Characterising the Disintegration Properties of Tablets in Opaque Media Using Texture Analysis

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Abstract

Tablet disintegration characterisation is used in pharmaceutical research, development, and quality control. Standard methods used to characterise tablet disintegration are often dependent on visual observation in measurement of disintegration times. This presents a challenge for disintegration studies of tablets in opaque, physiologically relevant media that could be useful for tablet formulation optimisation. In this study is explored an application of texture analysis disintegration testing, a non-visual, quantitative means of determining tablet disintegration end point, by analysing the disintegration behaviour of two tablet formulations in opaque media. In this study, the disintegration behaviour of one tablet formulation manufactured in-house, and Sybedia Flashtab placebo tablets in water, bovine, and human milk were characterised. A novel method is presented to characterise the disintegration process and to quantify the disintegration end points of the tablets in various media using load data generated by a texture analyser probe. The disintegration times in the different media were found to be statistically different ($P<0.0001$) from one another for both tablet formulations using one-way ANOVA. Using the Tukey post-hoc test, the Flashtab placebo tablets were found not to have statistically significant disintegration times from each other in human versus bovine milk (adjusted P value 0.1685).

Key words

Rapidly disintegrating tablet, texture analysis, infant drug delivery, breast milk, Nipple Shield Delivery System, NSDS

Acronyms

Active Pharmaceutical Ingredient (API), Nipple Shield Delivery System (NSDS), United States Pharmacopeia (USP)

1. Introduction

Tablet disintegration properties are characterised during pharmaceutical development to ensure formulation quality following manufacture. Tablet disintegration is also important to characterise because it is a precursor to dissolution (Anwar et al., 2005). Therefore there is a

60 continuing need to characterise tablet disintegration behaviour in vitro to ensure that safe and
61 reliable dosage forms of active pharmaceutical ingredients (APIs) are produced (Donauer and
62 Lobenberg, 2007).

63 Conventional tablet disintegration is characterised using methods harmonised across the
64 U.S. Pharmacopeia (USP), the European Pharmacopoeia, and the Japanese Pharmacopeia. As
65 described by the USP, to perform the disintegration test, tablets are placed in the USP Apparatus A
66 within a basket-rack assembly, churned in water, and visually examined to determine disintegration
67 completion (U.S. Pharmacopeial Convention, 2014a). In this method tablet disintegration is defined
68 as complete when the tablet appears to have no palpable firm core (U.S. Pharmacopeial Convention,
69 2014a). The standard method of visual discernment to assess tablet disintegration time could be
70 complemented with additional quantitative measurement techniques, to aid understanding of tablet
71 disintegration behaviour. This is especially true for fast release formulations, such as rapidly
72 disintegrating tablets, whose high speed of disintegration make visual assessment of disintegration
73 using the USP apparatus challenging. Currently there is no designated method of disintegration
74 characterisation specifically for rapidly disintegrating tablets in any of the three mentioned
75 pharmacopoeias (U.S. Pharmacopeial Convention, 2014a).

76 Experimental quantitative methods for the characterisation of tablet disintegration time has
77 been developed using a texture analyser (Dor and Fix, 2000)(el-Arini and Clas, 2002)(Szakonyi and
78 Zelkó, 2013). Disintegration testing via texture analysis could be broadly beneficial for disintegration
79 testing in opaque media since the technique does not require visually assessing completion of tablet
80 disintegration. Developing quantitative methods for disintegration testing of tablets in opaque
81 media, such as milk and other mixtures present in the digestive system, could further support
82 existing tablet disintegration characterisation methods. This data could be useful for optimising
83 tablet formulations, like those designed to disintegrate in milks, juices, or other opaque media prior
84 to administration. In the described study, texture analysis is used for a novel application, specifically
85 as a method to quantify disintegration time in opaque media. The specific application of developing

rapidly disintegrating and dispersible tablets to be used in a novel breast milk mediated drug delivery system for infants is used as an example for the usefulness of this technique.

During texture analysis disintegration testing, a probe is lowered against a disintegrating tablet in a liquid. In one method, the probe applies a constant load to the tablet and moves at a variable velocity. In another method, the probe moves at a constant velocity while applying a variable load to the tablet. In the constant load technique, the distance travelled by the probe as the tablet disintegrates is recorded (Abdelbary et al., 2005). In the constant velocity technique, a load-displacement curve is generated, from which the in vivo disintegration times have been predicted from an empirical equation (Szakonyi and Zelkó, 2013). Both methods have shown positive correlation with in vivo data (Abdelbary et al., 2005) (Dor and Fix, 2000) (Szakonyi and Zelkó, 2013). In this study, the constant load technique is used to characterize tablet disintegration in opaque media.

Rapidly disintegrating tablets, also known as fast disintegrating or orally disintegrating tablets, have formulations designed to disintegrate entirely in the mouth prior to swallowing. These tablets are defined by their administration method rather than by a disintegration time specification (U.S. Department of Health and Human Services, 2008). Additionally, dispersible tablets, which are administered after dispersion in liquids such as water or milk, also have very fast disintegration times, typically less than 3 min (UNICEF, 2013). There is therefore high patient compliance associated with the administration of rapidly disintegrating and dispersible tablets to children, elderly, and those with dysphagia because they reduce administration complications for populations with difficulty swallowing (Fu et al., 2004).

An administration method for delivering rapidly disintegrating and dispersible tablets specifically to infants has been proposed using a novel Nipple Shield Delivery System (NSDS) (Gerrard, Larson, et al., 2013) (Gerrard, Orlu-Gul, et al., 2013) (Hart et al., 2014) (Sokal et al., 2013). When worn by a mother during breastfeeding, an insert, such as a tablet, is held within the NSDS

and releases an API into breast milk consumed by the infant (Gerrard, Orlu-Gul, et al., 2013) (see Figure 1).

The NSDS could potentially provide a simple method for infant drug delivery and a hygienic and natural means of administering medications to infants. To understand the dosing and drug delivery of potential tablet formulations using the device, their disintegration behaviour in human milk needs to be characterised. A critical design specification for tablets used in the NSDS is that the entirety of the API is released into the breast milk within one breastfeed; therefore, disintegration characterisation of the tablets is especially important.

Characterisation of tablet disintegration in human milk via texture analysis provides a novel method of screening potential tablet formulations for the NSDS. In addition, disintegration testing in bovine milk serving as a fed-state gastric fluid model (Anwar et al., 2005) could prove widely applicable in pharmaceutical development.

2. Materials and methods

Characterisation of tablet disintegration was performed through analysis of position and load data of a texture analyser probe applying constant load to tablets disintegrating in various media.

2.1 Media

Disintegration was characterised in a variety of media including deionised water, human milk, and bovine milk. The three media used in the study were chosen due to their relevance in previous disintegration characterisation literature and their applications in facilitating tablet disintegration in numerous applications.

Water was selected because it is the media used in USP disintegration characterisation, and has been used in the literature for texture analysis disintegration testing previously (Abdelbary et al., 2005)(Dor and Fix, 2000). It is frequently used to dissolve and disintegrate tablets in a variety of applications including drug delivery, by facilitating reconstitution of dispersible tablets prior to administration.

Human milk was selected because thorough understanding of tablet disintegration behaviour in this fluid is critical to formulation development of tablets to be used in the NSDS. Other methods of characterising tablet disintegration behaviour in human milk is challenging since human milk is not transparent, obstructing visual observation. Therefore, to determine if texture analysis could be applied to screening tablets for development of dosage formulations appropriate for the NSDS, human milk was tested as one of the media.

The human milk was obtained from 10 healthy donors (screened negative for HIV 1 and 2, HTLV I and II, Hepatitis B and C, and Syphilis) who had consented for their milk to be used for research. The Cambridge Human Biology Research Ethics Committee at the University of Cambridge provided ethical approval for all human milk sample use. All of the milk was centrifuged (Sigma-Zentrifugen, Osterode, Germany) for 15 min at 5500 RPM, from which the fat later was removed and into which the protein layer was resuspended to produce fat-free milk. Milk batches of various fat compositions were produced through mixing various proportions of fat and fat-free milk, from which one composition was selected for use in this study (3.4 wt% fat, 1.8 wt% protein, Queen Charlotte's and Chelsea Hospital Milk Bank). Protein content was measured using a standard Bradford Agent (Sigma Aldrich, Dorset, UK) assay (Bradford, 1976).

Human milk fat content is highly variable, with average fat content varying between colostrum, transitional, and mature milk. The averages range from 2.6 w/v% to 4.1 w/v% depending on the time of day, the number of days post-partum, the time within the feed, and the mother (Emmett and Rogers, 1997). The composition of human milk for the study was chosen such that the fat content fell within this physiologically relevant range. Prior to the experiments, the human milk was thawed from -80 ˚C storage in a 3 ˚C refrigerator for 2 days.

The human milk fat content was calculated based on creamatocrit measurements performed on 1 mL milk samples centrifuged (Sigma-Zentrifugen) for 15 min in 4.6 mm inner diameter, 80 mm length tubes at 930g. Creamatocrit values were used in Wang et al.'s creamatocrit to fat correlation for thawed samples stored at -20 ˚C (Wang et al., 1999). The milk was thawed from -80 ˚C and this

correlation is assumed to adequately assess fat content for these conditions (Gerrard, Orlu-Gul, et al., 2013).

Bovine milk, a fluid which has been used to simulate fed-state stomachs in the literature (Jantratid et al., 2008), was selected because fluid conditions in the stomach are important to consider for characterisation of tablet medications which are swallowed whole and intended to disintegrate in the stomach. Like human milk, bovine milk, being opaque, is also challenging when used in disintegration characterisation methods which rely on visual observation. Therefore texture analysis testing, by providing an analytical method of determining disintegration end points, is advantageous for this fluid.

The bovine milk used in the study was pasteurised, homogenised, bovine milk (Whole Cow Milk, 4 w/v% fat, 3.3 w/v% protein, J.S. Sainsbury's, Cambridge, UK), which was thawed from -80 ˚C storage in a 3 ˚C refrigerator for 2 days prior to use.

2.2 Tablet formulation

Commercial grade as well as tablets manufactured in-house were characterised. Sybedia Flashtab placebo biconcave tablets with a proprietary composition were supplied by Ethypharm (Le Grand Quevilly Cedex, France). Biconcave directly compressed tablets containing Sulforhodamine B, hereafter referred to as SRB tablets, were formulated in-house using the components listed in Table 1. The SRB tablet excipients were chosen based on pre-existing formulations for rapidly disintegrating tablets (Charoo et al., 2012). These tablets serve as model tablets for NSDS development.

The SRB tablets were formulated by initially blending the filler, model compound, and superdisintegrants, followed by blending in the lubricant, sieving at 500 μm, and blending a final time. The powder blend was directly compressed using a Manesty F3 tablet press (Manesty, Liverpool, UK) with a biconvex 80 single punch and die set (Holland, Nottingham, UK).

2.3 USP characterisation of tablets

All tablets were physically characterised using USP methods, aside from the modification that disintegration testing was performed individually on each tablet rather than in a set of six. This modification to the USP method allowed more accurate discernment of the standard deviation of the average disintegration time since the tablets disintegrate so rapidly. This disintegration testing was performed using a disintegration apparatus with a basket rack assembly (Copley, Nottingham, UK). Tablet length, width, and height were measured using calipers. Crushing force was tested using an Erweka TBH200 hardness tester (Heusenstamm, Germany) with the tablets oriented diametrically. Physical characterisation data are shown in Table 2.

2.4 Texture analysis characterisation method

Texture analysis disintegration characterisation was performed using a TA.XT*plus* Texture Analyser (Stable Microsystems Ltd., UK) equipped with a 14.23 mm diameter probe set to maintain a constant load of 50g. The load value chosen was found to sufficiently hold the tablets in place during each experiment, and has been used in other texture analysis studies (Abdelbary et al., 2005). Exponent Software (Stable Microsystems Ltd., UK) was used to monitor the probe lowering distance and applied load over time as each tablet disintegrated.

During each test, a tablet was attached vertically to the probe using double-stick tape (Sellotape, Winsford, UK). This tablet orientation served to increase the surface area of tablet exposed to media when compared to the horizontal tablet orientation used in other studies (Abdelbary et al., 2005) (Dor and Fix, 2000) (Szakonyi and Zelkó, 2013) so as to more accurately represent the orientation of a tablet during use in a NSDS. Upon probe lowering, the tablet was immersed into 31 mL of media pre-heated to 37 ˚C using a hot plate (Gallenkamp, UK) in a 50 mL beaker. Immediately before experiments commenced, the beaker was moved to the texture analyser held at laboratory temperature, resulting in a media temperature always above 32˚C throughout the experiments. This temperature range includes the range of temperature of artificial saliva mimicked in a previous texture analysis study (Abdelbary et al., 2005) and is relevant to the physiological temperature range of human milk in the NSDS. Media volume was chosen to ensure

complete tablet immersion in the beaker. The platform contained concentric holes to minimize accumulation of disintegrated tablet material during testing and therefore more closely mimic the removal of disintegrated tablet that would occur in vivo or during delivery using the NSDS. The hole diameter and spacing was chosen based on ease of manufacture. The centre of the platform remained non-perforated to prevent the tablet from being pressed through the platform by the probe during testing. A diagram of the apparatus is shown in Figure 2.

Statistical analysis of the results was performed using GraphPad Prism (La Jolla, California, USA).

3 Results and discussion

3.1 Disintegration characterisation analysis method

Two sets of data over time were collected during the experiments including the texture analyser probe's vertical movement and the applied load by the probe. These data profiles were compared against each other in post-experimental analysis.

Three regions of the probe distance-time profile have been previously defined in the literature, termed the initial region (I), the ascending region (A), and the plateau region (P) as designated in Figure 3 (Abdelbary et al., 2005) (el-Arini and Clas, 2002). Previous studies have shown one ascending and one plateau region per tablet tested. In these previous studies, the critical point between the ascending and plateau region was defined as the termination of disintegration and used to calculate the onset of disintegration. This was based on extrapolation from the slope of the ascending region (Dor and Fix, 2000). At that critical time point, the probe plateaued because it could lower no further due to resistance from the platform.

Probe load was maintained over all time apart from when the load measured decreased momentarily when the tablet integrity was compromised. These local load minima were due to inherent lags in the feedback response of the system to changes in the tablet structure as disintegration occurred. The load then returned to the set value (as the probe moved further down into the beaker). This was due to resistance from the remaining portion of tablet being detected in

240 the load feedback loop used by the texture analysis software. When the load applied by the probe
241 was superimposed over the position data over time it became evident that load minima occur during
242 time frames of increased probe movement rate.

243 As with the USP disintegration experimental method, it was hypothesised that tablet
244 disintegration commenced from the moment of tablet contact with the media. Specifically for the
245 described method, tablet disintegration was considered to likely be occurring during the initial
246 region (I) due to mechanisms such as dissolution and material loss following tablet hydration. The
247 ascending region, labelled A in Figure 3, was then assumed to occur due to substantial tablet
248 fracture. This assumption was supported by load data, which indicated that there was a loss in tablet
249 integrity to resist the probe in this region. This drop in load would be expected from a sudden
250 change in tablet morphology such as tablet fracturing.

251 In some cases there were multiple ascending and plateau regions, as shown in Figure 4. The
252 detected local load minima in the ascending regions were hypothesised to indicate partial fracturing
253 of the tablet. This was hypothesised because maintenance of constant load would be expected to be
254 compromised due to sudden changes in the tablet owing to cracking. Following partial tablet
255 cracking the probe then regained the specified load against the remaining tablet core, causing a
256 plateau region. This observation suggests that partial disintegration of tablets and therefore tablet
257 structure can be quantifiably characterised using this previously unstudied novel method.

258 Since a disintegrated tablet is defined according to the USP 37 (U.S. Pharmacopeial
259 Convention, 2014a) by a lack of palpable core, tablet disintegration could therefore be defined as
260 complete at the time point corresponding to the local load minima within the final ascending region
261 (A). This is the time point at which the last remaining remnant of tablet core has been compromised.

262 The final plateau then corresponded to the probe pressing down on remaining disintegrated
263 tablet and the platform. Total disintegration time was calculated by summing the time from the
264 initiation of the initial region to the disintegration end-point with the time over which the tablet was
265 lowered into the media. The tablet lowering time, beginning with tablet to media contact, was

calculated using the height of the media above the platform and the speed of the probe as the tablet lowered. In this study, the lowering time was 2.6s. This value could be changed through manipulation of opaque media volume, beaker size, or platform height in future studies to study the impact on tablet disintegration. To our knowledge, this method is the first to use both position and load data in this way to identify absolute end points for disintegration.

3.2 Results of texture analysis disintegration characterisation using various media

Probe position data resulting from the texture analysis study of the SRB tablets and Flashtab placebo tablets in water, bovine milk, and human milk differ as shown in Figure 5. The tablet disintegration times, as identified using the described load data method, for which white markers are shown in Figure 5, are listed in Table 2.

During experimentation, it was expected that after the first observed ascending region, tablet disintegration would be complete, but further data analysis and longer experimental data collection demonstrated that the assumed palpable core was still present in many cases afterwards. This could be discerned by observing the total change in probe distance, which should be close to but not equal to the diameter of the tablet. The probe was not expected to move the entire tablet diameter distance because broken up tablet material remains at the end of testing preventing probe contact with the platform. It should be noted that this strategy of observing total probe movement can be used in order to assess completion of testing in future studies. Data sets for which complete disintegration did not occur were not analysed in this study, leading to varying sample sizes.

One Ethypharm Flashtab placebo tablet disintegrating in bovine milk as well as one in human milk stand out as having different position-time profiles than the others, as shown in Figure 5. These tablets are believed to have undergone disintegration in a different way than in the other tablets, potentially due to inherent internal or structural weaknesses leading to more large fractures, as suggested by the multiple ascending and plateau regions. These differences are clear using the texture analysis data, and provide additional understanding of disintegration behaviour to what

potentially would be observed using USP testing. This is hypothesised because the behaviour is identified before complete disintegration, the parameter tested in the USP method.

Considering that all tablets disintegrated within 6 min using the texture analyser, this method has demonstrated itself to be a comparable method to assess tablet disintegration behaviour to USP testing in terms of time-burden. Since each tablet must be tested individually though, this method takes more time than the USP method, in which six tablets are typically tested in parallel (U.S. Pharmacopeial Convention, 2014a).

In general, the SRB tablets disintegrated in a longer time frame than the Flashtab placebo tablets, and showed variability in repeat testing for various media types. This is likely due to compositional, geometry, size, surface area, and manufacturing method formulation differences between the tablets resulting in varying pore structures and tablet disintegration characteristics. Future testing would be necessary to determine the main cause of variability.

Based on one-way ANOVA, the disintegration time of the SRB tablets in the different media were found to be significantly different ($P<0.0001$), as were those for the Flashtab Placebo tablets ($P<0.0001$). Based on the Tukey multiple comparisons test, the SRB tablets and Flashtab Placebo tablets disintegration times were each statistically different in each milk compared to water, disintegrating faster in water (adjusted P value <0.0001 for both tablets). Based on this test, the disintegration time of the SRB tablets in each milk media were significantly different from one another also (adjusted P value <0.0001), disintegrating faster in human milk than bovine milk. The Tukey multiple comparisons test indicated that the Flashtab Placebo tablets had no significant difference between the disintegration times for the two milk media (adjusted P value = 0.1685). For each condition, the standard deviation of the average disintegration time was relatively small, indicating robustness of the method for reproducibly determining tablet disintegration times.

Differences in media viscosity, surface tension, and composition, as well as contact angle to the tablet are likely dominating factors in influencing tablet disintegration due to their influence on liquid penetration rates into the tablet (Abrahamsson et al., 2004) (Anwar et al., 2005). Tablets have

been shown to disintegrate slower in bovine milk than in water due to higher viscosity and lower surface tension that cause a decrease in liquid penetration rate, preventing wetting (Anwar et al, 2005). Whereas the viscosity of water and bovine milk is different (reported as 0.6915 mPa·s and 1.3 mPa·s, respectively) (Anwar et al, 2005), that of bovine and human milk (averaging 1.35 mPa·s - 1.5 mPa·s) is less so (McDaniel et al., 1989). This suggests viscosity may not be the main cause for the differing disintegration times of the SRB tablets between each milk media. Compositional differences between the media may have led to differing tablet disintegration times. Protein presence in media has been shown to have a large effect on tablet disintegration time due to protein and carbohydrate film formation on the tablets preventing liquid penetration (Abrahamsson et al, 2004). Protein concentration in the human and bovine milk differed (being 1.8 wt% and 3.3 w/v%, respectively), which may have caused differing film formation on the SRB tablets, resulting in differing tablet disintegration times. It is noted that fat content of the media, being 3.4 wt% for the human milk and 4 w/v% for bovine milk, were similar, and so are unlikely to be a main cause of tablet disintegration time variability.

Future studies assessing tablet disintegration in various other opaque media using texture analysis could be performed, such as fruit juices or other solutions to which tablets used as medicines, vitamins, minerals, or flavour enhancers are added. Studies which assess the impact of manufacturing processes on tablet solid fraction and the resulting tablet disintegration time uniformity could also be completed. These studies could be valuable in setting manufacturing specifications such as tableting compression values. Disintegration testing in opaque media could have wider implications outside of pharmaceutical commercialisation as well, such as for characterisation of tablets added to opaque emulsions, solutions, or mixtures in commercial processes. Additionally, texture analysis testing of tablets in mixing liquids could be performed to understand how media movement impacts tablet disintegration. These tests may serve to mimic the solution movement which may be present during various tablet disintegration processes, such as the

342 stirring of a media to which a tablet has been added, or the churning of the stomach into which a
343 tablet enters.

344 **4 Conclusion**

345 Assessment of tablet disintegration properties has been shown possible in opaque fluids
346 using texture analysis disintegration testing. This technique allows for quantitative determination of
347 disintegration end point times independent of observation. This is especially beneficial for
348 characterising disintegration of rapidly disintegrating and dispersible tablets, for which
349 characterisation can be challenging due to the fast speed at which the tablets disintegrate
350 complicating visual discernment of disintegration completion end point times in the USP method.
351 Additionally, this study demonstrates a novel analytical method of assessing data collected in the
352 constant load texture analysis method. In this method, load data is shown to be useful for
353 characterisation of tablet fracturing behaviour prior to complete tablet disintegration, a phenomena
354 which is not quantitatively measurable using USP methods. By identifying time points corresponding
355 to local probe load minima during the constant load texture analysis technique, corresponding
356 hypothesised instances of tablet fracture are identified. Final tablet disintegration is then defined as
357 complete following the time point corresponding to the final tablet fracture.

358 The results of the study have shown texture analysis could be useful in further characterising
359 the disintegration behaviour in human milk of potential tablet formulations for use in a nipple shield
360 delivery system, a novel method for delivery of life-saving medications or nutrients to breastfeeding
361 infants. Various supplemental or therapeutic tablet formulations could be studied in human milk
362 with compositions ranging in fat and protein content to robustly characterise potential formulations
363 in the range of conditions which may be present resulting from breastfeeding. Additionally, this
364 texture analysis method could allow for characterisation of tablet formulations in opaque media for
365 other commercial development purposes. Generally, this method could be used to assess the
366 likelihood of internal tablet fracture resulting from various tablet manufacturing methods. This
367 information could be used to define tablet solid fraction specifications and corresponding tablet

manufacturing process specifications. Further method development studies could also be performed to determine how load induced by the probe during testing may impact tablet disintegration uniformity for tablets in the presented vertical orientation, as has been performed with tablets placed horizontally in other texture analysis studies (Dor and Fix, 2000).

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Figure Captions

Figure 1. An illustration of the Nipple Shield Delivery System (NSDS) during use delivering an active pharmaceutical ingredient (API) into an infant during breastfeeding – provided courtesy of justmilk.org.

Figure 2. Illustrations of Experimental Setup. (a) Demonstration of the attachment of the tablet in a vertical orientation to the texture analyser probe. (b) Platform diagram (2)

Figure 3. Texture analyser probe data from the point of tablet contact with the platform for a single trial of a SRB tablet disintegrating in water. The initial, ascending and plateau regions are labeled I, A, and P, respectively, as based on the labeling conventions of Abdelbary et al.. (a) Position data. (b) Position data overlaid with load data.

Figure 4. Texture analyser probe data from the point of tablet contact with the platform for a single trial of a Sybedia Flashtab placebo tablet disintegrating in human milk. The initial, ascending and plateau regions are labeled I, A, and P, respectively, as based on the labeling conventions of Abdelbary et al.. (a) Position data. (b) Position data overlaid with load data.

461 Figure 5. Probe position data during texture analysis disintegration testing from the point of tablet to
462 platform contact. (a) SRB tablets and (b) Sybedia Flashtab placebo tablets in (i) Water, (ii) Bovine
463 Milk, and (iii) Human Milk. Calculated disintegration end points are shown as white circles (o).