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International Journal of Pharmaceutics 290 (2005) 121–127
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

An investigation of the disintegration of tablets in biorelevant media

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Received 19 July 2004; received in revised form 23 November 2004; accepted 23 November 2004

Abstract

The purpose of the study was to examine the disintegration of tablets in media designed to simulate conditions pertaining in the stomach. Although many studies have been performed to determine dissolution rates in these media, little work has been undertaken on the preliminary step in dissolution, namely disintegration.

Two tablet formulations were prepared. One disintegrated rapidly (under 25 s in water) and the other more slowly (8 min in water).

The disintegration times were measured by the BP 2000 test using discs. For the rapidly disintegrating tablets, disintegration times were similar in all media except for whole milk. This media is used to simulate the fed stomach and disintegration times were over five times longer than in the other media ($P < 0.05$). A similar effect was seen with the poorly disintegrating tablets in milk, and prolonged times were also observed in some of the other media. For these latter media, there was a good correlation between the penetration rate of the fluid into the tablet and the disintegration time. Penetration rates for milk were also slow which may be a reflection of its relatively high viscosity and low surface tension.

Keywords: Disintegration; Tablets; Simulated gastric media; Penetration

1. Introduction

The advent of the Biopharmaceutics Classification System (BCS) has lead to the reassessment of compendial dissolution test media in order to provide good predictability of the in vivo performance of a dosage form (Amidon et al., 1995). Current compendial in vitro test conditions are not designed to simulate the physiological environment of the gastrointestinal tract, particularly with respect to fluid composition and intensity of agitation. Thus compliance with compendial tests does not necessarily guarantee an ability to predict in vivo performance from in vitro data (Horter and Dressman, 1997). Simple media are of value for quality control

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doi:10.1016/j.ijpharm.2004.11.023

purposes and adequate for predicting the performance of highly soluble compounds which is, to a large extent, the basis of biowaver guidelines (CPMP, 1998; FDA, 1999), but may be inadequate for less soluble compounds.

The need for more predictive in vitro test methods has lead to the development of physiologically relevant dissolution media, which attempt to mimic the in vivo conditions of the gastrointestinal tract. Several physiologically relevant media have been proposed which have resulted in improved in vitro–in vivo correlations (IVIVCs) compared to the standard tests employed at present (Dressman et al., 1998; Galia et al., 1998).

The dissolution rate of a drug from a tablet results from a combination of the physico-chemical properties of the drug itself and the disintegration of the tablet. It is therefore of value to study the disintegration step in isolation, in order to examine the influence of physiologically relevant media on the preliminary step in the overall dissolution process. Additionally, disintegration is frequently used as an initial screen for formulations in development and a study of the influence of biorelevant media may lead to more clinically relevant tests.

Lowenthal (1972), cites a number of studies examining the disintegration of tablets, under various conditions using different formulations, the results of which showed little or no difference in disintegration times between water, diluted HCl solutions, simulated gastric and intestinal juices or sodium bicarbonate solutions. X-ray studies used to determine in vivo disintegration showed that there was a low degree of agitation in the stomach and thus, tablets which disintegrated in 30–40 min in vitro, reportedly disintegrated in >2 h in vivo, resulting in a lack of correlation with in vivo performance (Lowenthal, 1972). More recent studies regarding disintegration (Weitschies et al., 2001a,b) have attempted to evaluate the disintegration process in vivo rather than to establish more biorelevant disintegration tests and IVIVCs. Abrahamsson et al. (2004) found that tablet disintegration was delayed in simulated gastric fed media compared to a simple buffer both in vitro and in vivo. This delay appeared to be due to a film formed by precipitation on the tablet surface. These authors also inferred that the slower dissolution of drugs in milk, observed by Galia et al. (1998) and Macheras et al. (1986), was due to a delay in tablet disintegration as the drugs involved were highly soluble.

Compendial disintegration tests currently state water or 0.1 N HCl as the test media, and, as such, may lack physiological relevance from the viewpoint of composition and also agitation level. As the majority of tablets are designed to disintegrate in the stomach, the aim of this study was to evaluate the disintegration times of two tablet systems (rapidly disintegrating and poorly disintegrating) in simulated gastric media, previously proposed in the literature, in order to establish the influence of complex media on disintegration. The wetting properties of the proposed media were evaluated through the determination of the surface tension and contact angles using poly(methylmethacrylate) (PMMA) as a model surface (Luner and VanDer Kamp, 2001). The viscosities and penetration rates of the various media were also determined in order to assess whether there was any correlation between the physical data obtained and the disintegration times observed in the physiological media. This work is intended to establish relevant physico-chemical parameters influencing tablet disintegration prior to examination of the process in vivo.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH102, FMC, Belgium), lactose (Tabletttose 80, Meggle, Germany) and sodium starch glycollate (Explotab, Penwest Pharmaceuticals, USA) and magnesium stearate (BDH, UK) were used as received, for the tablets.

Lactic acid, pepsin A, sodium chloride, sodium citrate, sodium lauryl sulfate were all purchased from BDH, UK. Sodium malate and triton X-100 were obtained from Sigma–Aldrich, UK. The long life whole milk used contained 3.5% fat.

2.2. Preparation of tablets

Two sets of tablets were prepared representing a rapidly disintegrating system (35% microcrystalline cellulose: 61% lactose: 3% magnesium stearate, 1% sodium starch glycolate) and a poorly disintegrating

Table 1
USP simulated gastric fluid

Sodium chloride	2 g
Pepsin	3.2 g
HCl (10.2 M)	7.0 ml
Distilled water	To 1000 ml

Table 2
Media of Ruby et al. (1996); simulating gastric conditions (AGF)

5 M HCl	pH
Pepsin	1.25 g
Sodium citrate	0.5 g
Sodium malate	0.5 g
Lactic acid	420 μl
Acetic acid	500 μl
Distilled water	To 1000 ml

system (95% microcrystalline cellulose, 5% magnesium stearate). Tablets (0.5 g) were prepared manually in a 1.27 cm diameter flat-faced punch and die, using a hydraulic press (Beckman, UK) at a compression force of 3000 kg.

2.3. Preparation of media

Simulated gastric fluid was prepared according to the USP 23 with (SGF) and without pepsin (SGFsp). A further artificial gastric fluid (AGF) was prepared according to Ruby et al. (1996) at pH values of 1.2, 2.0 and 3.0 by adjusting the quantity of HCl and checking with a calibrated pH meter (Hanna pH 210, USA). The simulated gastric fluid of Dressman et al. (1998); was prepared with the addition of either Triton X-100 (SGF + 0.1%T) or sodium lauryl sulfate (SGF + SLS). The compositions of the above media are summarized for comparison in Tables 1–3.

2.4. Determination of surface tension

Surface tension values were determined by the Wilhelmy Plate method, utilising a platinum plate suspended from a microbalance (White Electrical Instruments Company Ltd., UK) accurate to 1 mg. The temperature of the media was maintained at $25 \pm 0.1\,^{\circ}C$ using a circulating water bath. The mean surface tension for each medium was calculated from an average of three readings taken from each of three separately prepared solutions.

Table 3
Media of Dressman et al. (1998); simulating fasted gastric conditions

HCl (10.2 M)	0.05 M
Sodium lauryl sulfate	2.5 g
Sodium chloride	2.0 g
Distilled water	To 1000 ml

2.5. Determination of contact angles

Contact angles were measured using the sessile drop technique on an ideal surface (PMMA) (prepared as described by Luner and VanDer Kamp, 2001), and on each of the tablet surfaces. Contact angle measurements were obtained using a microscope fitted with a protractor eyepiece and mounted on an optical bench. Measurements were repeated in duplicate for 10 readings in each run taken immediately after placing the drop on the solid surface. All solutions were passed through a 0.45 μm membrane filter (Millipore) prior to taking readings.

2.6. Determination of viscosity

The viscosity of the media was determined using a calibrated U-tube viscometer at a temperature of $37\,^{\circ}C$ using a thermostatically controlled water bath (Townson & Mercer E270 series, UK). Flow times were determined for each sample a minimum of 3 times until readings agreed within 0.5 s, and for at least three separately prepared solutions. The mean flow times and standard deviations were then calculated.

2.7. Penetration rate studies

The method used has been described by Wan and Heng (1987). The results are the mean of 20 separate measurements.

2.8. Disintegration time

The standard BP test (British Pharmacopoeia, 2004) with discs was employed to assess the disintegration times, using an Erweka Disintegration tester (model ZT31, Germany). Tests were carried out in 800 ml of the various media at $37 \pm 0.5\,^{\circ}C$. All tests were run in triplicate using six tablets for each test.

Table 4
Viscosities and surface tensions of biorelevant media

Medium	Kinematic viscosity (cP)	Surface tension (m/Nm^{-1})
Distilled water	0.6915	64.26
0.1 N HCl	0.7048	67.83
SGFsp	0.7054	69.7
SGF (USP 23)	0.7132	50.81
SGF + 0.1%T	0.7051	30.83
SGF + SLS	0.7085	33.3
AGF pH 1.2	0.7122	51.8
AGF pH 2.0	0.7096	50.07
AGF pH 3.0	0.7089	50.58
Whole milk	1.30	42.92

3. Results

3.1. Surface tension, viscosity and contact angle

Table 4 shows the mean values obtained for the surface tensions and viscosities for all the media. The only medium showing a significantly different viscosity value is whole milk. Surface tension values reflected the addition of surfactants. Media containing pepsin and milk also exhibited relatively low values.

Table 5 shows the mean contact angles for the biorelevant media on all three surfaces. The contact angles measured on PMMA and the tablet formulations were broadly similar. The exceptions were the lower contact angles formed with media containing surfactants and the higher angles obtained with whole milk.

3.2. Penetration rate studies

Figs. 1 and 2 illustrate the volume of liquid penetrated with time for the rapidly and poorly disintegrating tablets, respectively. For the rapidly disintegrating tablets, penetration was similar for most of the media, the exceptions being distilled water and whole milk that gave the fastest and slowest penetration times, respectively. For the poorly disintegrating tablets, the media all showed different rates of penetration with whole milk again exhibiting the slowest rate.

3.3. Disintegration times

Table 6 shows the average disintegration times observed for the tablets in the biorelevant media tested. A significant difference was not observed in the disintegration times of the rapidly disintegrating tablets in all except one media, with tablets disintegrating at an average of about 34 s in most of the media. The exception is whole milk in which the disintegration time was approximately four times longer than in the other media ($P < 0.05$).

A marked difference was observed between the disintegration times of the poorly disintegrating tablets when using the different media. Tablets showed disintegration times up to 2 times that in distilled water in AGF at pH1.2, 2.0 and 3.5 ($P < 0.05$), and an increase of up to three times was observed in SGFsp, SGF (USP 23) and 0.1N HCl ($P < 0.05$). The disintegration time in whole milk runs were up to 4 times longer than distilled water ($P < 0.05$).

For the gastric medium suggested by Dressman et al. (1998); 0.1% Triton X-100 also has a significant effect ($P < 0.05$), with tablets taking approximately twice as long to disintegrate than with the use of sodium lauryl sulfate as the surfactant.

Table 5
Mean contact angles of biorelevant media on PMMA and placebo tablets

Media	Mean contact angles ± S.D.		
	PMMA	Rapidly disintegrating tablets	Poorly disintegrating tablets
Distilled water	68.7 ± 1.9	23.3 ± 2.9	76.68 ± 2.4
0.1 N HCl	69.98 ± 2.1	24.3 ± 1.5	71.3 ± 1.68
SGFsp	68.7 ± 1.9	26.06 ± 1.9	71.8 ± 1.96
SGF (USP 23)	69.8 ± 2.0	26.5 ± 2.8	72.3 ± 3.9
SGF + 0.1%T	15.96 ± 3.7	22.2 ± 4.6	61.8 ± 1.4
SGF + SLS	20.05 ± 2.8	28.06 ± 3.63	58.44 ± 3.35
AGF pH 1.2	66.09 ± 2.8	29.6 ± 4.4	72.6 ± 2.1
AGF pH 2.0	70.94 ± 2.1	33.36 ± 3.86	71.1 ± 3.58
AGF pH 3.0	70.49 ± 1.78	34.85 ± 2.87	69.99 ± 2.8
Whole milk	71.8 ± 1.86	46.56 ± 3.14	98.95 ± 8.66

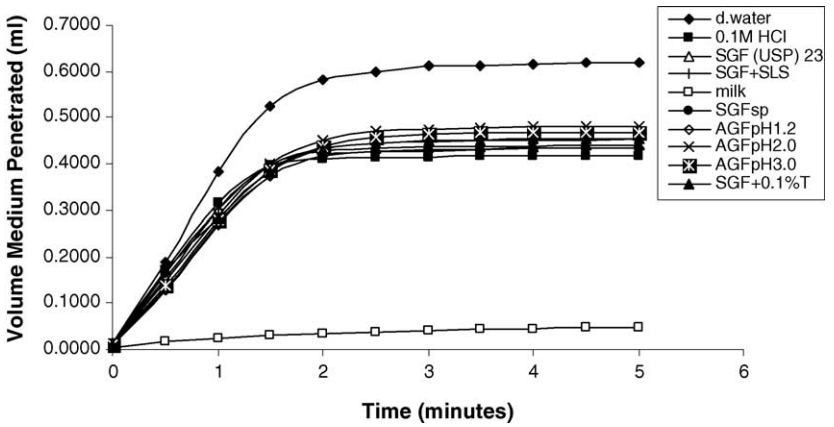

Fig. 1. Mean penetration volumes for biorelevant media into rapidly disintegrating tablets ($n = 20$).

4. Discussion

For the tablets designed to disintegrate rapidly, changing the composition of the media which lead to differences in both surface tension and viscosity, had little effect on the disintegration times of the tablets as measured by the British Pharmacopoeial test. The exception was whole milk that exhibited a significantly higher disintegration time. For the poorly disintegrating tablets, a range of disintegration times were observed, depending on the media used.

The preliminary step in the disintegration of a tablet is penetration of the liquid. For both tablets and powder beds, an analogy between their pore structures and a bundle of capillary tubes has lead to the successful application of the Washburn equation (Washburn, 1921) to analyze the results (Buckton, 1993). The Washburn equation is:

$$v^2 = \frac{r\gamma \cos\theta t}{2\eta}$$

where v is the volume of liquid penetrated in time t, γ the surface tension, θ the contact angle, η the viscosity and r the capillary radius.

This equation is not strictly applicable in the current study as the tablets are disintegrating and hence their pore structures are changing. Hence, plotting the results in the conventional manner, v^2/t against time, does not yield a straight line. None the less, the physical factors stated in the equation, namely viscosity, surface

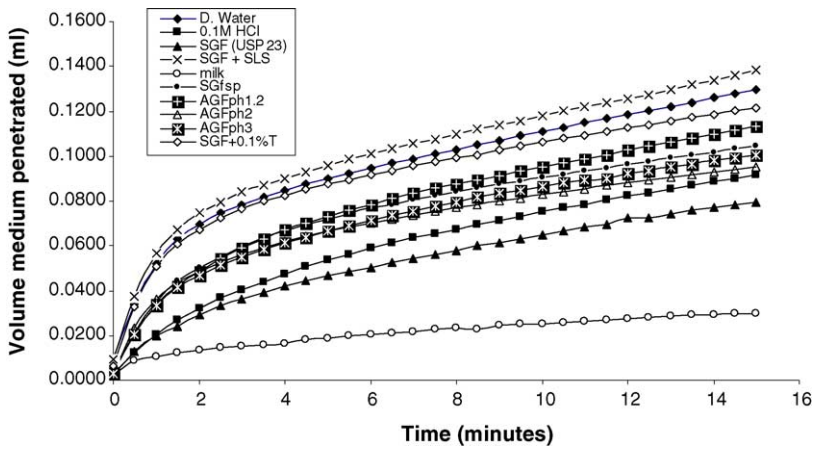

Fig. 2. Mean penetration volumes of biorelevant media into poorly disintegrating tablets ($n = 20$).

Table 6
Average disintegration times in the biorelevant media

Tablet	Mean disintegration times (min) ± S.D.								
Distilledwater	0.1 N HCl	SGF_{sp}	SGF (USP 23)	SGF + 0.1%T	SGF + SLS	AGF pH 1.2	AGF pH 2	AGF pH 3	Whole milk
Rapid	0.378 ± 0.038	0.393 ± 0.037	0.357 ± 0.037	0.341 ± 0.051	0.33 ± 0.028	0.277 ± 0.035	0.394 ± 0.037	0.382 ± 0.026	0.356 ± 0.025	2.19 ± 0.071
Poor	8.1 ± 1.5	20.5 ± 4.0	18.3 ± 2.2	20.2 ± 2.0	13.0 ± 2.5	7.9 ± 1.8	15.2 ± 1.5	14.2 ± 0.7	10.5 ± 1.5	33.4 ± 4.1

tension and contact angle, will influence the penetration of liquids into the tablets. For the rapidly disintegrating tablets, the result that is significantly different from the rest is that of whole milk. This medium has a high viscosity, a low surface tension and exhibits a relatively high contact angle against the tablets. The penetration rate is low and consequently the disintegration time is longer.

For the poorly disintegrating tablets, there is a good correlation between the penetration of liquid into the tablets and the measured disintegration time. Hence, SGF (USP23) and 0.1 M HCl show a slower rate of penetration than distilled water and SGF + SLS and exhibit longer disintegration times. Milk exhibits the slowest rate of penetration into these tablets and the tablets have the slowest disintegration time in this media.

The biorelevant media suggested for dissolution testing all differ in the physical properties that affect the penetration of liquids into tablets and therefore disintegration times in these media will differ. For rapidly disintegrating tablets, the differences observed, although significant, may not have a practical consequence. However, for tablets that do not disintegrate rapidly, the different disintegration times exhibited in the different media may play an important role in determining dissolution rates. A further factor, not reported in this study may also play a part. The swelling of disintegrant particles in and their interactions with different media may vary and this will be reported in a further communication.

5. Conclusions

It is evident from this study that changes in media composition can significantly influence the disintegration times of tablets. The biorelevant media suggested for dissolution testing all differ in viscosity, contact angle and surface tension and these factors influence tablet disintegration through changes in liquid penetration rates. Changes in disintegration times may, in part, be responsible for the different dissolution profiles observed in these different media.

Acknowledgements

The authors wish to acknowledge the financial support of AstraZeneca and the School of Pharmacy and

Pharmaceutical Sciences, University of Manchester to SA.

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