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Pharma Research Library
International Journal of Pharmacy and Natural Medicines
2013, Vol.1 (1): 92-107

Review Article

Pharma Research Library

A Review on Development and Evaluation of Lyophilised Fast-Disintegrating Tablets

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Abstract

Despite recent success, many fast-disintegrating tablets (FDTs) still face problems of low mechanical strength, poor mouth-feel and higher disintegration times. This study aimed to optimize FDTs using a progressive three-stage approach. A series of hardness, fracturability and disintegration time tests were performed on the formulations at each stage. During Stage I,tablets were prepared in concentrations between 2% and 5% w/w, and were formulated at each concentration as single and combination bloom strength gelatin (BSG) using 75 and 225 BSGs. Analysis revealed that both hardness and disintegration time increased with an increase in gelatin concentration. A combination (5% gelatin) FDT comprising a 50:50 ratio of 75:225 BSGs (hardness: 13.7 ± 0.9 N and disintegration time: 24.1 ± 0.6 s) was judged the most ideal, and was carried forward to Stage II: the addition of the saccharides sorbitol, mannitol and sucrose in concentrations between 10% and 80% w/w. The best properties were exhibited by mannitol containing formulations (50%-hardness: 30.9 ± 2.8 N and disintegration time: 13.3 ± 2.1 s), which were carried forward to the next stage: the addition of viscosity-modifying polymers to improve mouth-feel and aid pre-gastric retention. Addition of carbopol 974P-NF resulted in the enhancement of viscosity with a compromise of the hardness of the tablet, whereas Pluronic F127 (6%) showed an increase in disintegration time and viscosity with retention of mechanical properties.

Key words: Fast-disintegrating tablets,Gelatin,Saccharides, Lyophilisation, PluronicF127,Carbopol974P

Introduction

Oral fast-disintegrating dosage forms, also known as ‘fast-melt’,‘fast-disintegrating’ or ‘fast-dissolving’ dosage forms, are a relativelynovel dosage technology that involves the rapid disintegration ordissolution of the dosage form, be it a tablet (the most common form) or a capsule [1–3], into a solution or suspension in the mouth without

the need for water [4,5]. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration [6]. The solution containing the active ingredientsis swallowed, and the active ingredients are then absorbed throughthe gastrointestinal epithelium to reach the target and produce the desired effect.Oral fast-disintegrating tablets (FDTs) are designed for the purpose of improving patient acceptance and compliance. A survey of 6158 GP patients conducted in Norway indicated that approximately 26% of all patients do not take their prescribed medication as they encountered problems when swallowing conventional tablets. Often, the main complaints are the size,surface and taste of the tablets [7,8]. Oral FDTs help overcome some of these problems: the rapid disintegration of the tablet into a solution (containing the drug) enables those who find difficulty in or experience discomfort when swallowing, to have a more 'patient friendly' experience.

Target groups for oral FDTs are wide-ranging as people of all ages can experience difficulty in swallowing conventional tablets and capsules. This includes children and the elderly who either experience difficulty and cannot swallow or have not learnt to swallow the conventional solid dosage forms. In addition, institutionalised psychiatric patients as well as hospitalised or bedridden patients suffering from a variety of disorders such as stroke, thyroid disorders, Parkinson's disease and other neurological disorders such as multiple sclerosis and cerebral palsy [4] also find difficulty in swallowing and require 'fast-melt' tablets because of their physical condition. The convenience and ease of using FDTs is also important to normal consumers, with some adults preferring these dosage forms as they are easy to handle and swallow, can be taken without water and have a rapid onset of action [1,9]. For example, patients with a limited access to water would also find such FDTs extremely beneficial [2,4]. In addition to improving patient compliance, FDTs have been investigated for their potential in increasing the bioavailability of poorly water soluble drug through enhancing the dissolution profile of the drug [10,11]. Moreover, pharmaceutical companies also have commercial reasons for formulating FDTs. As a drug reaches the end of its patent, the development and formulation of the drug Into new dosage forms allows pharmaceutical companies to extend the patent life and 'market exclusivity' [12]. This allows pharmaceutical companies to attract new consumers through advertising and product promotion campaigns, and increase profits in the long term.

Despite the growing popularity and success of FDTs over the past decade, many FDTs still face problems of low mechanical strength, high friability and poor disintegration times. The European Pharmacopoeia [13] describes fast-disintegrating tablets or Porodispersable' tablets as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed', and as tablets which should disintegrate within 3min. However, some critics accuse the definition of being non-specific and incomplete as properties such as size, hardness and friability of the tablet are not mentioned in the definition [6]. Today, many FDTs have poor mechanical properties, and require protection in the form of specialized packaging such as the ZYDIS blister peel back packing [14,15].

This study aims to fabricate and optimise FDTs prepared by freeze drying to not only have sufficient mechanical strength/hardness to withstand manual handling, but also have a rapid disintegration time and improved viscosity upon the addition of bioadhesive polymers. A progressive three-stage approach was used in this study; each stage involved the addition of a different class of excipients (gelatin, sugar and sugar alcohols, and polymers, respectively) to alter the mechanical properties and disintegration times of the tablets. All FDTs were tested for their hardness, fracturability and disintegration times at every stage of the study. Stage I involved the addition of a gelatin binder, and the investigation of the effects of gelatin concentration and bloom strength on the properties of the tablet. FDTs were prepared in concentrations between 2% and 5% and were formulated at each concentration as single and combination bloom strength gelatin (BSG) tablets using 75 and 225 BSGs. The aim of this was to observe the effects of increasing the ratio of low (75) bloom strength gelatin in the combination mixture on the hardness and disintegration time of the tablet. The best of these formulations (judged based on properties of the tablet) were taken forward to Stage II, which involved the addition of the saccharides sorbitol, mannitol and sucrose in concentrations between 10% and 80%, which often serve as cryoprotectants and diluents in many formulations. Formulations of the tablet incorporating these saccharides were tested for their hardness, fracturability and disintegration time. The best of the Stage II formulation was taken forward to Stage III, namely the addition of the viscosity-modifying polymers, Carbopol _ 974P-NF and Pluronic F127, in concentrations between 2% and 10%. It was hoped that the addition of these polymers would increase the viscosity and consequently improve the retention (bioadhesion) of the dissolved tablet solution in the oral cavity, while maintaining or improving the mechanical properties and disintegration time of the FDT. Improvements in viscosity and the addition of bioadhesives would hopefully improve the oral absorption and bioavailability of any drug incorporated in the future.

Material and Methods

Materials

Gelatin from bovine skin, Type B with 75 and 225 bloom strengths, D-sorbitol (minimum 98%), D-mannitol powder (ACS reagent), Sucrose (ACS reagent), and Pluronic F127 were all purchased from SIGMA_. Carbopol_ 974P-NF was purchased from BF Goodrich. All the materials were used in the state they were supplied by the respective companies, without any modification to their properties.

Methods

Formulation of tablets to investigate the influence of gelatin bloom strength

Gelatin of different bloom strengths (75 and 225) was dissolved in double distilled water at about 40 _C to obtain concentrations of 2%, 3%, 4% and 5% w/w. 1.5 g of the solution was poured into a bijou tube, frozen at _80 _C for about 60 min and freeze-dried (ADVANTAGE Freeze-dryer, VIRTIS) according to an optimised regime (primary drying for 48 h at a shelf temperature of _40 _C, followed by secondary drying for 10 h at a shelf temperature of 20 _C, vacuum of 50 m Torr), which resulted in a moisture content of less than 3% w/w. All the formulations were prepared in triplicate from three independent batches. A total of 240 tablets in three batches with each batch comprising 80 tablets were prepared (3 _ 80).

The resultant tablets had an average diameter of 13.3 ± 0.1 mm and thickness of 8.3 ± 0.2 mm. 2.2.2. Formulation of tablets to investigate the influence of saccharide concentration Sorbitol, mannitol and sucrose were added individually to gelatin solution to obtain concentrations of 10%, 20%, 30%, 40%, 50%, 60%, 70%, and 80% of total solid material. 1.5 g of the solution was poured into a bijou tube, frozen at _80 _C for about 60 min and freeze-dried (ADVANTAGE Freeze-dryer, VIRTIS) according to the optimised regime (primary drying for 48 h at shelf temperature of _40 _C and secondary drying for 10 h at a shelf temperature of 20 _C, vacuum of 50 m Torr), which resulted in moisture content of less than 3% w/w. All the formulations were prepared in triplicate from three independent batches. A total of 360 tablets in three batches with each batch comprising 120 tablets were prepared (3 _ 120). The resultant tablets had an average diameter of 13.4 ± 0.1 mm and thickness of 8.4 ± 0.2 mm.

Formulation of tablets to investigate the influence of polymer concentration

Stage III involved the incorporation of the viscosity-modifying polymers: Pluronic F127 and carbopol 974P-NF, in concentrations ranging from 2% to 10% of the total solid material. Care was taken to ensure that the gelatin-mannitol solutions were clear (without residue) before adding any polymers. The freeze-drying regime outlined in Section 2.2.1 was employed to fabricate the tablets. All the formulations were prepared in triplicate from three independent batches. A total of 195 tablets in three batches with each batch comprising 70 tablets were prepared (3 _ 65). The resultant tablets had an average diameter of 13.3 ± 0.1 mm and thickness of 8.1 ± 0.2 mm.

Tablet disintegration testing

The in vitro disintegration time of the freeze-dried FDTs was determined according to the official US Pharmacopoeia monograph (h701i disintegration) for tablet disintegration testing, using the ErwekaZT3 type disintegration apparatus. The disintegration time was defined as the time necessary for the FDT to completely disintegrate until no solid residue remains. Distilled water (800 ml) was used as the immersion fluid, and was heated to and maintained at a temperature of 37 _C. The temperature of the water was constantly monitored with a thermometer. A digital stopwatch was used to measure the disintegration time to the nearest second. Only onetablet was analysed at a time in order to ensure maximum accuracy. At the end of each test, the basket rack assembly and the plastic disk were thoroughly washed and dried to remove any traces of the tablet excipients and water. A total of six tablets were tested for each concentration, and the values reported are mean ± standard deviation.

Texture analysis

A QTS 25 texture analyser (Stevens Mechtric, UK) coupled to a computer was used to analyse the hardness and the fracturability of the tablets. The hardness of the tablet was tested using a compression probe (5 mmdiameter) to compress the tablet to a depth of 2mmexactly, at a speed of 6mm/minute. The peak force (in Newtons; N) after 1mm of compression was measured. The fracturability of the tablet was tested using a penetration probe (1mm diameter) to penetrate the tablet to a depth of 4mm exactly, at a speed of 6mm/min. The peak force (in Newtons; N) after 3mm of penetration was measured. Once the measurement was complete, the data were stored and analysed using the TexturePro program powered by Microsoft Excel. A total of six tablets (3 tablets for hardness testing and 3 tablets

for the determination of fracturability) were tested for each concentration, and the values reported are mean ± standard deviation.

Viscosity testing
FDTs incorporated with viscosity-modifying polymers were tested for their viscosity using the automated micro-viscometer (Anton- Parr, AMVn, Graz, Austria). This instrument measures the viscosity of a liquid by determining the rolling ball time between a fixed distance (principle based on Stokes Law) (Anton-Parr GmBH, 2001). Samples were prepared by completely dissolving the FDTs in 2Ml of water while homogenizing themthrough stirring on a heated magnetic stirrer (27–30 _C).

Each sample (400 ll) was loaded into a glass capillary (diameter: 1.8 mm) using a 1 ml syringe, and care was taken to ensure that no air bubbles were present in the loaded sample within the capillary. The glass capillary was loaded into the capillary block, where the temperature of the sample was equilibrated at 25 C. Viscosity measurements were conducted by measuring the rolling ball time (ball diameter: 1.5 mm) four times through the capillary at an angle of 50_. Triplicate measurements were performed for each formulation to check for reproducibility and ensure precision.

Scanning electron microscopy
Scanning electron microscopy (SEM) was performed on the formulations taken forward from each stage. Cross-section samples were prepared by cutting a thin slice of the tablet using a scalpel. The cut samples were mounted onto standard specimen stubs using a double-sided adhesive tape. The stubs in turn were loaded and fastened to a universal specimen holder. Since the FDTs are electrically non-conductive, the samples were subjected to lowvacuum gold sputter coating in the presence of argon gas (Polaron SC500, Polaron Equipment, Watford,UK).

Differential scanning calorimetry
The glass transition temperatures (Tg) and the process of crystallization of the formulations were studied by performing differential scanning calorimetry (DSC) (Perkin-Elmer, Wellesley, USA). Approximately 10–15 mg of each sample was initially cooled to _65 _C using an attached intracooler (2P Perkin-Elmer, Wellesley, USA), and then heated to 20 _C at a rate of 5 _C/min with a nitrogen purge of 20 ml/min. Liquid samples which consisted of a combination of gelatin and saccharide with or without the polymer in the same ratio as that used in the formulations were used in order to simulate the thermal events occurring during freeze-drying of the tablets as close as possible. The resulting graphs were analysed using the Pyris Manager software.

The glass transition and melting point (Tm) were determined from the intersection of relative tangents to the baseline. All the measurements were performed in triplicate using individually prepared samples. The DSC was calibrated for temperature and heat flow using standard samples of indium (melting point 156.6 _C) and zinc. An empty pan was used as a reference.

Determination of the diameter and thickness of the tablet
The thickness and the diameter of the freeze-dried tablets were measured using screw gauge (LINEAR, Farnell). A total of three tablets from three independent batches were measured for each concentration, and the values reported are mean ± standard deviation.

Statistical analysis
Statistical analysis was carried out by analysis of variance followed by Bonferroni t test using Primer of Biostatistics software. Significant differences were judge as $P < 0.05$.

Results and Discussion

3.1. Stage I: influence of gelatin bloom strength and concentration on the hardness and disintegration time
Originally derived from the Latin word ‘gelatus’, meaning frozen or stiff, gelatin is a water-soluble structural protein extracted from collagen present inside the connective tissue (skin, cartilage and bone) of hogs, cattle and fish [15]. Gelatin is considered a key component in a large number of industries, including the food, cosmetic, photographic and pharmaceutical industries; where it is used in the production of hard and soft gelatin capsules, pastes and suppositories and in tablet binding and coating and microencapsulation [16,17].

The first stage of the study entailed the formulation of FDTs with Type B bovine gelatin in concentrations between 2% and 5% (w/w) in water. Tablets at each concentration were formulated individually with different ratios of 75 and 225 bloom strength gelatins: (i) 225 BSG only; (ii) 25:75 ratio of 75:225 BSGs; (iii) 50:50 ratio of 75:225 BSGs; (iv) 75:25 ratio of 75:225 BSGs. This was done to observe the effect of decreasing the concentrations of high bloom strength gelatin on the mechanical properties (hardness and fracturability) and disintegration time of the tablet. The resultant tablets had an average diameter of 13.3 ± 0.1 mm and thickness of 8.3 ± 0.2 mm irrespective of the concentration and bloom strength of gelatin (Table 1). The quality of an individual gelatin product is determined by its designated bloom strength.

Table 1

Diameter(*D*) and thickness(*T*), in mm, of freeze-dried tablets based on different combinations of 225 and 75 BSGs at varied concentrations (Stage I). The values represented are mean ± standard deviation ($n = 3$).

Gelatin ratio 75:225 BSGs	2% w/w		3% w/w		4% w/w		5% w/w	
	D	*T*	*D*	*T*	*D*	*T*	*D*	*T*
0:100	13.4±0.1	8.2±0.2	13.3±0.1	8.2±0.1	13.3±0.1	8.3±0.1	13.2±0.1	8.5±0.2
25:75	13.3±0.1	8.3±0.1	13.4±0.1	8.2±0.2	13.2±0.1	8.4±0.2	13.2±0.2	8.4±0.1
50:50	13.3±0.1	8.3±0.2	13.4±0.1	8.4±0.1	13.3±0.1	8.3±0.1	13.3±0.2	8.5±0.2
75:25	13.4±0.2	8.3±0.1	13.5±0.1	8.4±0.1	13.4±0.2	8.5±0.2	13.2±0.1	8.4±0.2

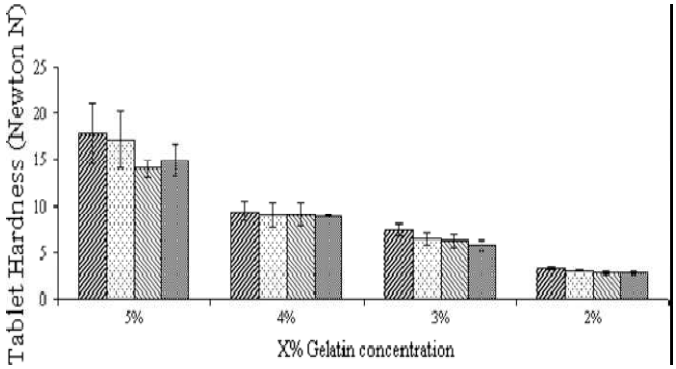

Fig. 1. Comparison of hardness (Newton) in formulations comprising 225 BSGs 25:75 ratio of 75:225 BSGs, 50:50 ratio of 75:225 BSGs, and 75:25 ratio of 75:225 BSGs, in gelatin concentrations of 2%, 3%, 4% and 5% (w/w) in water.

The cohesive strength of a specific gelatin gel and is tested by measuring the force (grams) required to press a 17.7 mm diameter plunger 4 mm into a 112 g 6.67% (w/w) gelatin gel held for 17 h at 10 _C [15]. Based on the definition, it was hypothesized that the hardness of the tablet would increase with higher concentrations of high (225) bloom strength gelatin. However, the data obtained (Fig. 1) reveal that such a trend does not exist. Decreasing the ratio of high bloom strength gelatin did not have any significant impact upon the hardness of the formulation ($P > 0.05$). The same trend was seen throughout the entire concentrations studied (2–5%). Similar results were obtained in our laboratory previously when two different bloom strengths of gelatin were formulated individually instead of a combination approach as in the present study. Fig. 1 shows that hardness of the tablet progressively decrease with a decrease in gelatin concentration, irrespective of the concentration of high (225) bloom strength gelatin present in the formulation. Moreover, the mechanical properties of the 2% gelatin FDTs were so poor that the slightest manual handling caused them to break apart.

This trend can be attributed to the fewer number of crosslinks formed between the gelatin strands as the concentration decreases. When aqueous solutions of gelatin are rapidly cooled below 40 _C, a rough 3D gel network

with water trapped in the mesh is formed [16]. Freeze-drying of the frozen gelatin solution causes the trapped frozen water to sublimate, leaving behind only the 3D network.

An increase in gelatin concentration would result in a more stable and extensive 3D network due to an increase in the number of gelatin fibres forming crosslinks and interchain Hbonds, thereby causing an increase in the overall hardness of the FDT [16]. Measurement of fracturability (Fig. 2) for the various combinations and concentrations did not show any particular trend. The values ranged from 2 to 4 N. Fracturability tests could not be carieed-out on 2% formulations due to the spongy nature of the resultant tablets. With regard to the disintegration times of the tablet (Fig. 3), increasing gelatin concentration resulted in an increase in the disintegration time. For example, the average disintegration times of the tablet in formulations with a 50:50 ratio (75:225 BSGs) gradually rose from 5 s in the 2% formulation to reach a maximum time of 24.1 ± 0.6 s in the 5% formulation. Other formulations were also shown to follow similar trends

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Gelatin bloom values are indicative of gelatin gel cohesiveness, with gelatins of higher bloom strengths forming more cohesive, stronger and stable gels that are less likely to break up or dissolve in water. As such, it was expected that increasing the ratio of high bloom strength gelatin would increase the disintegration times of the tablet. The only exception to the trend was the 5% formulation comprising 75:25 of 75:225 BSGs. This difference could be explained by the highly subjective nature of disintegration time tests, with results largely depending on an individual's personal judgment and opinion. Neither the EU Pharmacopoeia nor the US Pharmacopoeia has outlined disintegration tests specifically for fast-melt tablets; and disintegration tests currently used to test fast-melt tablets are those that are normally used to test dispersible and effervescent tablets. Moreover, in vitro disintegration tests only provide approximations to the true disintegration time in the mouth in vivo.Experiments have shown that in vitro disintegration times may be significantly higher or lower than the disintegration time in vivo [6]. Selection of the FDT formulation that is to be taken forward to Stage II of the study depended on the tablet having sufficient hardness to withstand manual handling, and a disintegration time of less than 3 min: the designated cut off time for this study as per the EU pharmacopoeia. A formula termed the Lyophilised Tablet

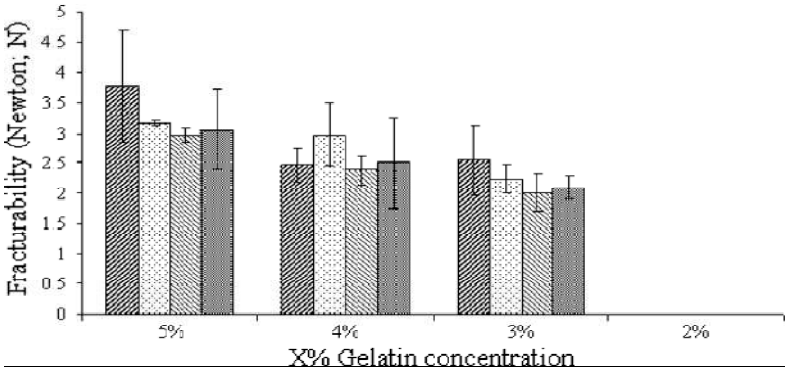

Fig. 2. Comparison of fracturability (Newton) in formulations comprising 225 BSGs, 25:75 ratio of 75:225 BSGs , 50:50 ratio of 75:225 BSGs, and 75:25ratio of 75:225 BSGs, in gelatin concentrations of 2%, 3%, 4% and 5% (w/w) in water.

Index (LTI = tablet hardness/disintegration time) took both the above-mentioned factors into consideration and was used in making a decision as to which FDT to take forward. Ideally, the LTI value for a formulation would be as high as possible. However, it is possible for tablets with poor mechanical strength to have high LTI values if their disintegration time is fast. Such is the case with the 3% and 2% gelatin FDTs, which were excluded from the study based on their extremely poor hardness, despite having high LTI values. Of the remaining formulations, the 3% gelatin formulation with a 50:50 ratio of 75:225 BSGs was show to have the highest LTI value (0.7). However, this formulation was excluded based on its comparatively poor hardness (6.2 ± 0.7 N) despite having rapid disintegration times (9.0 ± 1.0 s). The same reasoning was used for the 4% gelatin formulation with a 75:25 ratio of 75:225 BSGs (LTI = 0.6). The 5% gelatin formulation with a 50:50 ratio of 75:225 BSGs, with an LTI of 0.6, was found to have adequate hardness (13.7 ± 0.9 N) and an acceptable average disin-

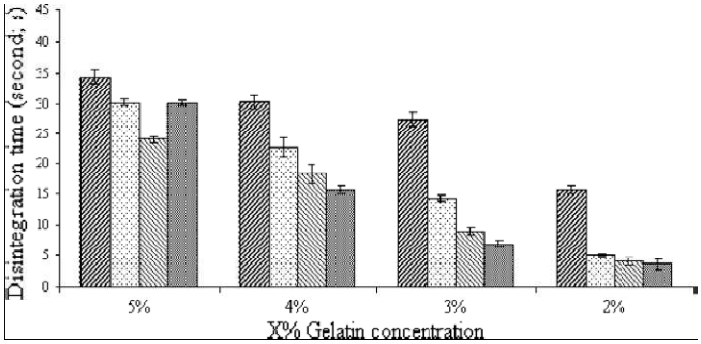

Fig. 3. Comparison of disintegration time (second) in formulations comprising 225 BSGs , 25:75 ratio of 75:225 BSGs, 50:50 ratio of 75:225 BSGs , and 75:25 ratio of 75:225 BSGs, in gelatin concentrations of 2%, 3%, 4% and 5% (w/w) in water.

Disintegration time (24.1 ± 0.6 s). Additionally, SEM micrographs reveal that the anatomical makeup of the formulation comprises a highly porous structure with an average pore size of approximately 80–100 lm (Fig. 4A and B). Accordingly, this formulation was taken forward to Stage II of the study. 3.2. Stage II: influence of varied concentrations of different saccharides on the hardness and disintegration time The second stage of the study involved the addition of the saccharides: mannitol, sorbitol and sucrose to the 5% gelatin formulation brought forward from Stage I, in concentrations ranging between 10% and 80%. Similar values were obtained for both the diameter and the thickness (Table 2) as in Stage I. Mannitol was chosen on the basis of previous work in which it was shown that its incorporation into FDT formulations reduced the disintegration times [2,4]. Furthermore, mannitol has been incorporated into several successful ZYDIS_ technology products such as Claritin Reditab and Maxalt-MLT. Its isomer, sorbitol, was chosen to observe the effects of isomeric structural differences on the properties of the FDT. Sucrose was primarily chosen for the purpose of providing a comparison between the effects of adding a saccharide on the properties of the tablet and that of polyols.

Mannitol:

Fig. 5 clearly shows that the addition of mannitol resulted in a significant increase in the average hardness of the tablet, improving from 13.7 ± 0.9 N in the 5% gelatin FDT to 18.9 ± 2.6 N in the 10% mannitol tablet ($P < 0.01$). The average hardness of the tablet was found to progressively increase with an increase in mannitol concentration, with 30%, 50% and 80% mannitol FDTs having increasing hardness values of 24.9 ± 1.9 N, 30.9 ± 2.8 N and 58.3 ± 1.1 N (the maximum hardness), respectively. However, slight degradation (lack of smooth surface and appearance of cracks) and brittleness of the tablet were observed in the 80% mannitol tablets, some of which were found to crack when subjected to hardness stress tests. As a result, no fracturability tests could be performed for the 80% mannitol tablets. As expected, the fracturability of the tablet also increased with an increase in mannitol concentration (Fig. 6), gradually rising from 2.9 ± 0.2 N (10% mannitol) to 9.9 ± 1.3 N (70% mannitol). Fig. 7 shows that disintegration times were at their lowest in tablets with mannitol concentrations between 20% and 50% (_10–14 s), with the 30% FDT achieving disintegration times as fast as 10.7 ± 1.5 s. However, disintegration times for mannitol FDTs progressively increased when concentrations were raised above 50%, with a time of 67.0 ± 4.2 s being recorded for the 80% tablet.

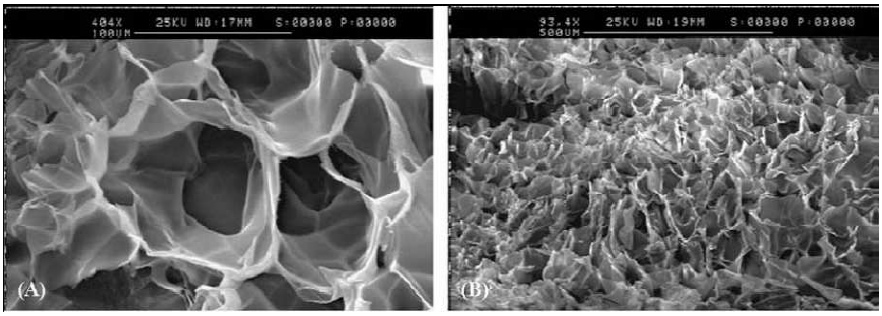

Fig.4. High (A) and low (B) magnification SEM pictures of cross-sections of the FDT taken forward from Stage I: the combination 5% gelatin FDT, with a 50:50 ratio of 75:225 BSGs. Pore size: _80–110 lm.

Table 2

Diameter (*D*) and thickness (*T*), in mm, of 5% gelatin-based freeze-dried tablets after inclusion of varied concentrations of saccharide (Stage II). The values represent mean ± standard deviation ($n = 3$). (–) represents no tablet formed.

Saccharide	10% w/w		20% w/w		30% w/w		40% w/w		50% w/w		60% w/w		70%w/w		80%w/w	
	D	*T*	*D*	*T*	*D*	*T*	*D*	*T*	*D*	*T*	*D*	*T*	*D*	*T*	*D*	*T*
Mannitol	13.5 ± 0.1	8.5 ± 0.2	13.4 ± 0.1	8.5 ± 0.2	13.4 ± 0.1	8.4 ± 0.2	13.5 ± 0.1	8.4 ± 0.2	13.4 ± 0.2	8.5 ± 0.2	13.5 ± 0.2	8.3 ± 0.2	13.5 ± 0.2	8.4 ± 0.2	13.5 ± 0.2	8.3 ± 0.2
Sorbitol	13.3 ± 0.1	8.6 ± 0.1	13.5 ± 0.1	8.5 ± 0.2	13.4 ± 0.2	8.4 ± 0.2	-	-	-	-	-	-	-	-	-	-
Sucrose	13.4 ± 0.1	8.6 ± 0.2	13.3 ± 0.1	8.5 ± 0.1	13.4 ± 0.2	8.4 ± 0.2	13.5 ± 0.2	8.4 ± 0.1	1.4 ± 0.1	8.4 ± 0.2	13.5 ± 0.2	8.2 ± 0.2	-	-	-	-

Fig. 5. Comparison of hardness (Newton) for FDTs comprising the saccharides sorbitol ( ), sucrose ( ), and mannitol ( ), in concentrations ranging between 10% and 80%. R. Chandrasekhar et al. / European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 119–129 123

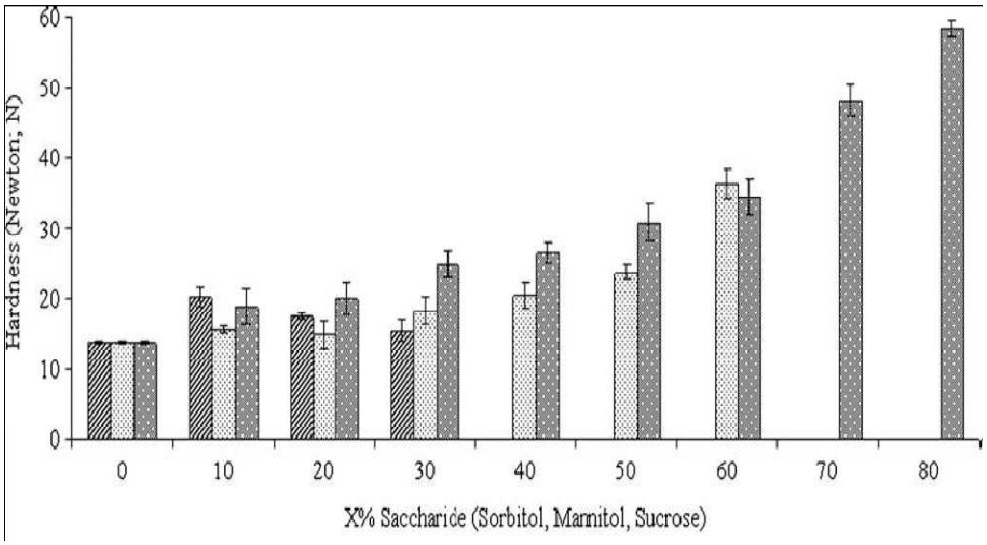

Fig. 5. Comparison of hardness (Newton) for FDTs comprising the saccharides sorbitol , sucrose , and mannitol , in concentrations ranging between 10% and 80%.

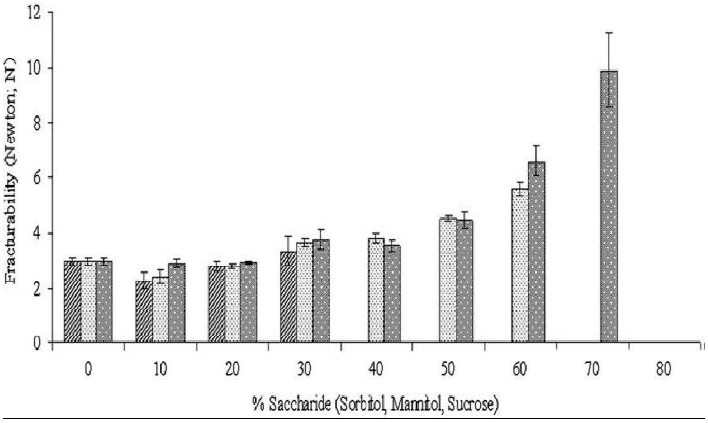

Fig. 6. Comparison of fracturability (Newton) for FDTs comprising the saccharides sorbitol ( ), sucrose ( ), and mannitol ( ), in concentrations ranging between 10% and 80%.

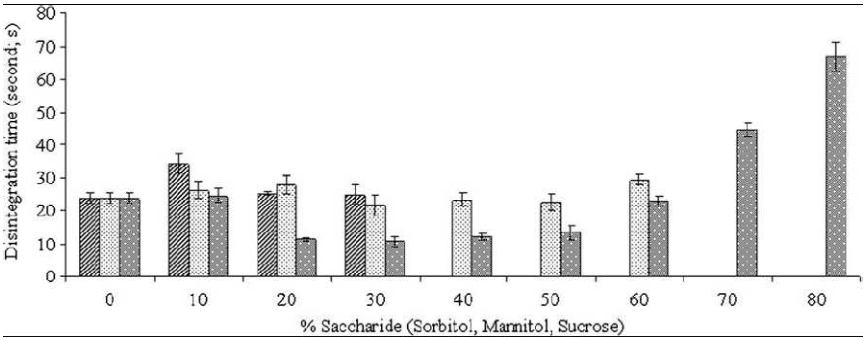

Fig. 7. Comparison of disintegration time (second) for FDTs comprising the saccharides sorbitol ( ), sucrose ( ), and mannitol ( ), in concentrations ranging between 10% and 80%.

The addition of small amounts of mannitol (10% concentration) also appeared to have little effect on the disintegration time (24.7 ± 2.0 s), compared to the 5% gelatin formulation taken forward (24.1 ± 0.6 s). Disintegration times for mannitol are, therefore, best within a concentration window of 20–50%. Findings from experiments conducted in another study described similar trends in granulated saccharide FDTs, with mannitol being described as a poorly compressible (or mouldable) saccharide as it possesses a lower surface free energy of the polar component of saccharides compared to the surface free energy of highly compressible saccharides such as sorbitol and trehalose [2]. The results obtained in our study suggest that the addition of mannitol to a gelatin binder base maintains the rapid disintegration mannitol offers, and provides a synergistic effect to improve the hardness the gelatin base already provides. FDTs were found to show adequate hardness while maintaining a low disintegration time of 20 s.

Sorbitol:

In significant contrast to the formulations comprising the isomeric mannitol, only formulations with sorbitol concentrations between 10 and 30% were successful in producing acceptable FDTs. Deformation in sorbitol FDTs was clearly seen to increase with an increase in sorbitol concentration, with tablets containing sorbitol concentrations beyond 30% prone to collapse. In order to determine the cause for the differences between sorbitol and mannitol tablet formation, the glass transition temperatures of both sorbitol and mannitol were compared. DSC was performed on one sorbitol formulation that formed (30%) and one that did not form (60%). These glass transition temperatures (Table 3) obtained were compared to those of the 30% and 60% mannitol formulations, both of which formed acceptable tablets (Fig. 8). Table 3 clearly shows that both the 30% sorbitol and mannitol formulations had very similar glass transition temperatures. However, the 60% sorbitol formulation had a significantly lower ($P < 0.01$) glass transition temperature (_36.2 ± 0.3 _C) compared to both the 30% sorbitol formulation and the 60% mannitol formulation (_29.8 ± 0.3 _C). Furthermore, it is important to note that the difference between the 30% and 60% mannitol transition temperatures is small. It is believed that these significant changes in the transition temperatures of the sorbitol formulations, and the fact that the transition temperature and the collapse temperature (usually 2–3 _C higher than the glass temperature) of 60% sorbitol are close to the shelf temperature of the freeze-dryer (_40 _C). Fig. 8 resulted in the saccharide being unable to retain its intact cake structure, and led to the deformation and collapse of the tablet. The addition of sorbitol improved the strength of the tablet, with the hardness of the FDT rising from 13.7 ± 0.9 N (tablet without sorbitol) to 20.3 ± 1.4 N in tablets with 10% sorbitol.

Table 3
Glass transition temperatures (Tg °C) for the saccharides sorbitol, mannitol and sucrose at concentrations of 30% and 60%

Saccharide	30% (Tg °C)	60% (Tg °C)
Sorbitol	−27.523 ± 0.186	−36.150 ± 0.316
Mannitol	−27.507 ± 0.123	−29.823 ± 0.305
Sucrose	−18.590 ± 0.560	−24.327 ± 0.737

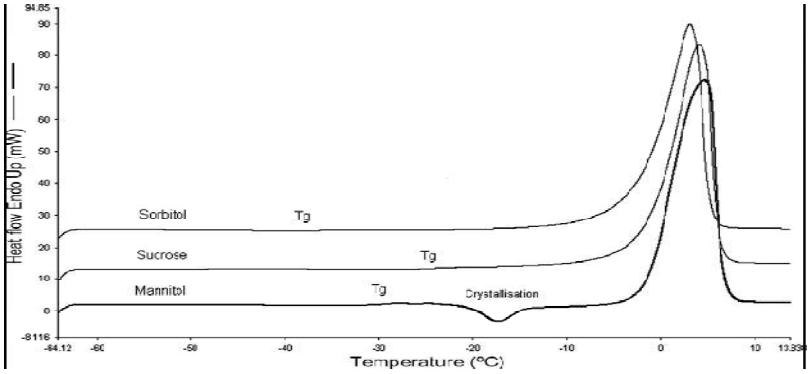

Fig. 8. Differential scanning calorimetry graph clearly illustrating the glass transition temperatures (Tg) of the saccharides mannitol, sorbitol and sucrose.

However, increasing the sorbitol concentration beyond 10% appeared to reduce the strength of FDT, with hardness values decreasing to 15.5 ± 1.5 N, as exhibited by the 30% sorbitol tablet. The hardness of the tablet could not be measured in FDTs with sorbitol concentrations above 30% because of the increasing degradation of FDTs with greater concentrations of sorbitol. Conversely,

Fig. 6 shows the fracturability of the tablet to follow an opposite trend, with values eventually reaching 3.4 ± 0.5 N in the 30% sorbitol FDT. Fig. 7 illustrates that the addition of sorbitol in low concentrations had a negative effect on the disintegration time, which rose from 24.1 ± 0.6 s (5% gelatin FDT) to 34.0 ± 3.0 s, as exhibited by the 10% sorbitol tablet. The average disintegration times decreased when sorbitol concentrations were raised beyond 10%, with the 20% and 30% sorbitol FDTs having disintegration times of 25.3 ± 0.6 s and 25.0 ± 3.0 s, respectively. These values are not an improvement on the disintegration time offered by the 5% gelatin formulation. These results can be explained by previous studies conducted on saccharide FDTs prepared by conventional compaction methods. Sastry et al. stated that any individual saccharide FDT, prepared by conventional compaction, either boasted a rapid disintegration time or hardness, but never both.
Saccharides such as mannitol, lactose and sucrose were described to have rapid in vivo disintegration times, but poor hardness (termed 'low mouldable sugars'), whereas saccharides such as sorbitol, trehalose and maltitol (termed 'highly mouldable sugars') were described to have adequate hardness upon compaction, but poor disintegration times [4]. The results for sorbitol follow the above trend despite the different method of preparation of the tablets. However, incorporation of either mannitol or sucrose (see discussion below) did not obey that trend. The differences in the properties of the tablets of sorbitol and mannitol can only be attributed to the small difference in the structure of the isomers.

Sucrose:
The addition of sucrose to the tablets resulted in the formation of intact tablets up to 60% concentration. DSC revealed the glass transition temperatures to decrease with an increase in sucrose concentration, from _18.6 ± 0.6 _C (30% sucrose) to _24.3 ± 0.7 _C (60% sucrose) (Table 3 and Fig. 8). The decrease in the glass transition to _24 _C even upon the addition of 60% sucrose is way too high compared to the shelf temperature, which was _40 _C, thus resulting in the formation of intact tablets at higher concentrations. Collapse of freeze-dried formulation usually occurs when the collapse temperature (two to three degree higher than the glass transition) is close to the shelf temperature as seen in the case of inclusion of sorbitol (_36.2 ± 0.3 _C at 60% concentration).

Fig. 5 shows that the addition of sucrose improved the overall strength of the tablet, with the hardness of FDT rising from 13.7 ± 0.9 N in FDTs without sucrose to 15.6 ± 0.4 N in tablets with a 10% sucrose concentration. Increasing the concentration of sucrose further steadily improved the hardness of the tablet, with the 60% sucrose FDT exhibiting a maximum hardness of 36.4 ± 2.0 N. Fracturability tests also showed a similar trend with increase in values as a result of increase in concentration (Fig. 6).

Fig. 7 illustrates that the addition of sucrose did not improve the disintegration time of the FDT, despite other literature indicating that sucrose FDTs (prepared through conventional compression techniques) possess rapid disintegration times. 3.2.4. Selecting the formulation to take forward Selection of the formulation to take forward to

Stage II of the study depended on the LTI value of the individual formulations of the tablet (data not shown). Each LTI value was also compared to the LTI value of the combination 5% gelatin (50:50 ratio of 25:75 BSGs) brought forward to Stage II, using an equation termed the Relative Lyophilised Tablet Index (RLTI) [(saccharide LTI)/(gelatin LTI)]. The RLTI value provided a ratio indicative of whether the new saccharide formulation was better than the gelatin formulation alone.

Results revealed that all three saccharides formulations had RLTI values above 1 irrespective of their concentrations (exception: 20% sucrose, RLTI: 0.9), indicating that the addition of any saccharide improved the formulation. It is clear that the majority of the mannitol formulations had higher LTI and RLTI values that are indicative of their superiority. The 30% and 50% mannitol formulations were selected on the basis of having the highest RLTI values among all the FDTs: 4.1. Both mannitol tablets had excellent disintegration times, with times of 10.7 ± 1.5 s and 13.3 ± 2.1 s, respectively, being recorded for the 30% and 50% FDTs.

However, the 50% mannitol FDT was taken forward despite the lower RLTI value, due to its significantly greater hardness (30.9 ± 2.8 N) compared to the 30% mannitol FDT (24.9 ± 1.9 N) ($P < 0.01$). It was deemed that the _3-s improvement in the disintegration time offered by the 30% mannitol FDT was not as significant as the improvements in the hardness of the tablet offered by the 50% mannitol FDT. Similarly, SEM pictures show a porous matrix with a slightly larger pore size (Fig. 9) when compared to formulation without the addition of mannitol (Fig. 4), suggesting that an increase in pore size of the matrix promotes rapid disintegration of the tablets.

3.3. Stage III: influence of varied concentrations of different polymers on the hardness and disintegration time The next stage entailed the addition of two viscosity-modifying polymers to the existing formulation: the poloxamer Pluronic F127 and the carbomer carbopol 974P-NF, in concentrations of 2%, 4%, 6%, 8% and 10%. The rationale behind this was to improve the viscosity of the formulation after disintegration into a solution to enhance pre-gastric retention and improve the mouthfeel. Both Pluronic F127 and carbopol 974P-NF are widely used as viscosity-increasing and bioadhesive agents in conventional dosage forms, and it was hoped that improving the viscosity of the dissolved tablets would increase pre-gastric absorption and bioavailability of any active ingredients added to the formulation in the future. All the tablets obtained had similar values for boththe diameter and the thickness (Table 4) as in Stage I and stage II.

Table 4
Diameter (*D*) and thickness (*T*), in mm, of the optimised freeze-dried tablets formulation from Stage III after inclusion of varied concentrations of the viscosity-modifying polymers. The values represent mean ± standard deviation ($n = 3$).

Polymer	2% w/w		4% w/w		6% w/w		8% w/w		10% w/w	
	D	*T*	*D*	*T*	*D*	*T*	*D*	*T*	*D*	*T*
Pluronic F217	13.2 ± 0.1	8.3 ± 0.2	13.2 ± 0.1	8.1 ± 0.2	13.1 ± 0.1	8.2 ± 0.2	13.4 ± 0.2	8.0 ± 0.2	13.2 ± 0.1	8.2 ± 0.2
Carbopol 974P-NF	13.3 ± 0.1	8.2 ± 0.2	13.1 ± 0.1	8.1 ± 0.1	13.1 ± 0.1	8.2 ± 0.2	13.3 ± 0.1	8.2 ± 0.2	13.3 ± 0.1	8.2 ± 0.2

Pluronic F127:
Fig. 10 shows that the addition of Pluronic F127 (PF127) at concentrations between 2% and 10% did not cause huge losses to FDT hardness, which dropped only slightly from 30.9 ± 2.8 N (no pluronic) to 24.9 ± 2.0 N for the 2% PF127 FDT ($P > 0.05$). Raising them concentration of the polymer further caused a gradual increase in the hardness of the tablet, eventually rising to 28.1 ± 1.1 N for the 8% PF127 FDT. Fig. 11 reveals that the average fracturability of the tablet also remained relatively unaffected when compared to that of the 50% mannitol formulation, indicating consistency in the mechanical strength throughout the tablet. The formation of tablet was poor for formulations with a 10% PF127 concentration, with many of the tablets demonstrating a gel-like rubbery texture. This can be attributed to the non-crystallization of the formulation excipients.

Fig. 12 shows that the addition of PF127 greatly affected the disintegration times, despite SEM revealing the pore size to have increased from _100–130 lm (50% mannitol: Fig. 9) to 130–190 lm (Fig. 15). The addition of even small amounts (2%) of PF127 caused the disintegration time to rise from 13.3 ± 2.1 s (50% mannitol) to 33.7 ± 3.2 s. Raising the PF127 concentrations further caused disintegration times to increase to as high as 194.0 ± 2.0 s, as demonstrated by the 10% PF127 tablet. The increase in the disintegration time upon increasing the concentration of

PF127 can be attributed to the water imbibing and swelling nature of the polymer. Pluronic F127 is a hydrophilic block polymer that absorbs water, swells and finally dissolves in the aqueous environment. Despite the slight increase in disintegration time, formulations containing PF127 up to 8% polymer provide a practical formulation as European Pharmacopeia stipulates a disintegration time of 3 min for FDT. On the other hand, measurement of microviscosity (Fig. 13) shows a significant enhancement in viscosity ($P < 0.05$) when concentrations greater than or equal to 4% are used. Previous studies have shown that when PF127 solutions of high concentrations are heated to temperatures above 23 _C, a thermoreversible transformation occurs that causes the solution to start gelling. As the gel forms, the viscosity of the solution increases sharply due to the formation of a gel network [18]. As

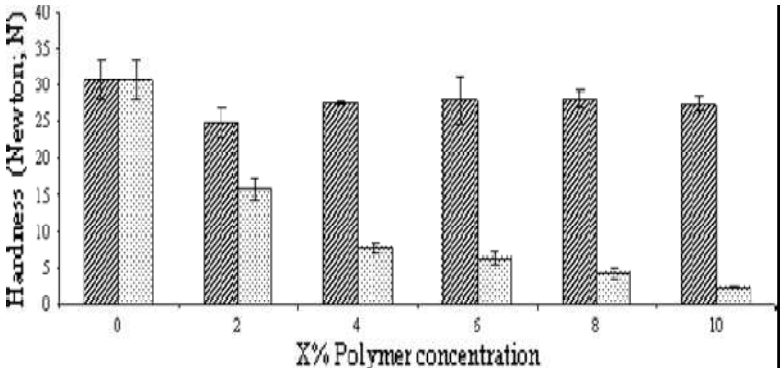

Fig. 10. Comparison of hardness (Newton) for FDTs comprising the viscositymodifying polymers Pluronic F2127and carbopol 974P-NF ( ), in concentrations ranging between 2% and 10%.

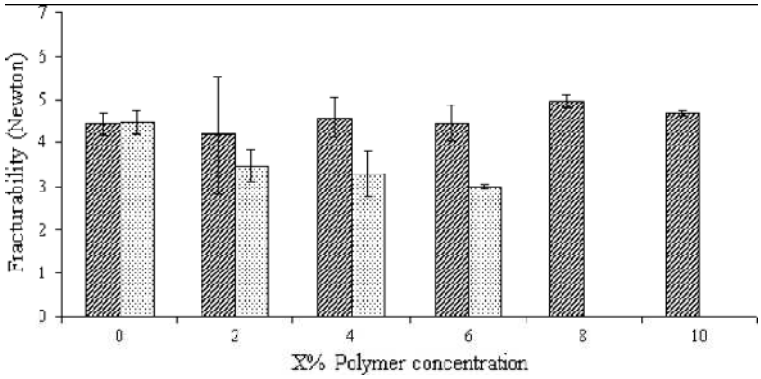

Fig.11.Comparison of factorability (Newton) for FDTs comprising the viscosity modifying polymers Pluronic F2127 and carbopol 974P-NF ( ), in concentrations ranging between 2% and 10%.

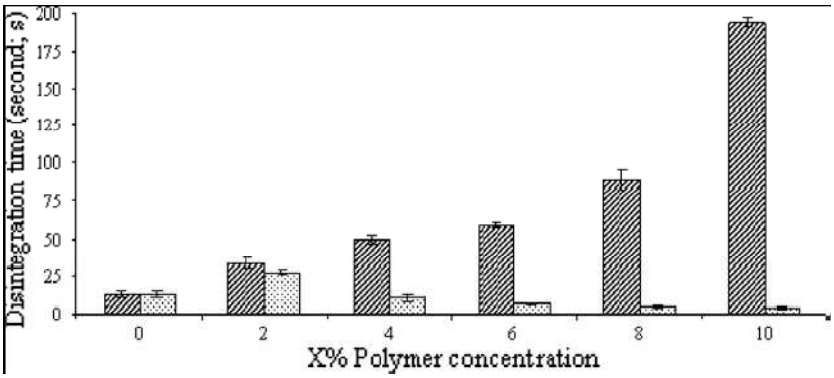

Fig.12. Comparison of the disintegration time (second) for FDTs comprising the viscosity-modifying polymers Pluronic F2127 ( ) and carbopol 974P-NF ( ), in concentrations ranging between 2% and 10%.

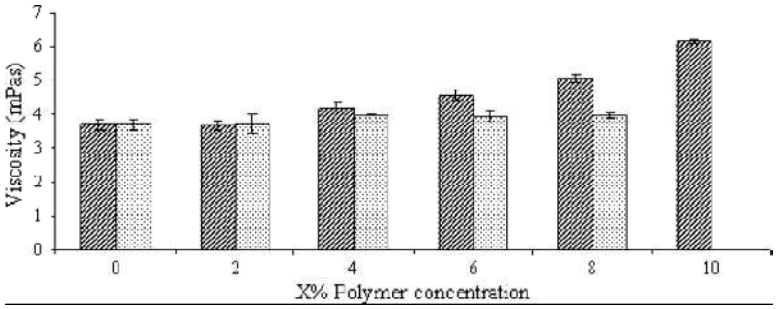

Fig.13. Comparison of the viscosity of the tablet (mPas) for the viscosity-modifying polymers pluronic F217 and carbopol 974P-NF, in concentrations ranging between 2% and 10%.

The concentration of PF127 in the solution increases, the gel network tightens, causing an increase in the solution's viscosity [19]. The increase in viscosity together with the retention of mechanical properties provides a significant improvement for the fabrication of FDT intended for enhancing pre-gastric absorption and bioadhesive properties resulting in longer duration of action together with improving the mouth-feel due to the viscous nature of the polymer.Similar work investigating the formulation of lipophilic drug using polymer solution of Pluronic F127 showed better bioadhesive retention (79%) of the formulation when compared to another polymer solution investigated (polyethylene glycol distearoyl phosphatidyl ethanolamine). Thus, incorporation of PF127 provides an ideal opportunity to increase bioavailability of drug candidates together with enhancement of solubility due to the formation of micelles [20]. Carbopol 974P-NF Figs. 10 and 11 both show that the addition of carbopol 974P-NF (C974P) had a negative effect on the mechanical properties of the tablets, with both hardness and fracturability decreasing with an increase in carbomer concentration. The addition of small amounts (2%) of C974P caused a decrease in the hardness of the tablet from 30.9 ± 2.8 N (50% mannitol FDT) to 15.6 ± 1.5 N ($P < 0.0001$). Tablets with C974P concentrations beyond 4% were found to exhibit increasingly poor mechanical properties, with the 10% FDTs exhibiting the lowest hardness: 2.3 ± 0.1 N. All the tablets were observed to be dry and powdery to the touch, with the slightest physical contact causing them to break apart. Fracturability also decreased considerably with an increase in carbopol concentration, falling from 4.5 ± 0.3 N (50% mannitol) to as low as 3.0 ± 0.1 N as exhibited by the 6% C974P tablets. Fracturability tests were not conducted on the 8% and 10% C974P FDTs, as all the prepared tablets disintegrated during the fracturability tests. These findings are contrary to those observed in previous studies [21] which have shown that the addition of C974P to formulations produced tablets of high mechanical strength, low friability and improved viscosity. DSC studies conducted on the formulations comprising ternary system consisting of gelatin, mannitol and carbopol resulted in a reduction in the glass transition temperature (_31.7 ± 0.7 _C with the polymer and _27.5 ± 0.1 _C without the polymer) (Fig. 14 and Table 5).

This reduction in the glass transition was expected due to an increase in the total solid content of the formulation due to the addition of the polymers. However, an interesting finding from the DSC scans (Fig. 14) showed that the temperature for the onset of crystallisation of mannitol remained unaffected upon the addition of Pluronic F127, whereas formulations comprising carbopol showed a lowering of temperature at the onset of crystallisation of mannitol (Fig. 8). Previous studies that investigated the crystallisation behaviour of mannitol in the presence of other excipients such as polymers/drugs have shown that lowering of melting temperature of mannitol is associated with hydrogen bond interactions between the polyol and the drug [22]. Similarly, other studies have shown that carbopol has a high tendency to form intermolecular hydrogen bonds [23,24]. It may be possible that the reduction in the crystallisation temperature for formulations containing carbopol may be associated with the formation of hydrogen bonds between the carbopol and the OH groups in mannitol.

Additionally, SEM images for the formulations containing carbopol show the formation of sheet-like structures (Fig. 15c and d) when compared to spherical, porous mesh-like structure for formulations containing mannitol or pluronic with mannitol (Fig. 15a and b). Therefore, the above two factors: drift in the crystallisation temperature of mannitol, suggesting an interaction between carbopol and mannitol, and the formation of layered sheet-like structures, as suggested by SEM, may explain the failure of carbopol in the fabrication of a lyophilised fast-disintegrating tablets. Fig. 12 shows that, barring the initial increase in disintegration time exhibited by the 2% C974P tablet (from 13.3 ± 2.1 s to 27.3 ± 1.5 s), disintegration times were consistently lowered with an increase in carbopol concentration, falling as low as 4.0 ± 1.0 s (10% C974P tablet). The decreased disintegration times can be attributed to the dry,

powdery nature of the tablet and its poor mechanical properties. Disappointingly, the addition of C974P failed to improve the viscosity of the dissolved tablet solution significantly (P > 0.05) (see Fig. 13). The reason for this failure is unclear, although it is speculated that the freeze-drying of C974P caused a change in the basic properties of the carbomer. Previous studies on C974P were primarily conducted on tablets prepared by conventional compaction methods.

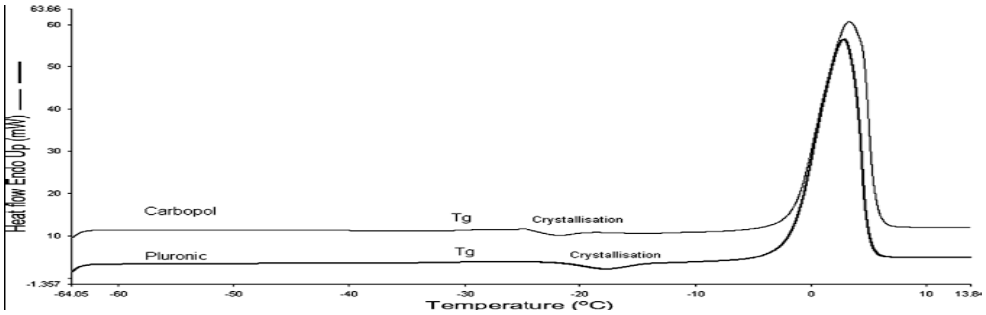

Fig.14. Differential scanning calorimetry graph clearly illustrating the glass transition temperatures (Tg) of the formulation incorporating viscosity-modifying polymers Pluronic F127 and carbopol 974P-NF. 10–15 mg of each sample was initially cooled to _65 _C, and then heated to 20 _C at a rate of 5 _C/min with a nitrogen purge of 20 ml/min.

Selecting the best formulation

Selection of the best formulation depended on the LTI value of the individual formulations of the tablet. Each LTI value was alsomTable.5mGlass transition temperatures (Tg _C) of the formulation incorporating viscositymodifying polymers Pluronic F127, carbopol 974P-NF., Polymer Tg _C, Carbopol 974P-NF _31.7 ± 0.7, Pluronic F127 _32.1 ± 0.4

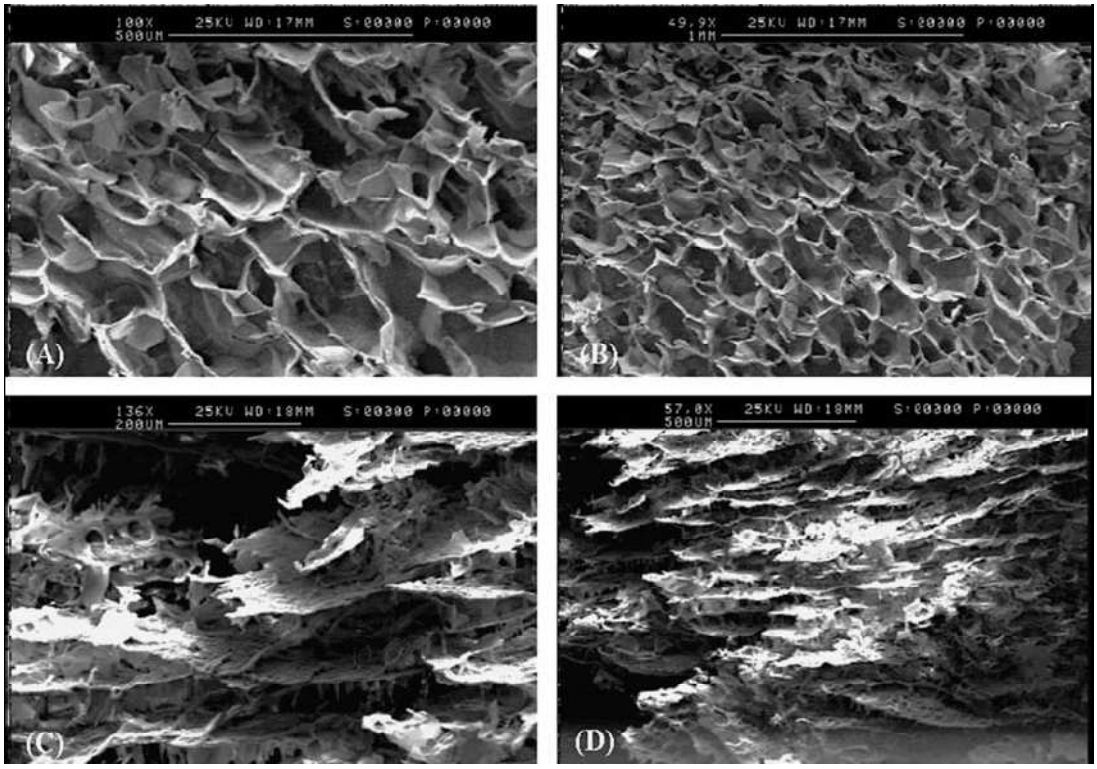

Fig. 15. SEM pictures of viscosity-modifying polymers to be taken forward for future studies. (A and B) High (A) and low (B) magnification pictures of FDT containing 2% Pluronic F127. Pore size: _130–190 lm. (C and D) High (C) and low (D) magnification pictures of FDT containing 4% carbopol 974P-NF. Pore size cannot be measured, as SEM pictures appear layered.

Compared to the LTI value of the 50% mannitol formulation brought forward to Stage III, using an equation termed the Modified Relative Lyophilised Tablet Index (MRLTI) [(polymer LTI)/(saccharide LTI)]. The MRLTI value provided a ratio indicative of whether the new polymer formulation was potentially better than the previous mannitol formulation. The results showed (data not shown) that all the formulations appeared to have affected the properties of their tablet . The addition of C974P in increasing concentrations greatly affected the mechanical strength of the tablet, while failing to improve the viscosity of the dissolved tablet solution. As such, all C974P formulations were disregarded in the final analysis. However, the addition of PF127 in increasing concentrations caused an improvement in the viscosity of the tablet, while maintaining the mechanical properties of the tablet. However, this also caused the disintegration times to slow, although formulations with PF127 concentrations of 8% and below did exhibit times within the 3 min specified by the EU pharmacopoeia. Based upon the hardness, disintegration times, viscosity and MRLTI values of the tablet, the 6% PF127 formulation is judged to be the best for future studies (hardness: 28.0 ± 3.3 N; disintegration time: 58.7 ± 1.5 s).

Conclusion

This study aimed to fabricate and optimise FDTs prepared by freeze-drying to have sufficient mechanical strength to withstand manual handling, rapid disintegration times, and sufficient viscosity and bioadhesiveness to maximize oral absorption. The tablets were fabricated using a progressive three-stage approach, which involved the stage-wise addition of gelatin, saccharides and viscosity-modifying polymers, respectively. Stage I of the study, which involved determining the ideal gelatin concentration and bloom strength ratio, revealed that increasing the concentration of gelatin increased the strength and disintegration time of the tablet. Increasing the ratio of high (225) bloom strength gelatin did not influence the hardness of the tablet, but appeared to have an effect on the disintegration times. The 5% gelatin formulation, comprising a 50:50 ratio of 75:225 BSGs, was judged most ideal (hardness: 13.7 N, disintegration time: 24.1 s) based on LTI values, and was taken forward to Stage II: the addition of the saccharides sorbitol, mannitol and sucrose in concentrations between 10% and 80%. Of the three saccharides, the addition of mannitol in concentrations between 20% and 50% was found to improve the properties of the tablet the most, with the 50% mannitol formulation being judged as the best (hardness: 30.9 N; disintegration time: 13.3 s). This formulation was taken forward to the third stage, which involved the incorporation of the viscosity-modifying polymers Pluronic F127 and carbopol 974P-NF in concentrations between 2% and 10%. The addition of carbopol 974P-NF had a severe detrimental effect on the mechanical properties of the FDTs, and failed to improve the viscosity of the dissolved FDT solution significantly ($P > 0.05$). Pluronic F127, however, did improve the viscosity of the dissolved tablet solution with an increase in polymer concentration, although the disintegration times of the tablet worsened as the concentration of PF127 in the formulation increased. These results provide a platform for the development of FDT characterized by improved mechanical properties and enhancement in viscosity. Currently work is underway to investigate the extent of bioadhesion offered by incorporation of polymers and a range of model drug compounds and their impact on
the physical properties of the tablets.

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