tr>
</tbody>
</table>
Table 5.9 The results of the tests (Additional Specification, Part B) for lithium titanate made at 720°C for 24 hours (Batch No. 720-5, Batch size 1 kg)

<table>
<thead>
<tr>
<th>TEST</th>
<th>SPECIFICATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR spectrum</td>
<td>no (-\text{CO}_2) peaks</td>
<td>Complies</td>
</tr>
<tr>
<td></td>
<td>appeared</td>
<td>[see Fig. 5.1(a)]</td>
</tr>
<tr>
<td>Loss of weight on heating</td>
<td>not less than 28.6%</td>
<td>28.72%</td>
</tr>
<tr>
<td>Density (g/cm(^3))</td>
<td>not less than 3.4</td>
<td>3.46</td>
</tr>
<tr>
<td>Particle size ((\mu m))</td>
<td>40-45</td>
<td>36</td>
</tr>
<tr>
<td>Surface area (m(^2)/g)</td>
<td>1.2 to 1.8</td>
<td>2.33</td>
</tr>
</tbody>
</table>
| Dissolution (USP method II, 100 rpm, at 37°C in 1000 ml of 0.1N HCL solution) | 2 hrs: 40-50%  
6 hrs: 60-75%  
12 hrs: 80-100% | 2 hrs 71%  
6 hrs 92%  
12 hrs 105% |
| SEM                          | see photos 5.1 (Middle)          | see Photos 5.1 (Top)         |
Table 5.10 The results of the tests (Additional Specification, Part B) for lithium titanate made at 820°C for 24 hours (Batch No. 820-5, Batch size 1 kg)

<table>
<thead>
<tr>
<th>TEST</th>
<th>SPECIFICATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR spectrum</td>
<td>no -CO₂ peaks appeared</td>
<td>Complies [see Fig.5.1(b)]</td>
</tr>
<tr>
<td>Loss of weight on heating</td>
<td>not less than 28.6%</td>
<td>28.80%</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>not less than 3.40</td>
<td>3.45</td>
</tr>
<tr>
<td>Particle size (μm)</td>
<td>40-50</td>
<td>40</td>
</tr>
<tr>
<td>Surface area (m²/g)</td>
<td>1.2 to 1.8</td>
<td>1.37</td>
</tr>
<tr>
<td>Dissolution (USP method II, 100 rpm, at 37°C in 1000 ml of 0.1N HCL solution)</td>
<td>2 hrs: 40-50% 6 hrs: 60-75% 12 hrs:80-100%</td>
<td>2 hrs 45% 6 hrs 70% 12 hrs 88%</td>
</tr>
<tr>
<td>SEM</td>
<td>see photos 5.1(middle)</td>
<td>Complies</td>
</tr>
</tbody>
</table>
Table 5.11 The results of the tests (Additional Specification, Part B) for lithium titanate made at 920°C for 24 hours (Batch No.920-5, Batch size 1 kg)

<table>
<thead>
<tr>
<th>TEST</th>
<th>SPECIFICATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR spectrum</td>
<td>no -CO$_2$ peaks appeared</td>
<td>Complies [see Fig.5.1(c)]</td>
</tr>
<tr>
<td>Loss of weight on heating</td>
<td>not less than 28.6%</td>
<td>28.86%</td>
</tr>
<tr>
<td>Density (g/cm$^3$)</td>
<td>not less than 3.40</td>
<td>3.42</td>
</tr>
<tr>
<td>Particle size ($\mu$m)</td>
<td>40-50</td>
<td>40</td>
</tr>
<tr>
<td>Surface area (m$^2$/g)</td>
<td>1.2 to 1.8</td>
<td>0.78</td>
</tr>
<tr>
<td>Dissolution (USP method II, 100 rpm, at 37°C in 1000 ml of 0.1N HCL solution)</td>
<td>2 hrs: 40-50% 6 hrs: 60-75% 12 hrs: 80-100%</td>
<td>2 hrs 23% 6 hrs 40% 12 hrs 51%</td>
</tr>
<tr>
<td>SEM</td>
<td>see photos 5.1(Middle)</td>
<td>see Photos (Bottom)</td>
</tr>
</tbody>
</table>
APPENDIX 1. General Specification of lithium titanate

LITHIUM TITANATE

\[
\text{Li}_2\text{TiO}_3 \quad 109.78 \\
(\text{Li}\% 12.65, \text{TiO}_2\% 72.78, \text{Li}_2\text{O}\% 27.22)
\]

Lithium titanate contains not less than 98.0 per cent and not more than 100.5 per cent of \(\text{Li}_2\text{TiO}_3\).

DESCRIPTION:
A white or almost white powder, odourless

SOLUBILITY:
Practically insoluble in water, dilute mineral acids and 96% ethanol; slowly soluble in hot sulphuric acid.

IDENTIFICATION:

A: When moistened with hydrochloric acid, imparts a red colour to a non-luminous flame.

B: To 5 ml of solution A (see as following) add 0.1 ml of hydrogen peroxide solution (100 vol.). An orange-red colour is produced.

SOLUTION A: To 0.5 g of lithium titanate powder add 5 g of anhydrous sodium sulphate and 10 ml of water, mix and add 10 ml of sulphuric acid. Boil gently in long-necked combustion flask until clear (about 20-25 minutes), cool, add slowly 40 ml of cooled sulphuric acid (25%), cool again and dilute with water to 100 ml.

C: To 5 ml of solution A add 0.5 g of granulated zinc, after 45 minutes a violet-blue colour is produced.
CLARITY AND COLOUR OF SOLUTION

Solution A is not more opalescent than reference suspension II. (BP Appendix IV A, and colourless, BP Appendix IV B, method II.

ACIDITY OR ALKALINITY

Shake 5 g of the powder with 50 ml of carbon dioxide-free water for 5 minutes and centrifuge or filter until a clear solution is obtained. To 10 ml of the solution add 0.1 ml of bromothymol blue solution. Not more than 2 ml of either 0.1 M hydrochloric acid VS or 0.1 M sodium hydroxide VS is required to change the colour of the solution.

WATER SOLUBLE MATTERS

Boil 10 g of the powder for 5 minutes with 150 ml of water containing 0.5 g of ammonium sulphate. Cool, dilute to 200 ml with water and filter until a clear solution is obtained. Evaporate 100 ml of the filtrate to dryness and ignite. The residue weighs not more than 250 mg.

ANTIMONY

To 10.0 ml of solution A add 10 ml of hydrochloric acid and 10 ml of water. Cool to 20°C, if necessary, and add 0.15 ml of sodium nitrite solution. After 5 minutes add 5 ml of a 1% w/v solution of hydroxylamine hydrochloride, mix, add 10 ml of a freshly prepared 0.01% w/v solution of rhodamine B and mix. Add 10 ml of toluene, shake vigorously for 1 minute and collect the toluene layer. Prepare a reference solution at same time and in the same manner using a solution prepared by adding 10 ml of hydrochloric acid and 15 ml of a solution containing 0.5 g of anhydrous sodium sulphate and 2 ml of sulphuric acid to 5 ml of antimony standard solution (1 ppm Sb) in place of the solution of the substance being examined. Any pink colour in the toluene layer of the test solution is not more than intense than in the toluene layer of the reference solution.

ARSENIC

To 0.20 g of the powder in a 100 ml long-necked combustion flask add 2 g of
anhydrous sodium sulphate, 7 ml of sulphuric acid and 5 ml of nitric acid. Heat gently until a clear solution is obtained (about 20 minutes), cool, add 10 ml of water, cool again and add 5 g of hydrazine reducing mixture and 10 ml of hydrochloric acid. Immediately attach an air condenser and distil into 15 ml of cooled water until a total volume of 30 ml is obtained. Rinse the condenser and dilute the combined distillate and rinsing to 40 ml with water. 20 ml if the solution complies with the limit test for arsenic, BP Appendix VII (7 ppm). Use a mixture of 0.5 ml of arsenic standard solution (1 ppm As) and 24.5 ml of water to prepare the standard.

BARIUM

Shake 20.0 g for 1 minute with 30 ml of hydrochloric acid, add 100 ml of distilled water and boil. Filter while hot through a hardened filter paper until a clear filtrate is obtained. Wash the filter with 60 ml of distilled water. To 10 ml of the solution add 1 ml of 1 M sulphuric acid. After 30 minutes any opalescence is not more than that of a mixture of 10 ml of the test solution and 1 ml of distilled water.

HEAVY METALS

Dilute 10.0 ml of the solution prepared in the test for Barium to 20 ml with water. 12 ml of the solution complies with limit test A for heavy metals, BP Appendix VII. Use lead standard solution (2 ppm Pb) to prepare the standard.

IRON

To 8.0 ml of solution A add 4 ml of water, mix and add 0.05 ml of bromine water allow to stand for 5 minutes, remove the excess of bromine with a current of air and add 3 ml of 1M potassium thiocyanate. Any colour in the solution is not more intense than in a standard prepared at the same time and in the same manner using a mixture of 4 ml of iron standard solution (2 ppm Fe) and 8 ml of a 20% w/v solution of sulphuric acid.

CALCIUM

5 ml of solution B (see as following) dilute to 15 ml with distilled water complies with the limit test for calcium, BP Appendix VII.
SOLUTION B: To 2 g of the powder add 40 ml of 7 M hydrochloric acid solution, heat gently for about 3 hours until a clear solution is obtained. If not, filter it until a clear solution is obtained and wash the solid with distilled water and filter again. Dilute the combined filtrate to 100 ml with distilled water.

MAGNESIUM

Dilute 1 ml of solution B to 15 ml with water. 10 ml of the resulting solution complies with the limit test for magnesium, BP Appendix VII.

POTASSIUM

Not more than 300 ppm when 5 ml of the solution B determined by atomic emission spectrophotometry, BP Appendix II D, at 766.5 nm and using potassium solution ASp, suitably dilute with water, for the standard solution.

SODIUM

Not more than 300 ppm when 5 ml of the solution B determined by atomic emission spectrophotometry, BP Appendix II D, at 589.0 nm and using sodium ASp, suitably dilute with water, for the standard solution.

CHLORIDE

2.5 ml of solution A diluted to 15 ml with water complies with the limit test for chlorides, BP Appendix VII.

SULPHATE

Disperse 1.25 g of the powder in 5 ml of distilled water and 5 ml of 7 M hydrochloric acid, heat gently for 20 minutes, cool and neutralise with 2 M sodium hydroxide. Filter it to get a clear solution and dilute to 25 ml with distilled water. The resulting solution complies with the limit test for sulphates, BP Appendix VII.

ASSAY

1. Titanium dioxide (TiO₂)
To 300 g of granulated zinc add 300 ml of a 2% w/v solution of mercury(II) nitrate and 2 ml of nitric acid, shake for 10 minutes and wash with water. Pack the amalgamated zinc into a glass tube (400 mm x 20 mm) fitted with a tap and a filter plate. Pass through the column 100 ml of 1M sulphuric acid followed by 100 ml of water, ensuring that the amalgam is covered with liquid throughout. Pass slowly through the column, at a rate of about 3 ml per minute. 200 ml of 0.5 M sulphuric acid followed by 100 ml of water. Collect the combined elutes in a flask containing 50 ml of a 15% w/v solution of ammonium iron(III) sulphate in sulphuric acid (25%) and titrate immediately with 0.1 M ammonium cerium (IV) nitrate VS using ferroin sulphate solution as indicator ($n_1$, ml). Pass slowly through the column 200 ml of 0.5 M sulphuric acid followed by 20 ml of solution A, wash with 100 ml of 0.5 M sulphuric acid followed by 100 ml of water. Collect the combined elutes in a flask containing 50 ml of a 15% w/v solution of ammonium iron(III) sulphate in sulphuric acid (25%) and titrate immediately with 0.1 M ammonium cerium (IV) nitrate VS using ferrous sulphate solution as indicator ($n_2$, ml). Calculate the percentage content of TiO$_2$ from the expression $3.99 \times (n_2 - n_1)/w$ where $w$ is the weight, in grammes, of the substance being examined taken to prepare solution A.

2. Lithium

Pipette 5 ml of solution B to a 250 ml of volumetric flask and dilute to the mark with distilled water (solution 1). Pipette 2 ml of solution 1 to a 100 ml of volumetric flask and make up to the volume with distilled water (solution 2). Solution 2 is determined by flame emission spectrophotometry at 670.8 nm, using lithium solution ASp, suitably diluted with distilled water, for the standard solution.
CHAPTER 6

GENERAL DISCUSSIONS AND CONCLUSIONS

&

FUTURE WORK
6.1 GENERAL DISCUSSIONS AND CONCLUSIONS

Lithium titanate (Li$_2$TiO$_3$) is one of the compounds in the Li$_2$O-TiO$_2$ system, which has never been used in lithium preparations for lithium treatment in psychiatric disorders. Because it has high ion selective property, many studies have been focused on its ion exchange properties. Although the kinetics and enthalpy of formation of lithium titanate was well established, little information has been published on its physical and chemical properties, which are primary important for drug release system.

Lithium titanate was prepared by heating the mixture of lithium carbonate and titanium dioxide powders at molar ratio 1:1 at four formation temperatures (680, 720, 820 and 920°C) for 24 hours. The samples produced were evaluated and characterized (see Chapter 3). The reaction between lithium carbonate and titanium dioxide was found to be incomplete at 680°C, but complete at 720°C or higher. The chemical composition of lithium titanate is independent of the formation temperatures, as shown in their IR, NMR and X-ray diffraction spectra (Chapter 3). It depends on the molar ratio of the mixture (lithium carbonate and titanium dioxide). The properties (loss of weight on heating, purity of the product, lithium content and density) of the lithium titanate samples made at 720°C or higher showed no great differences. However, the sample produced at 680°C had lower values of loss of weight on heating, purity of the product, lithium content and density. This is the result of the incomplete reaction at 680°C (Chapter 3).

The densities of the samples made at these four temperatures were all greater than 3.0 g/cm$^3$. The particle size distributions of the samples were found to be dependent on the particle size of the starting materials used in the preparation (Chapter 3). No great differences were found in their particle sizes, because the same batches of lithium carbonate and titanium dioxide powders were used in the preparation of these samples. However, the surface areas of the samples differed greatly. With increasing the formation temperatures form 680 to 920°C, the surface area decreased from 4.3738±0.012 m$^2$/g to 0.7805±0.223 m$^2$/g respectively. The crystallite of lithium
titanate on the surface of the powder particle increased with increasing the temperatures. That is why the particle sizes of these samples were similar, but the surface areas were different (Chapter 3).

The amount of lithium released from the lithium titanate powders decreased greatly when the forming temperature increased, which correlates well with the surface area. With increasing the temperature, the surface area of lithium titanate powder decreased dramatically. The lower the surface area, the less amount of lithium released. Three basic release patterns of lithium were obtained: fast, intermediate and slow. The samples made at 720, 820 and 920°C release lithium at a fast rate, an intermediate rate and a slow rate respectively. As the reaction was not complete at 680°C, the sample made at this temperature was not considered as a pure product. The differences in the release profile of lithium in vitro were produced mainly by the variations in the initial release rate \( r_i \) of lithium titanate samples. The initial release rate is characteristic for each sample made at 680 or 720 or 820 or 920°C. The lithium ion was found to be released mainly by an ion exchange mechanism in dilute acid solution. The formation temperature was found to be one of the determining factors for the release mechanisms of lithium for the powders, since it controls the purity and the degree of the crystallization of lithium titanate, which results in the differences in the surface areas of the powders and the initial release rate \( r_i \). The presence of the intermediate Li\(_2\)O from the reaction could also contribute to the variations in the in-vitro release profile of lithium. The powder made at a lower temperature (i.e. 680°C) may contains more Li\(_2\)O left in the final product than that made at a higher temperature (i.e. 920°C) (Chapter 3).

The dielectric property of lithium titanate were found to be different between the four samples prepared at different temperatures. The dielectric response of the powders increased with increasing the formation temperatures. It could be caused by the differences in the crystallization. It is known that the dielectric property is associated with the nature of the compound. Therefore, the dielectric spectroscopy can be used as one of the methods to identify the difference between the samples made
at different temperatures (Chapter 3).

Above all, the formation temperature mainly controls the crystallization of lithium titanate. Different temperatures produce different crystallite on the surface of the powder particles. It, therefore, results in the differences in the surface areas and \textit{in-vitro} release pattern of lithium. By changing the temperature, the release pattern of lithium can be altered from a fast to a slow pattern. Different release profiles of lithium can be achieved accordingly. The composition of lithium titanate and the properties (density, loss of weight on heating, particle size, lithium content and purity of the product) are independent of the formation temperatures, as long as the chemical reaction between lithium carbonate and titanium dioxide is complete (Chapter 3).

The particle size of the starting material, lithium carbonate, has a great effect on the particle size of the final product, lithium titanate, and the release pattern of lithium. The smaller particle size of lithium carbonate powder used in the preparation produces lithium titanate powder with smaller particle size, and \textit{vice versa}. By controlling the particle size of lithium carbonate, both the particle size of lithium titanate powder and the \textit{in-vitro} release of lithium could be controlled, therefore, to achieve the uniformity and reproducibility in particle size and the release pattern. In addition, the crystal form of lithium carbonate was also found to contribute to the effects on the \textit{in-vitro} release of lithium. This result may be also applied to titanium dioxide, another starting material used in the reaction, although the particle size of the powder was not investigated. The particle size of titanium dioxide should also be controlled, even though the batch variation in the particles size is small for titanium dioxide (Chapter 3).

Different heating periods were found to cause differences in the release rate of lithium, especially in the initial release rate ($r_1$). The reaction between lithium carbonate and titanium dioxide was complete at $820^\circ$C during 6 hours of heating. However, the crystallization of lithium titanate was not fully accomplished during the 6 hours of heating. A satisfactory heating time of 24 hours is necessary in terms of
the completion of the crystallization (Chapter 3).

The equipment (furnace) used in the preparation of lithium titanate was found to have a limited influence on the properties of lithium titanate. The higher the temperature, the less the influence. The mixing process employed in the preparation of the mixture before heating can also affect the crystallization of the product, because it changes the contact between lithium carbonate and titanium dioxide powders (Chapter 3).

The quantity of the mixture of lithium carbonate and titanium dioxide placed inside the furnace was observed to affect the release characteristics of lithium from lithium titanate powder. The properties, however, are independent of the quantity of the mixture loaded inside the furnace. Increasing the loading size causes an decrease in the initial release rate \( (r_i) \) of lithium \textit{in vitro}. This influence can be minimized by using the same loading size of the mixture for each preparation of lithium titanate (Chapter 3).

When the particle sizes of lithium carbonate and titanium dioxide powders, the process of the mixture preparation and the formation conditions (heating temperature and heating time) are well controlled to be identical for each batch of lithium titanate production, lithium titanate can be reproduced. The reproducibility of the method of preparing the product is satisfactory in terms of the properties and the release characteristics of lithium from the powder. A chemically identical lithium titanate product can be obtained at 720, or 820, or 920°C (Chapter 3).

The lithium titanate capsules release lithium with the same characteristics of the lithium titanate powders. Therefore, by controlling the formation conditions of lithium titanate, different release patterns of lithium from the capsules could also be achieved. As the powder has a slow-release characteristic, the sustained release of lithium titanate capsules can be prepared by simply filling the powder into the capsule shell and may provide a simple oral dosage form of lithium (Chapter 4). The process
of preparation is much simpler than those systems described in Chapter 1.

Non-disintegrating, disintegrating and erodible tablet formulations were obtained by introducing different binders and water soluble channelling agents. Both non-disintegrating and erodible tablet formulations provided a zero order of release during 6 hours dissolution in vitro. The disintegrating tablet formulation gives a first order of release. However, the quantity of lithium released from these tablet formulations, regardless the order of release, is much less than that of lithium from the capsules or the powder (Chapter 4).

The weight of the tablets for a constant diameter effects the quantity of lithium released in vitro. The quantity of lithium decreased when the tablet weight increased. Although reducing the tablet weight could increase the release rate of lithium, the release rate did not exceed the rate of the capsules or the powder (Chapter 4).

The size of non-disintegrating tablets has an affect on the in-vitro release of lithium. An decrease in tablet size led to an increase in the release of lithium and the total quantity of lithium released from the tablets. However, the preparation of the small size of tablet such as 3 mm diameter involves more difficulties in the technique and the formulation design. Even though, the 3 mm tablets were used, the amount of lithium released was about 50% within 12 hours in vitro, which is far less than that from the capsules or the powder (80% approximately). Therefore, the tablet formulation provided no additional advantages in terms of the release rate of lithium and the quantity of lithium released, although a zero order of release was achieved (Chapter 4).

Two types of specifications of lithium titanate were proposed: general and additional specifications. The general specification is to control the general chemical impurities and to ensure the potency of lithium. All three batches of lithium titanate powders made at 720, 820 and 920°C have passed the tests in the specification. It provides the similar type of specification that could possibly be used for an official
monograph. The additional specification is to control the special characteristics of lithium titanate found in this study. The specification defined the product specifically and therefore lithium titanate can be produced as required in terms of the in vitro release pattern of lithium and be well identified by the additional specification. Both specifications are essential for controlling the quality of the product, standardizing the product and ensuring that the product is appropriate and reproducible (Chapter 5).

6.2 FUTURE WORK

A. Bioavailability Study in Healthy Human Subject

Bioavailability is defined as a measure, relative to some standard, of the rate and amount of drug which reaches the systemic circulation unchanged following the administration of a suitable form. It is well known that only a drug that is absorbed completely into the general circulation can produce a biological response or clinical response. The drug bioavailability characteristics play an important role in the onset and control the intensity and duration of desired pharmacological effect. Although the vitro release patterns of lithium from lithium titanate were obtained, but they may not reflect the vivo release patterns. The bioavailability study of lithium titanate should be carried out in male healthy subjects to assess the vivo release rate and the fraction of lithium released from the dosage form, to establish the relationship between the vitro and vivo release, and therefore, to chose a suitable release pattern of lithium (or lithium titanate product) and an appropriate dose which gives plasma lithium concentration within the therapeutical window. The study would also predict the vivo release from the vitro release when the correlation between in-vitro and in-vivo is established.

B. GI Transit Time Study

As discussed in Chapter 1, the GI transit time plays a critic role in drug absorption and bioavailability for oral dosage form. Lithium titanate system was designed to influence the GI transit time by increasing the density to delay the gastric emptying, therefore, to extend the total GI transit time of the lithium preparation. To
evaluate whether the new lithium titanate system is satisfactory in terms of delaying gastric emptying and to assess whether the product releases lithium at an appropriate rate during its transit through the GI tract, a GI transit study should be carried out with monitoring the plasma lithium level at same time. The study would assist in understanding these aspects of the dosage form.
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