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Novel risperidone orally disintegrating minitablets for pediatric use: patient acceptance and dose adjustment

Abstract

Objective: Risperidone is a potent psychotropic agent has been approved for symptomatic treatment of irritability in children and adolescents with autism spectrum disorders. However, its bitter taste and dose adjustment of liquid dosage forms is a main hurdle for patient acceptance.

Significance: Thus, this recent study investigate the formulation of taste masked risperidone orally disintegration minitablets (ODMT) as a way of enhancing patient acceptance.

Methods: Taste masked risperidone hydrogenated castor oil or Cetyl alcohol based granules were prepared using a simple melt granulation technique in different drug to lipid ratios; drug release, bitterness score of the prepared granular formulations were evaluated. DSC was also performed to detect the possible drug lipid interaction. The selected lipid-based granules were further compressed into ODMT formulations. Bitterness score was assessed by gustatory sensation test and results were compared to marketed liquid formulations of risperidone.

Results: All the prepared ODMT formulations showed high content uniformity, with minimum dose fluctuation compared to marketed oral liquid preparations.

Conclusion: In conclusion, risperidone lipid-based granules could be formulated in different ratios by simple techniques and commonly used excipients into taste masked risperidone ODMT with accurate and flexible doses suitable for pediatric use with high taste preference and acceptability.

Introduction

The development of pediatric formulations, particularly those suitable for very young children, can be challenging to the pharmaceutical industry and research [1]. There is only limited knowledge available on the acceptability of different dosage forms, administration volumes, dosage form size, taste, and the safety of formulation excipients in relation to the age and development status of the child [2].

Risperidone is a used for the treatment of schizophrenia and other similar psychotic disorders including Autism [3, 4], where Risperidone has become the first medication with US Food and Drug Administration (FDA) approved labeling for the symptomatic treatment of irritability (including aggressive behavior, deliberate self-injury, and temper tantrums) in children and adolescents suffering from autistim spectrum disorders (ASD)[5, 6]. Risperidone is a potent psychotropic agent but its bitter taste is main hurdle for the acceptability of liquid formulations [7].

Risperidone is supplied in the form of tablets, orally disintegrating tablets (ODT) prepared by lyophilisation for immediate action, and 1mg/ml solution with a measuring device. Regarding risperidone solution, measuring the dose with the supplied pipette may be highly challenging and inaccurate due to the possibility of incorporation of air bubbles; thus dose adjustment is the major problem for pediatric use. Available solid formulations may be impractical due to the inability of pediatrics to swallow conventional tablets [8, 9]. Moreover some physicians may require an increase in the dose by 0.1 mg, which cannot be achieved by using the available tablets; as tablet breaking will not guarantee accurate dosing, or by using liquid formulations; due to inaccurate volume measuring.

The production of a palatable dosage form is very important for patient compliance, especially for pediatric population [10]. Thus bitter taste masking is an important consideration in the formulation of many therapeutics which may suffer from unacceptable taste, the principle of taste masking depends mainly on minimizing the direct contact between the bitter drug and the taste receptors in the buccal cavity of the subject [11, 12]. The palatability of pharmaceutical product could be achieved through many techniques, which do not only improved the taste, but also the stability of the drug in the formulation and acceptability of the final product [13, 14].

Minitablets can be defined as small tablets with a diameter of 5 mm or less [15] or even the size could be more restricted to be less than 3 mm [16], they can be formulated easily through conventional tablet presses. The ability to swallow minitablets and its safety of use o has been recently reported for young children , in infants and toddlers (1 month to 2 years), depending on the tablets properties[17]. Thomson et al. recently investigated the acceptability of placebo mini-tablets in 100 preschool children. Forty-six per cent of the children at the age of two years and up to 86% of the 5-year-old children swallowed the mini-tablet. None of the children choked or aspirated the minitablet [18]. Moreover, the acceptability of 2 mm solid dosage forms (minitablets) as an alternative administration modality in young children in comparison with syrup were evaluated , where in the overall patient population, the acceptability of uncoated mini-tablets was superior to syrup [19]

Orally disintegrating minitablets (ODMT) have gained much interest in the past decade [20], combining advantages of ODT including palatability together with the safety and ease of modulation of minitablets, in addition to the small size which helps in the ease of dose control as well as avoiding chocking for pediatrics in case of ingestion [21]. The recent study investigate the formulation of taste masked risperidone ODMT, where the major drawback for the use of risperidone is the unacceptability of commercial liquid formulations due to its bitter taste, in addition to its the high potency thus incorrect control of the required dosing that may occur upon the use of commercially available ODT of liquid formulations , may result in toxic effects, even when small doses (less than 0.1 mg) is required [22].

Materials and methods
Materials

Risperidone was kindly provided by Pharaonia Pharmaceutical Co., Alexandria, Egypt. Cetyl alcohol (CA), Talc powder and ammonium bicarbonate were obtained from Al Nasr pharmaceutical chemicals Co., Alexandria, Egypt. Hydrogenated castor oil (HCO), Croscarmellose, (Ac-Di-Sol), Crospovidone, Poly vinyl pyrollidone (PVP k30), Sucralose and Camphor were purchased from Pharaonia pharmaceutical Co., Alexandria, Egypt. Quinine HCl; BP grade, was obtained from BDH Chemical Ltd., England. Mannitol DC, was a courtesy of Pharco Co., Alexandria, Egypt. Lactose DC, was obtained from Evonic Pharmaceuticals, Mumbai, India. Hydrochloric acid (HCl); Analar grade, was purchased from Cornell® labs,

Cairo, Egypt. All other materials were of analytical grade. Methanol and Acetonitrile; HPLC grades, Fisher Scientific UK Ltd., Bishop Meadow Road, Loughborough, Leics,UK. Commercial Risperidone liquid dosage forms (1mg/ml).

Preparation of risperidone lipid-based granules

Taste masked risperidone lipid-based granules were prepared using a simple melt granulation technique[23]. Lipid carriers namely; Cetyl alcohol (CA) or hydrogenated castor oil (HCO), were allowed to melt separately with continuous stirring at 60˚C and 90˚C respectively using a thermostatically controlled water bath (model UV-1601PC, Shimatzu, Japan).

The drug powder was added portion wise to the molten base with a continuous stirring. Different drug to lipid ratios were depicted in Table I to form 14 different risperidone granular formulations G1 – G14. The molten mass was immediately removed from the water bath, and then allowed to congeal under continuous stirring to a mass of plasticity suitable enough to be forced through a sieve of mesh size 1.2 mm (Retsch, Germany). The formed granules were then cooled at room temperature, reduced in size and screened through 250-400 μm sieves (Retsch, Germany).

Table 1: Composition of different risperidone lipid-based granules

Characterization of risperidone lipid-based granules

In-vitro release study

Studies were carried out on risperidone granular formulations (G1-G14) equivalent to 5 mg risperidone using USP dissolution apparatus II (PHARMA TEST PTWS 600, Germany) at 37˚C ± 0.5˚C. The dissolution medium was composed of 500 ml 0.1 N HCl, stirred at 50 rpm for 2 hours. Samples (10 ml) were withdrawn at predetermined intervals, compensated with fresh dissolution medium. The samples were filtered, and assayed spectrophotometrically at the predetermined λ_{max}

Differential scanning colorimetry (DSC)

Thermal analysis [24] was performed on risperidone, cetyl alcohol, hydrogenated castor oil and some selected risperidone lipid-based granular formulations. The instrument (Differential Scanning Calorimeter, Perkin Elmer, Germany, DSC 6) was calibrated with indium, dry nitrogen

was used as a carrier gas with a flow rate of 20 ml/min and a scan speed of 10˚C / min up to 250˚C [25].

Gustatory sensation test

Bitterness score of lipid-based risperidone granules and two marketed liquid dosage forms; was evaluated using the gustatory sensation test [26]. A series of concentration of standard aqueous quinine hydrochloride solutions ranging from 0.0003 – 1 millimolar (mM) were prepared. Each solution was designated a score from 0-5.

Seven adult human well trained volunteers; 3 males and 4 females capable of informed consent, having a body mass index less than 30 kg/m^2 and ranging in age between 20 and 40 years (mean = 31.7 years), participated in the study**.**

They have no history of drug allergic reaction including risperidone. They are healthy (have no heart diseases, hypertension, metabolic or psychiatric disorders, renal or hepatic disorders or any comorbidities). They do not experience any blood disorders as anemia, hemophilia, or any disorder interfering with blood coagulation.

None of the subjects was a smoker and will be excluded from the study if they had taken any over-the-counter or prescription medication within the duration of the study, used tobacco or other nicotine containing products, or had a history of alcohol or drug abuse

Moreover, the experiment was carried out under the regulation of the Institutional Ethics committee number 181205. An agreement of the Committee and the Dean of School of Pharmacy, Alexandria University, was obtained prior to the in study.

During the screening; subjects who have been diagnosed of Schizophrenia or bipolar disorders, recurrent gastrointestinal lesions or any mouth ulcers, a concurrent disease state that requires long-term daily medication were excluded from the study. Additionally, a positive test result of hepatitis B, hepatitis C, or human immunodeficiency virus antibody for any of the volunteers were excluded as well from the study.

Subjects were provided with adequate counselling regarding the steps of the experiment including avoiding the minitablets ingestion, as well as potential side effects of risperidone including rare and serious side effects (if any) in case of ingestion. The general well-being of the

subjects will be monitored by a physician collaborator. An emergency contact number will be provided to the subjects should the event of a distressful side effect arise The subjects were asked to refrain from eating and drinking for at least 1 hour prior to the test.

Before testing, the volunteers were asked to take quinine HCl sample (1ml) of each score which is placed on their tongue outside the mouth cavity for 30 seconds, then rinse their tongue thoroughly with water and wait at least 10 minutes before applying another sample. The volunteers were told the score of bitterness of each sample, this method was modified according to El-Refaie et al. [27]

Afterwards, test samples, equivalent to 0.25 mg risperidone were placed separately on the tongue of each volunteer, kept for 30 seconds and the subjects were then asked to give each sample a bitterness score.

Each volunteer was then asked to gargle well with water, wait for at least 10 minutes before tasting the next sample. All results were shown as a mean value of 3 different measurements ± SD.

Preparation of placebo oral disintegrating minitablets

Different placebo orally disintegrating minitablets (ODMT) were prepared either by using sublimable components or by direct compression technique using super-disintegrants, the prepared ODMT matrices were evaluated with regards to the routine quality control testing in addition to disintegration time to choose the best matrix formulation, the chosen formulation was of suitable hardness and acceptable friability in addition to fast disintegration time measured both in vitro and in vivo.

Preparation of risperidone lipid-based oral disintegrating minitablets

The selected risperidone lipid-based granular formulations (containing risperidone equivalent to 0.1 mg and to 0.25 mg) were mixed with the excipients of the selected ODMT matrix and the powder blend was compressed using a single punch tablet machine equipped with a flat-faced 2 mm and 3 mm punch forming two different patches of medicated ODMT (F1'-F8', 15 mg, 2mm) and (F1- F8, 20 mg, 3mm).

Evaluation of the prepared risperidone lipid-based ODMT

Quality control testing

The prepared ODMT containing risperidone lipid-based granules were evaluated in terms of weight and thickness variation hardness and friability.

Gustatory sensation test

Bitterness score of selected lipid-based risperidone ODMT (F1-F8), ODMT matrices containing risperidone free form as a positive control, risperidone lipid-based granules and two marketed liquid dosage forms were evaluated using the gustatory sensation test [26] with some modifications according to Wessam M. El-Refaie et al. as mentioned before. Results were expressed as a mean value of 3 different measurements ± SD.

In-vitro drug release:

The release of risperidone from the selected ODMT formulations was measured in 500 ml 0.1 N HCl at 50 rpm at $37°C ± 0.5°C$ using USP dissolution apparatus II in triplicates for 2 hours.

Release studies were carried out ODMT containing an amount of risperidone equivalent to 1.25 mg. Release profiles of some selected risperidone ODMT formulations were compared to those of the corresponding, lipid-based risperidone granules under the same conditions of release.

At the selected time intervals, aliquots each 10 ml were withdrawn through 0.45 μm membrane filter (Merck Millipore, Darmstadt, Germany) and replaced by an equivalent volume of the fresh dissolution medium. The samples were assayed spectrophotometrically at the predetermined λmax. Results were depicted as a mean value of 3 different measurements ± SD.

Drug content and content uniformity of lipid-based risperidone ODMT

Accurately, a sample equivalent to 0.5 mg risperidone was weighed after crushing 10 ODMT [28] of the selected formulations separately. The mobile phase; methanol: acetonitrile, 80:20 % v/v, was added and the mixture was sonicated for 20 minutes until a clear solution is formed. The volume was then completed to obtain a dilution of 10 μg/ml, and then filtered using 0.22 μm millipore filters.

50 µl sample volume was injected into the HPLC and assayed as described. Tests were conducted in triplicates; mean values of the area under curves were reported and the content of was expressed as a percentage of the claimed amount [29].

Content uniformity was carried out on a batch of 10 ODMTs each containing 0.1 mg risperidone. Each tablet was transferred separately to a 10 ml volumetric flask, dissolved in 5 ml 0.1 N HCl followed by mechanical shaking, then the volume is completed to 10 ml with 0.1 N HCl. The solution was filtered through 0.22 µm millipore filter and was scanned spectrophotometrically at 280 nm.

The content uniformity of the prepared ODMTs was compared to the uniformity of dosing of the two marketed liquid formulations in order to show the difference in the fluctuation of dosing. . Results were expressed as a mean value of 3 different measurements ± SD.

Stability studies

A stability study was conducted to study the effect of storage on the selected ODMT formulations containing lipid-based granules equivalent to 0.25 mg risperidone. ODMTs were packed in stoppered, dark glass bottles, stored over the shelf at room temperature for 1 year. Samples were withdrawn after 12 months and examined for their taste, drug release as well as any change in their physical properties as hardness and disintegration time. Statistical analysis was done using one way Anova test. . Results were expressed as a mean value of 3 different measurements ± SD.

Statistical analysis

All results were depicted as mean values ±SD. All statistical comparisons were performed using Microsoft Excel 2010. The obtained data of repeated measurements was subjected to Anova analysis, a p-value ≤0.05 was considered as significant.

Results and discussion

In this work, lipid-based granular formulations containing Risperidone were prepared using hot melt extrusion technique. Preparation of the granules by solvent evaporation technique could not be applied because of the residual solvent that may remain in the final product which may be toxic for pediatric use [30]. In the granular formulations prepared, two lipids were chosen for the formulations, namely hydrogenated castor oil (HCO) and cetyl alcohol (CA), being cost effective and easy to compress into tablets .These characteristics rendered the chosen 2 lipids suitable candidates for the study. To formulate these granules into the final dosage form, pharmaceutical excipients such as fillers, sweetners , disintegrants and lubricants were required.

Characterization of risperidone lipid-based granules

In-vitro release study

The release data from all the prepared CA and HCO-based risperidone granules was summarized in Figures 1a and 1b respectively. According to the USP guidelines for the monograph of risperidone conventional tablets, not less than 75% of the drug should be released within the first 45 minutes, release data reveled that formulae G1, G2, G3, G8, G9, G10 and G11 with lipid to drug weight ratio ranging between 1:1 to 1:5 (Table 1) fulfilled this parameter.

Figure 1 a

Figure 1 b

It is obvious, that all the prepared granules − irrespective of the lipid nature − shared a common property of an abrupt release of the drug initially, followed by a relatively slower rate of drug release as shown in Figures (1a&1b). This may be due to the presence of some drug particles on the surface of granules which were initially released into the surrounding medium[31].

The release data showed that the drug release was highly dependent on the drug: lipid weight ratio used Figures (1a &1b); as the lipid content increased, the rate of risperidone release significantly decreased ($p < 0.05$, Anova). Such results suggested that the matrix with higher lipid content provided a more tortuous and longer diffusion pathway of the drug. The dissolution tests displayed the significant ($p < 0.05$, Anova) retardation of drug release from the granules

compared to the pure drug, which may attribute to delaying the appearance of the unpleasant taste in the oral cavity.

Release data revealed also that there was no great difference in the release pattern of risperidone from HCO or CA lipid-based granules, although CA granules (as in G9 & G11) showed a slight better release profile than (G2 & G4 respectively); this may be attributed to the lower melting point of CA (50˚C) compared to HCO (90˚C); which may result in granules softening in the release medium, increasing the porosity of the granules and thus fastening the release.

Differential scanning colorimetry (DSC)

DSC was performed to ensure the incorporation of risperidone in the lipid matrices. Free risperidone powder thermogram was characterized by a single sharp melting endothermic peak at 170 ˚C with an enthalpy of fusion (ΔH) of 91.9 J/g, which revealed a crystalline substance typical behavior. Thermograms of hydrogenated castor oil (HCO) and cetyl alcohol (CA) showed endothermic peaks at 90 ˚C and 50 ˚C respectively corresponding to their melting.

It was observed as shown in Figure 2 that the endothermic peak of risperidone at 170 ˚C has disappeared in all thermograms of tested risperidone loaded lipid granules; G2, G3, G9, G10 indicating complete incorporation of risperidone in the lipid matrices and the presence of the drug in amorphous form in the tested lipid-based granules.

Figure 2

Gustatory sensation test

This test was used to screen the taste masking potential of the prepared lipid-based granules of risperidone, two marketed liquid formulations compared to standard quinine hydrochloride as a standard bitter drug.

Figure 3 shows the different bitterness scores of the different formulations. It is clear that the lipid-based risperidone granules showed less bitter taste compared to the marketed formulations. It was observed that HCO-based granules (G1-G7) showed slightly better taste masking ability than CA (G8-G14), this may be attributed to the lower melting point of CA compared to HCO which results in faster release of the drug in the mouth cavity due to softening of the lipid matrix.

It was also noticed that the taste masking ability is highly related to the amount of the drug released in the mouth cavity, formulae with higher lipid content exhibited retarded release (Figures 1a, 1b) and hence better taste masking properties.

Moreover, increasing the lipid concentration increased the ability to coat the drug particles and the coat thickness, thus decreasing the contact of the drug with the taste buds.

The higher concentrations of HCO as in G5-G7, the best taste masking is, with bitterness score approximately zero, however they resulted in further retardation of the release which in turns does not fulfill the pharmacopeial requirements. However, CA granules are of lower melting point and of higher porosity; hence they showed better release compared to those prepared from HCO leading to increased bitterness score. To sum up, CA may be more beneficial taste masking candidate in the process of minitablets formulation; due to its slower hardening time, which makes it easier for handling and granulation on large scale.

Figure 3

Preparation of risperidone lipid-based oral disintegrating minitablets

Based on results of the screening study preformed on the prepared lipid-based risperidone granules; granules prepared from hydrogenated castor oil and cetyl alcohol with risperidone:lipid ratios 1:1, 1:2.5, 1:3.5 and 1:5 (*G1-G4 and G8-G11, respectively*) were found to have a suitable taste masking potention without affecting the release rate profoundly. In addition, their minimum lipid content compared to other granular formulations may allow a better incorporation of various excipients without affecting the quality of the final formulation. Thus , they were chosen to be used in the preparation of taste masked ODMT.

To formulate these granules into the final dosage form, pharmaceutical excipients such as fillers, sweetners , disintegrants and lubricants were required. The choice of the type and the amount of excipients depended on the technique used for preparation , porosity and particle size, all can contribute to the quality and taste of the dosage form. Accordingly different formulations; (F1'-F8') and (F1-F8) were directly compressed into 2 mm, 3 mm ODMT respectively containing 0.1 and 0.25 mg risperidone respectively.

Evaluation of the prepared risperidone lipid-based ODMT

Quality control testing

The prepared medicated ODMT showed consistent weight (14.8 ± 0.2, 20.2 ± 0.4) for both the prepared 2 mm and 3 mm ODMTs respectively. ODMTs were of uniform shape and dimensions with no apparent variations observed by naked eye, they all exhibited white color and smooth surface.

Concerning hardness and friability, ODMTs batch exhibited suitable hardness values; 13.2 ± 1.1, 22.5 ± 1.22 Newton (N) for the 2 mm and 3 mm minitablets respectively. % Friability for all the prepared ODMTs was less than 1%. All the ODMT have oral disintegration time of 21.3 ± 2.4 seconds.

There was no significant variation between the prepared ODMTs containing lipid-based risperidone granules compared to the used ODMT matrix (D8).

Gustatory sensation test

Figure 4 revealed the bitterness scores of the prepared risperidone ODMT formulations (F1-F8), ODMT matrices containing risperidone free form, compared to the marketed risperidone products. It was concluded that the formed formulations have significantly improved the taste of risperidone, moreover the formed ODMTs have lower bitter scores compared to their corresponding granular formulations (Figure 4) which may be attributed to the excipients incorporated in the preparation of the ODMT; sucralose, which is an artificial sweetener, is 400 times sweeter than sucrose, mannitol has a cooling sweet taste [32]. However, when used alone in the positive control the bitter taste of risperidone was not significantly masked, but the incorporated lipids masked the taste more efficiently in the presence of the mentioned excipients that may help masking the taste of risperidone upon release from the formed granules.

Statistical analysis was done by Anova single factor analysis. The data revealed a significant difference in the bitterness values between the different lipid-based risperidone ODMT and the marketed liquid formulation at p-value 2.3×10^{-31} ,where the F value was > $F_{critical}$ which indicates a significant difference and successful taste masking ability of the prepared formulations.

Figure 4

In-vitro drug release studies

Figures 5a and 5b show release profiles of different lipid-based risperidone ODMT (F1- F 8) & those of the prepared ODMT containing lipid-based risperidone granules (F3 & F6) compared to their corresponding lipid-based granules (G3 & G10 respectively) respectively. The release profiles of risperidone from different ODMTS (F1-F8) are shown in Figure 5a, F7 and F 8 showed a more retarded release profile, failing the release parameters stated according to the USP (not less than 75% in the first 45 minutes), this may be due to the higher lipid content in the incorporated granules (G 4 and G 11) in these ODMTs, which may increase the compaction of the formed minitablets upon compression, retarding the release significantly(p<0.05).

It was deduced that the used matrix; D8, incorporating different risperidone lipid-based granules didn't affect their release profiles significantly (at P < 0.05) compared to the release rate from the corresponding granules (G3 and G10 composed of drug to lipid ratio of 1: 3.5 HCO or CA respectively), as shown in Figure 5b, this occurs consequently for ODMT containing granules of lower lipid content.

Figure 5a

Figure 5b

Drug content and content uniformity of lipid-based risperidone ODMT

Based on the pharmacopeial requirements, the preparation complies with the test if each individual content is between 85% and 115% of the average content and relative standard deviation (RSD) is not more than 6%. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75–125% of the average content [33]. The prepared ODMT formulations 2 mm diameter (F1'-F6') passed the test of content uniformity with average content of each tablet between 95.6 − 105.6% and RSD not more than 3.91 %, none of the tablets was outside the range of (85-115%).

All the prepared formulations showed high content uniformity, where this minimum dose fluctuation is highly necessary to avoid dose variations and any possible toxicity especially for pediatrics.Figure 6 shows the content uniformity of the ODMTs compared to uniformity of dosing of the two marketed liquid formulations, it was observed that liquid dosage forms shows higher dose fluctuation compared to the prepared solid dosage form, this may be attributed to air

bubble entrapment and the high rate of subjective errors. The results showed the higher dose precision in case of solid dosage form compared to the marketed liquid formulation, which provides a safe and accurate dose especially for pediatrics, where risperidone is a very potent drug with a narrow safety margin and small dose, dose variation my lead to therapeutic failure or serious central nervous system CNS toxicity especially for pediatrics [34, 35].

Figure 6

Stability studies

Stability study was conducted to examine the effect of storage, over the shelf for 12 months, on the chosen medicated ODMT (F1-F6). Parameters were monitored before and after storage included taste score and drug release as well as hardness.

F2, F3, and F6 revealed stable taste profiles with statistically insignificant change (p>0.05) in taste masking properties, on the other hand, F1, F4 and F5 showed a slight increase in the bitter taste score over the period of storage; where the fluctuation in temperature upon storage may have softened the lipid particles on the tablets surface leaving some uncoated drug particles causing subsequent increase in the bitter taste, this occurs mainly in case of granules of lower lipid ratios; F1 and F4. ODMT containing CA- based granules showed an increase in bitter taste in higher concentration; F5, which may be attributed to the lower melting point of CA compared to HCO.

Figures 7a and 7b showed the release profiles of the selected ODMT formulations containing either HCO or CA – based granules respectively before and after storage for 12 months over the shelf. Results demonstrated that ODMTs containing HCO - based granules; F1-F3, resulted in insignificant increase in the release profiles (p>0.05), while ODMTs containing CA based granules; F4-F6, revealed a slight more increase in the release rate upon storage which may be attributed, as previously mentioned, to the relatively lower melting point of CA which allowed lipid to be softened and to release more drug during the storage period.

A marked increase in tablet hardness was demonstrated upon storage which is most probably due to the softening of lipid by the effect of heat, holding the granules together in the matrix form resulting in harder tablets. However the disintegration time was not markedly affected as the tablets still dissolve in the mouth in less than 30 seconds as reported by the volunteers.

Figure 7a

Figure 7b

Conclusion

Risperidone lipid-based ODMT showed a suitable taste masking potential compared to their risperidone control (without lipids) indicating the efficient taste masking potential of the used lipids. Moreover, they showed a better taste masking potential compared to their corresponding granules due to the positive effect of the used excipients. Two techniques were adopted for preparation of ODMT, sublimation technique was not suitable as it has unacceptable hardness and friability due to their high porous structure, and also heating used for sublimation may be unsuitable for the lipid containing formulations as it may result in softening of the lipid matrix leading to compact tablets with improper drug release. Direct compression using mixture of super-disintegrants showed proper hardness and friability, in addition to suitable disintegration time. Formulae with lower lipid content (F1-F6) maintained a suitable release rates that passed the pharmacopeial requirements. However, formulae with high lipid content (F7 and F8) delayed the release, which may be attributed to the compaction of lipid upon direct compression. Content uniformity showed minimum dose fluctuation compared to the marketed liquid formulation of risperidone, which may guarantee dose adjustment in case of pediatric patients. In additions, The prepared ODMT formulations showed acceptable hardness and friability upon storage in addition to suitable drug release and taste masking potential. Finally, it could be concluded that the prepared risperidone lipid-based granules could be formulated in different ratios by simple techniques and commonly used excipients into taste masked risperidone ODMT with accurate and flexible dose were two doses were prepared (0.1 mg and 0.25 mg).
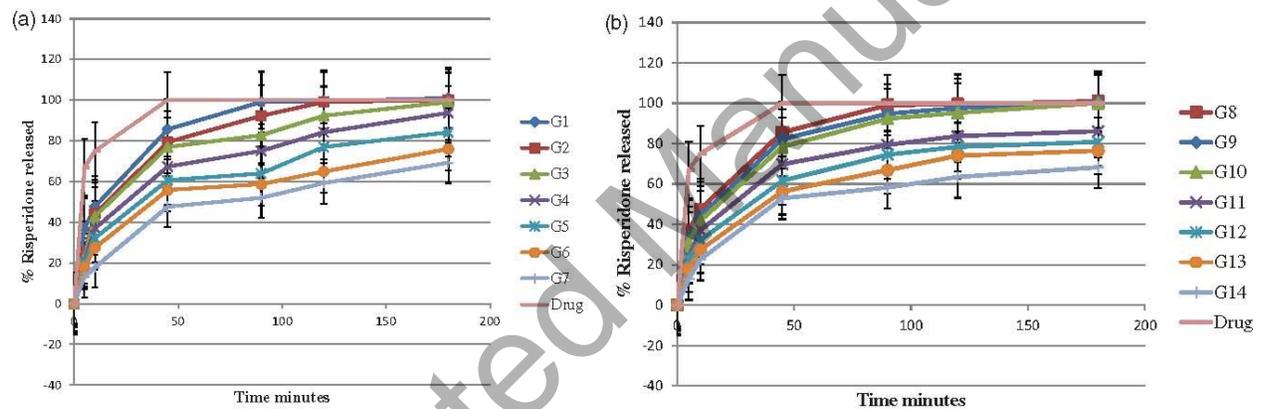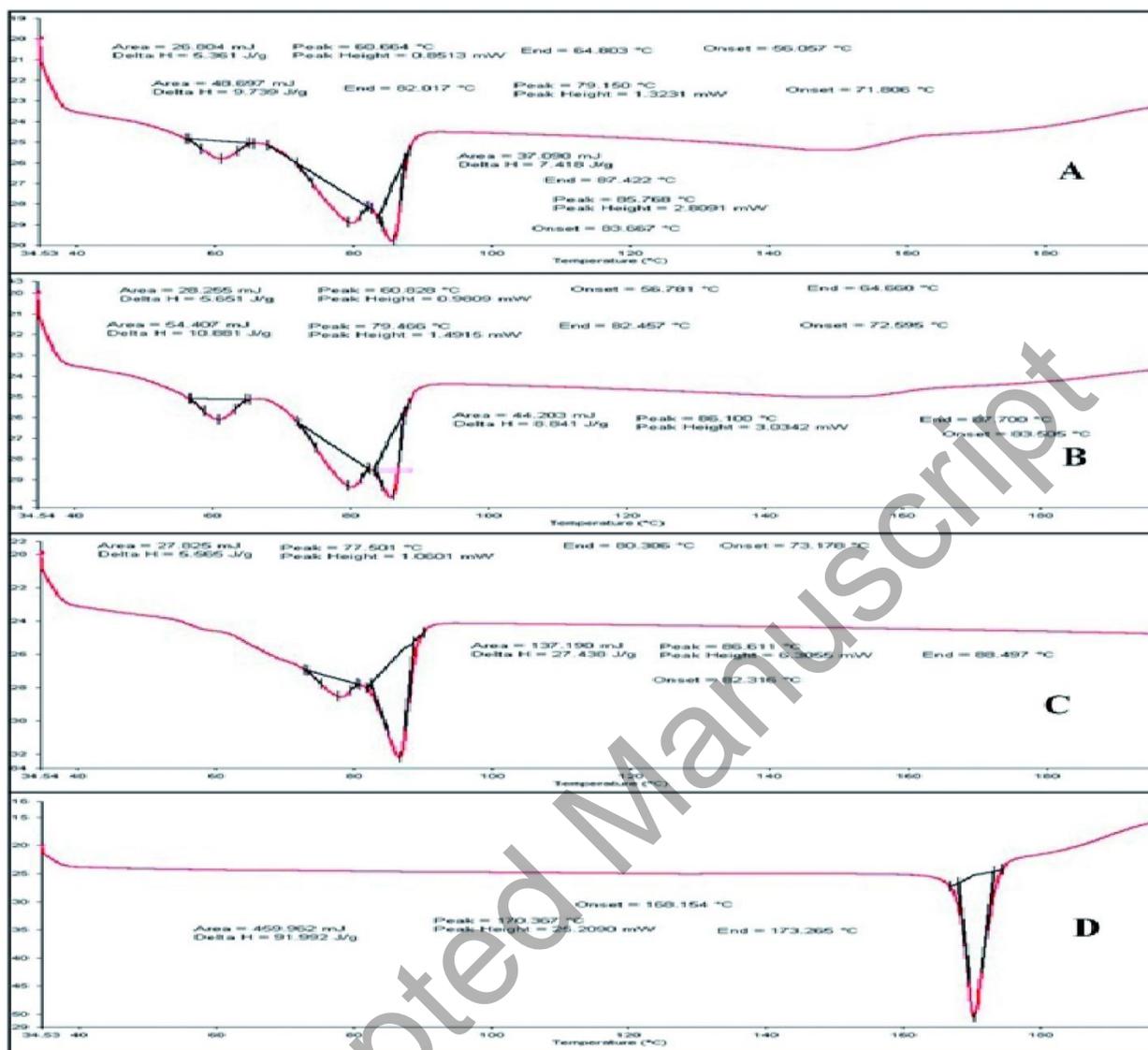
FIGURE CAPTIONS

Figure 1a: Release profiles of risperidone from different Hydrogenated castor oil-based granules compared to release profile of risperidone powder in 0.1 N HCl for 2 hours at 50 rpm at 37 ± 0.5 ˚C

Figure 1b: Release profiles of risperidone from different Cetyl alcohol-based solid lipid granules compared to release profile of risperidone powder risperidone powder in 0.1 N HCl for 2 hours at 50 rpm at 37 ± 0.5 ˚C.

Panel A:
Area = 26.804 mJ   Peak = 60.664 °C   End = 64.803 °C   Onset = 56.057 °C
Delta H = 5.361 J/g   Peak Height = 0.8513 mW

Area = 48.697 mJ   End = 82.017 °C   Peak = 79.150 °C   Onset = 71.806 °C
Delta H = 9.739 J/g   Peak Height = 1.3231 mW

Area = 37.090 mJ
Delta H = 7.418 J/g
End = 87.422 °C
Peak = 85.768 °C
Peak Height = 2.8091 mW
Onset = 83.667 °C

Panel B:
Area = 28.255 mJ   Peak = 60.828 °C   Onset = 56.781 °C   End = 64.660 °C
Delta H = 5.651 J/g   Peak Height = 0.9809 mW

Area = 54.407 mJ   Peak = 79.466 °C   End = 82.457 °C   Onset = 72.595 °C
Delta H = 10.881 J/g   Peak Height = 1.4915 mW

Area = 44.203 mJ   Peak = 86.100 °C   End = 87.700 °C
Delta H = 8.841 J/g   Peak Height = 3.0342 mW   Onset = 83.505 °C

Panel C:
Area = 27.825 mJ   Peak = 77.501 °C   End = 80.306 °C   Onset = 73.178 °C
Delta H = 5.565 J/g   Peak Height = 1.0601 mW

Area = 137.190 mJ   Peak = 86.611 °C   End = 88.497 °C
Delta H = 27.438 J/g   Peak Height = 6.3055 mW
Onset = 82.316 °C

Panel D:
Onset = 168.154 °C
Peak = 170.367 °C
Area = 459.962 mJ   Peak Height = 25.2090 mW   End = 173.265 °C
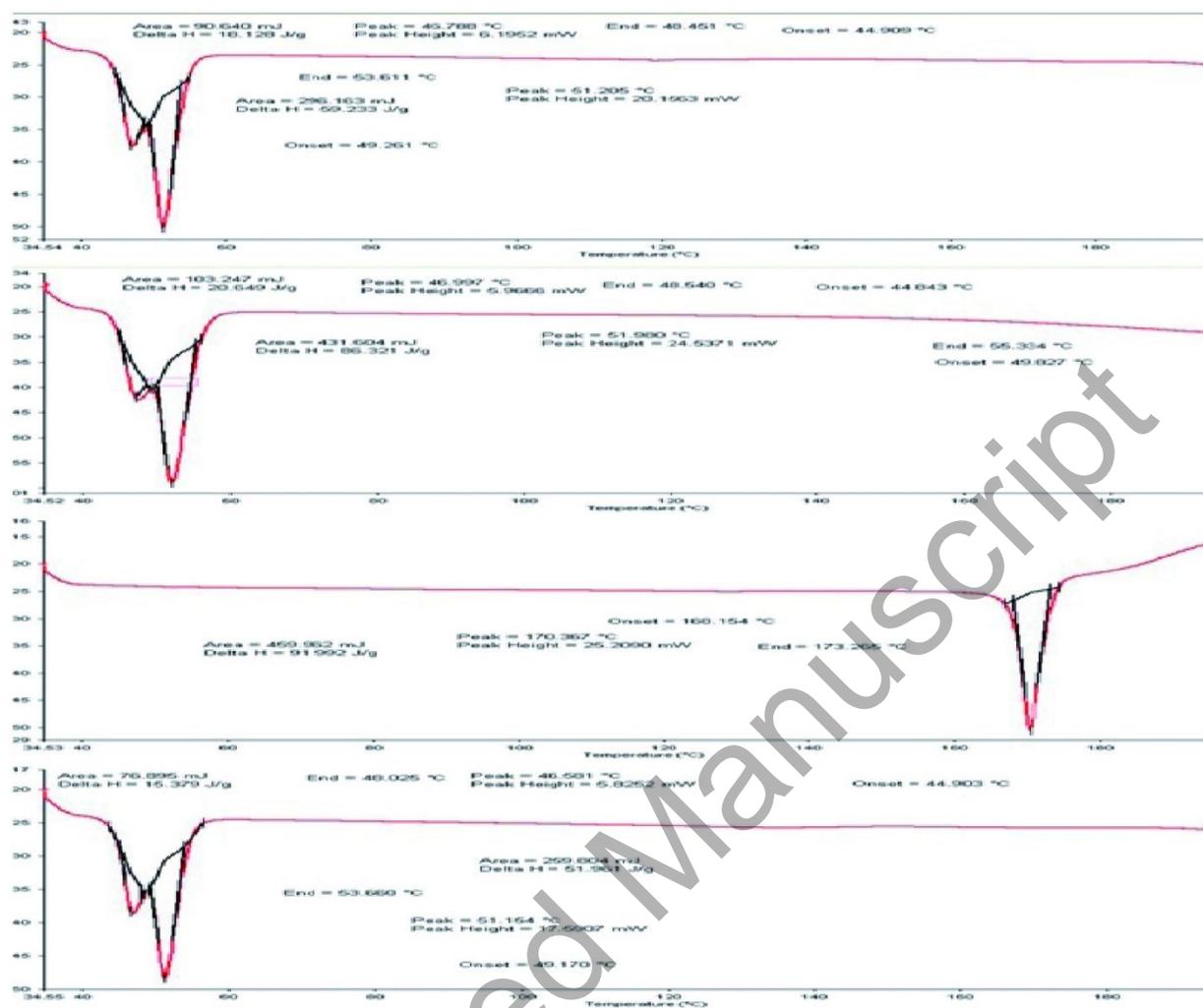Delta H = 91.992 J/g

Figure 2: DSC thermograms, A ➔ G3 (1:3.5 HCO w/w), B ➔ G2 (1:2.5 HCO w/w), C ➔ HCO, D ➔ Risperidone, E ➔ G9 (1:3.5 CA w/w), F ➔ G10 (1:2.5 CA w/w), G ➔ Risperidone, H ➔ CA
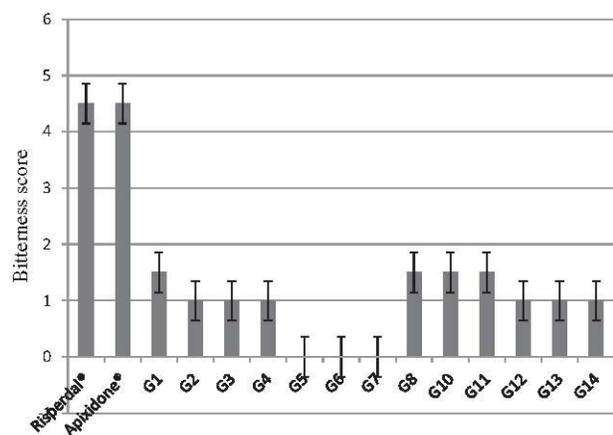
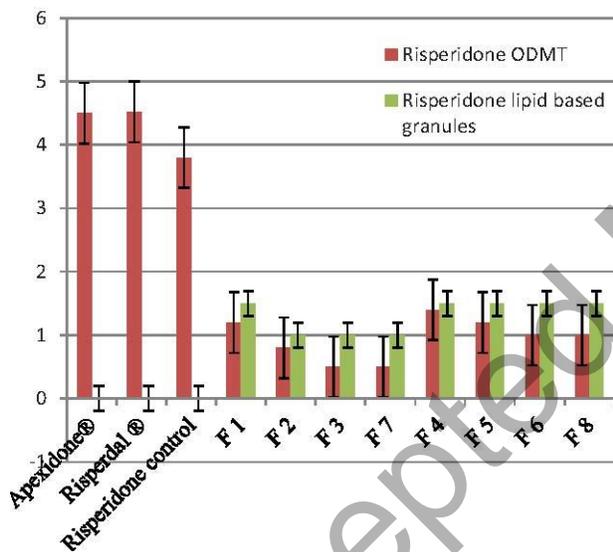Figure 3: Bitterness scores of liquid formulations, and risperidone lipid-based granules (G1 - G14).

Figure 4: Bitterness scores of liquid dosage forms, risperidone ODMT positive control, different ODMT containing risperidone lipid-based granules (F1- F8) & their corresponding risperidone lipid-based granules.
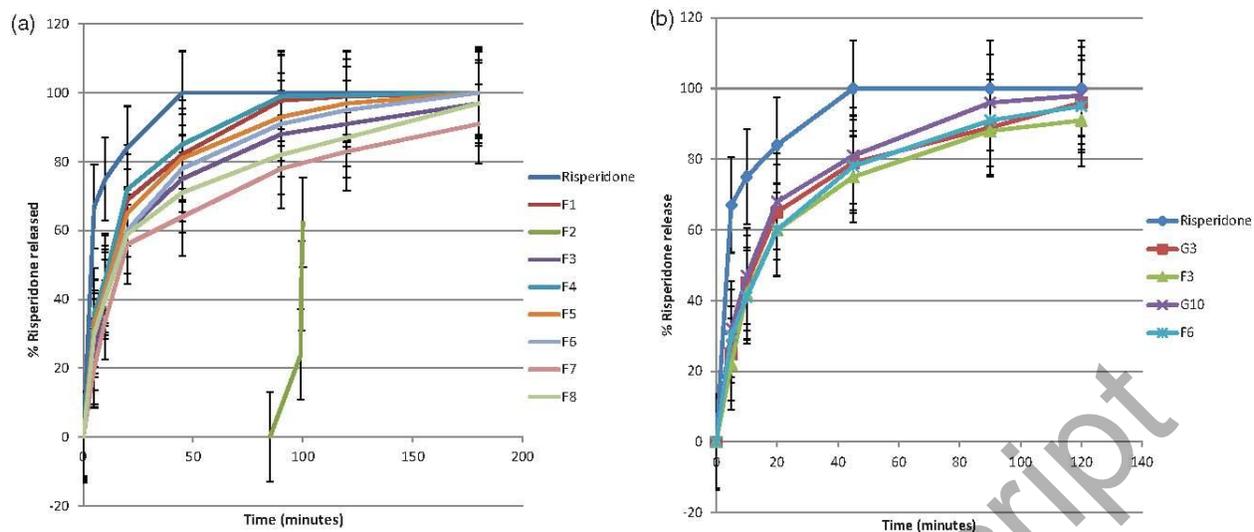
Figure 5a: Release data for different lipid-based risperidone ODMT (F1- F 8) in 0.1 N HCL at 50 rpm & 37°C.

Figure 5b: Release data for lipid-based risperidone granules (G3 and G10) compared to that of the corresponding prepared ODMT (F3 and F6 respectively) in 0.1 N HCL at 50 rpm & 37°C
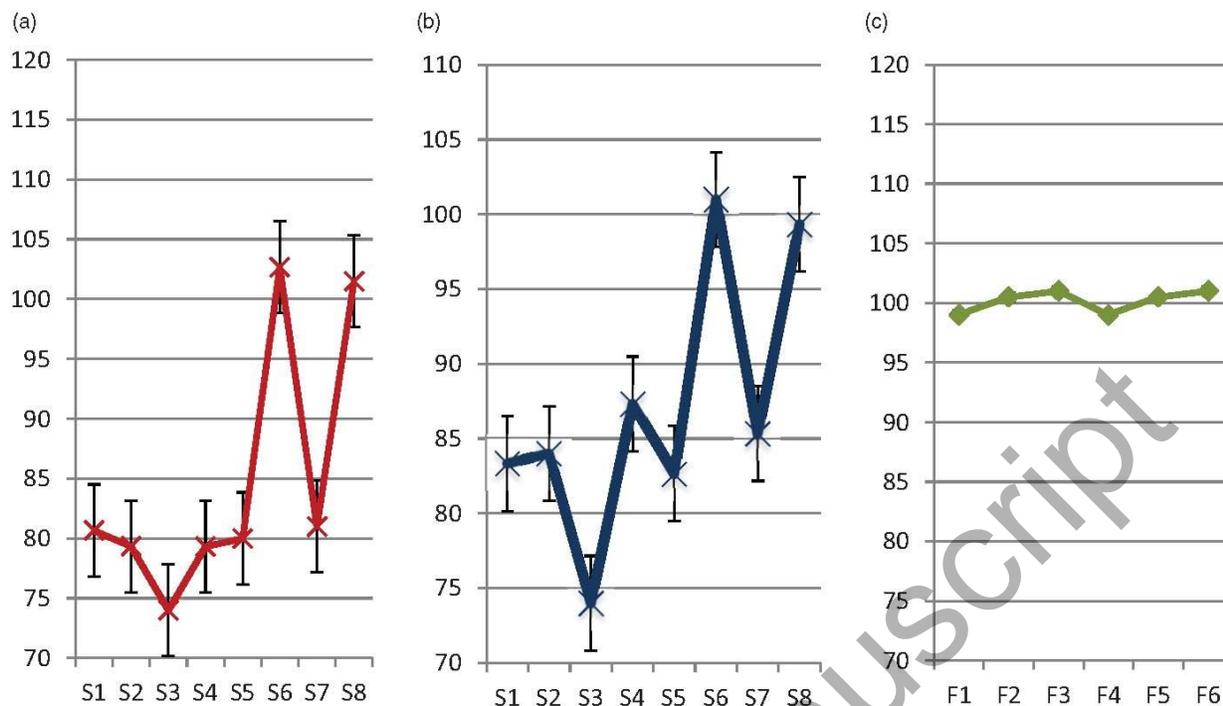
Figure 6: Dosing fluctuation of A) the marketed liquid formulation (A) measured as triplicate by 8 subjects B) the marketed liquid formulation (R) measured as triplicate by 8 subjects C) content uniformity of 10 ODMT (0.1 mg each) measured for 6 formulations (F1'-F6').
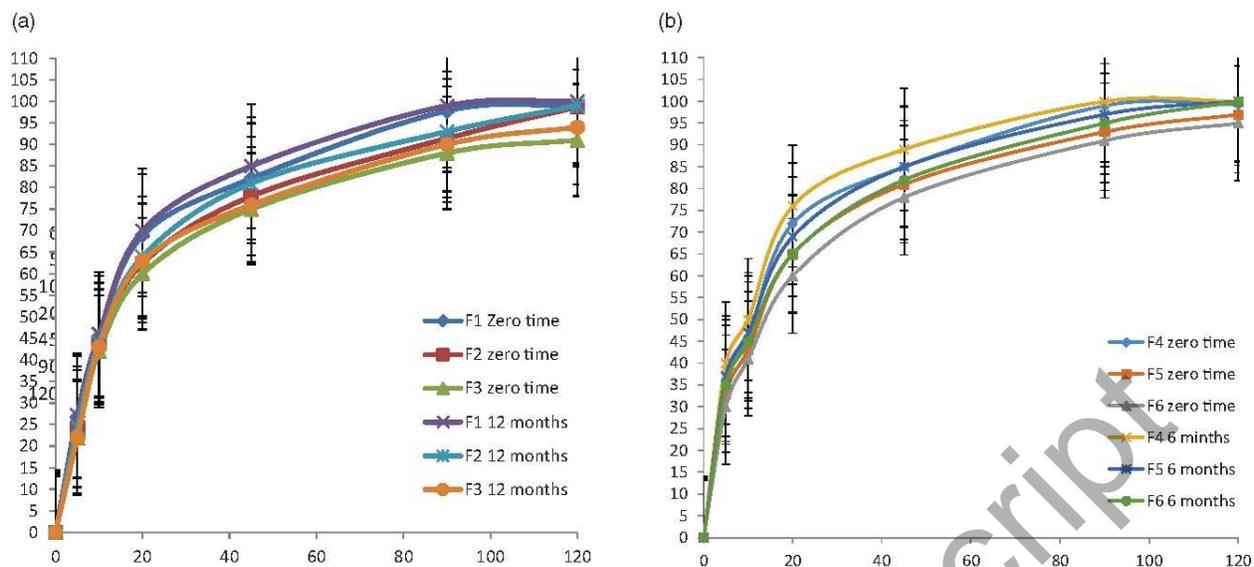
Figure 7a: Drug release profiles of taste masked risperidone ODMT containing HCO- based granules (F1-F3) at zero time and after storage for 12 months over the shelf.

Figure 7b: Drug release profiles of taste masked risperidone ODMT containing CA-based granules (F4-F6) at zero time and after storage for 12 months over the shelf.

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Formula code	Lipid used	Risperidone : Lipid (w/w)
G1		1:1
G2		1:2.5
G3		1:3.5
G4	Hydrogenated castor oil	1:5
G5		1:7
G6		1:10
G7		1:15
G8		1:1
G9		1:2.5
G10		1:3.5
G11	Cetyl alcohol	1:5
G12		1:7
G13		1:10
G14		1:15

Table 1: Composition of different risperidone lipid-based granules