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Application of poly(acrylic acid) superporous hydrogel microparticles as a super-disintegrant in fast-disintegrating tablets

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Abstract

Poly(acrylic acid) superporous hydrogel (SPH) microparticles possessing a unique porous structure were used as a wicking agent to decrease disintegration time of fast-disintegrating tablets (FDTs). The compression behaviour of poly(acrylic acid) SPH microparticles was evaluated using the Kawakita equation. Effects of various SPH microparticle sizes and a 19-run fractional factorial design were evaluated. The factorial design was based on four factors consisting of ketoprofen, SPH microparticle, filler, and tableting pressure, and each factor contained three levels on the disintegration time and tensile strength of the prepared FDTs. The poly(acrylic acid) SPH microparticles existed in an amorphous state and swelled approximately 80-times in distilled water and 50-times in pH 6.8 0.2 M phosphate buffer. The compressibility of SPH microparticles increased significantly as the microparticle size increased. The FDTs made of SPH microparticles in the range of 75–106 μm showed the fastest disintegration time and higher tensile strength. SPH microparticle, tableting pressure and ketoprofen had significant effects on disintegration time and tensile strength of ketoprofen FDTs. The FDTs that were prepared with 2.5% w/w SPH microparticles of 75–106 μm at 63 MPa pressure possessed a tensile strength of 84.4 ± 4.1 N cm^{-2} and disintegrated in 15.0 ± 2.0 s. It was concluded that the poly(acrylic acid) SPH microparticles could serve as a good super-disintegrant decreasing the disintegration time of FDTs.

Introduction

Drug delivery using fast-disintegrating tablets (FDTs) is rapidly gaining interest in the pharmaceutical industry since the tablets either disintegrate or dissolve in the mouth rapidly, without requiring any water to aid in swallowing. This novel dosage form is suitable for all age groups, particularly for children, the elderly and schizophrenic patients who have difficulty in swallowing conventional tablets and capsules (Lindgren & Janzon 1993). To ensure the tablet's fast-disintegrating property, water must be quickly absorbed into the tablet matrix causing rapid disintegration of the tablet. The current approaches of making fast-disintegrating tablets are maximizing the porous structure of the tablet matrix and incorporating appropriate disintegrating agents and/or highly water-soluble excipients in the tablet formulation (Chang et al 2000; Habib et al 2000; Sastry et al 2000; Dobetti 2000).

Direct compression is the easiest way of manufacturing tablets. The biggest advantages are the low manufacturing cost and high mechanical property of the tablets (Takao et al 1996). Disintegration and solubilization of direct-compression tablets are based on single or combined actions of disintegrants, water-soluble excipients, and effervescent agents (Shangraw et al 1980). In many cases, the disintegrants play a major role in the disintegration and dissolution process of FDTs made by direct compression. The choice of a suitable type and an optimal amount of disintegrant is critical for ensuring fast disintegration (Dobetti 2000). The super-disintegrants, such as sodium starch glycolate and sodium croscarmellose, have been used as wicking agents in the FDT formulations (Bi et al 1999; Khankari et al 2001; Mattsson et al 2001).

Recently, superporous hydrogel (SPH) blocks with fast swelling and super-absorbent properties have been developed (Park et al 2001b) for developing a gastric

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retention device (Chen et al 1999; Chen & Park 2000). SPHs are hydrogels with numerous pores connected together to form open channel structures. Water is absorbed into the dried SPHs by capillary wetting rather than by diffusion. The dried SPH hydrogels swell extremely fast with the swelling ratio easily reaching more than 100-times within minutes (Chen et al 1999; Park et al 2001a).

SPH microparticles, having a unique porous structure for fast transport of water through capillary forces, are expected to result in an extremely fast wicking effect into the tablet core. Tablets prepared by direct compression in the presence of SPH microparticles are thought to disintegrate very quickly due to the fast uptake of water into the core of the tablets (Park 2002). To evaluate the effect of SPH microparticles on the disintegration and tensile strength of FDTs prepared by direct compression, FDTs containing sugar-based excipients and ketoprofen, a model drug, were prepared using SPH microparticles as a disintegrant. A SPH based on poly(acrylic acid), sodium salt, was synthesized and characterized. The fast disintegrating tablets composed of various amounts of SPH microparticles were prepared using a fractional factorial design. The formulation and process were optimized according to the disintegration time and tensile strength of resultant tablets.

Materials and Methods

Materials

Acrylic acid, ammonium persulfate, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMED), and poly(ethylene glycol) diacrylate (PEGDA) were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI). Sodium hydroxide, sodium bicarbonate and citric acid were bought from Mallinckrodt Baker, Inc. (Paris, KY). Mannitol was a gift from SPI Pharma Inc. (New Castle, DE). Ketoprofen was purchased from Nordic Synthesis (Karlskoga, Sweden). Dextrates (EMDEX, NF) was a gift from Penwest Pharmaceuticals Co. (Patterson, NJ). Fumed silica (CAB-O-SIL) was bought from CABOT corporation Cab-O-Sil division (Tuscola, IL). Magnesium stearate was obtained from Mallinckrodt Specialty Chemicals Company (St Louis, MO). Aspartame was purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA).

Synthesis of poly(acrylic acid) SPH

Synthesis of the SPH was based on the methods described previously (Chen et al 1999; Chen & Park 2000). Briefly, the monomer solution was prepared by neutralizing acrylic acid with NaOH solution to make a final pH of 6.0 and the final monomer solution equivalent to 6.0 M of total acrylic acid and sodium acrylate. The following components were added sequentially to a beaker at ambient temperature: 1.25 M (208.0 mL) of the 6.0 M sodium acrylate solution; 6.25×10^{-3} M (21.9 mL) 20% w/w PEGDA; 11.56 M (208.0 mL) distilled water; 1.25×10^{-2} M (9.0 mL) acrylic acid; 1.25×10^{-2} M (14.25 mL) 20% w/w ammonium persulfate; 1.25×10^{-2} M (7.25 mL) 20% w/w TMED; and 1.25×10^{-1} M (10.5 g) $NaHCO_3$. The whole solution was stirred vigorously by magnetic stirring to accelerate foaming and to evenly distribute the gas bubbles. The gelling started within 30 s. Synthesis process was carried out under a nitrogen atmosphere.

Synthesis of the poly(acrylic acid) hydrogel and poly (acrylic acid) was similar to the synthesis of poly(acrylic acid) SPH, but the foaming agent $NaHCO_3$ was omitted in the synthesis of poly(acrylic acid) hydrogel; and $NaHCO_3$ and crosslinker PEGDA were deleted in the synthesis of poly(acrylic acid). The synthesized poly(acrylic acid), SPH and hydrogel were purified with absolute ethyl alcohol and dried in an oven at 50 °C. The dried samples were milled using IKA A11 BASIC (IKA Works, INC; Wilmington, NC) and the resultant microparticles were screened using different sieves to get various particle size ranges.

Swelling of SPH microparticles

Samples of SPH microparticles (0.10 g) were placed in a series of graduated cylinders (50 mL). Deionized water or 0.2 M phosphate buffer (25 mL) was added into the cylinder. The system was mixed and left to stand at 37 °C. After 60 min, the volumes of the swollen samples at equilibrium were measured and the swelling value calculated using the following equation (Edge et al 2002):

$$\text{Swelling value} = \text{volume of sample}/\text{weight of a dry sample} \quad (1)$$

X-ray SPH microparticle diffraction

Analysis of poly(acrylic acid) SPH microparticles was carried out on a Shimadzu XRD-6000 X-ray microparticle diffractometer (Kratos Analytical, Inc., Chestnut Ridge, NY) equipped with a fine-focus X-ray tube using Cu radiation (1.5406 Å). The tube voltage and amperage were set at 30 kV and 30 mA, respectively. The divergence and scattering slits were set at 1, and the receiving slit was set at 0.15 mm. A sodium iodide scintillation detector was used to detect diffracted radiation. Theta-two-theta continuous scans at 5° min^{-1} (with a step size of 0.02°) from 3 to 40° 2θ were used. The instrument was calibrated using silicon standard.

Vapour sorption gravimetry

Moisture sorption isotherm of the SPH microparticles was determined using a Symmetric Gravimetric Analyzer Model 100 (SGA-100, VTI corporation, Hialeah, FL). SPH microparticles (5.0 mg) ranging from 44 to 106 μm were placed in the sample holder and dried at 60 °C for 3 h. The relative humidity was then set to zero until stable mass was recorded and the balance was zeroed. The sorption balance was programmed to generate relative humidity steps in an absorption/desorption cycle. The target relative humidity, under a continuous nitrogen flow of 200 cm^3 min^{-1}, used during absorption of the sample was

in the range of 10–90% relative humidity. The relative humidity was held at each 5% relative humidity increment until equilibrium occurred. During the desorption period the same steps were taken in the reverse order, starting from 90% relative humidity. The temperature in the incubator was controlled at 25 °C. Sample mass was represented as a percentage of the dried mass.

Tablet preparation

Tablets of 500 mg were compressed on a single punch Carver Laboratory Press (Carver Inc. Wabash, IN) at different compression pressures using plane-face punches with a diameter of 0.5 inch.

Compression data analysis

Poly(acrylic acid) SPH microparticles in the range 25–250 μm were dried at 60 °C for 12 h. The pure SPH microparticle tablets were compressed at pressure ranging from 7 to 615 MPa. Changes in density or porosity of SPH tablets were obtained by measuring the thickness of resultant tablets at zero pressure. The densification behaviour of SPH microparticles was evaluated by means of the Kawakita equation (Kawakita & Ludde 1971; Denny 2002) as follows:

$$P/C = P/a + 1/ab \quad (2)$$

where C is the relative volume decrease i.e.

$$C = (V_0 - V)/V_0 \quad (3)$$

where V_0 is the initial volume and V is the volume of the particle under the applied pressure P. A plot of P/C against P should give a straight line for deriving a and b as the constant characteristics to particles being compressed. The constant a is equal to the value of the initial porosity, and the constant b has the dimension of the reciprocal of stress.

Experimental design

As a result of preliminary experiments on variables that have effects on the disintegration time and tensile strength of ketoprofen FDTs, four variable factors were chosen for our experiment, ketoprofen, SPH microparticles, filler (dextrates and granular mannitol) and tableting pressure, and each factor had three levels (Table 1). All other factors that might influence the responses were kept the same in all runs.

A 19-run experiment created by fractional factorial design using a SAS 8.2 program was performed. Analysis of variance of the factors on the disintegration time and tensile strength of ketoprofen FDTs were analysed using the SAS program.

Tensile strength of tablets

The crushing force F (N), thickness T (cm) and diameter D (cm) of tablets were determined using a VK 200 Tablet Hardness Tester (Vankel, 36 Meridan Road, Edison, NJ). The tablet tensile strength (σ_x) of FDTs was calculated from the following equation (Fell & Newton 1970):

$$\sigma_x = 2F/\pi DT \quad (4)$$

Table 1 Factors and levels in the fractional factorial experimental design.

Factor	Label	Level		
		1	2	3
A	Ketoprofen (% w/w)	0	10	20
B	SPH* (% w/w)	0	2.5	5
C	Dextrates:mannitol	1:0	4:1	3:2
D	Pressure (MPa)	42	63	84

*SPH microparticles of 75–106 μm.

Disintegration time

The disintegration time of the resultant tablets was measured using a Basket-rack assembly according to the USP24/NF19 method.

Results and Discussion

Synthesis of SPH

SPH was synthesized by crosslinking polymerization of sodium acrylate using PEGDA as a crosslinker in the presence of carbon dioxide bubbles that were generated by the reaction of sodium bicarbonate with acrylic acid (Chen et al 1999). In the synthesis of SPH, the molar ratio of acrylic acid to PEGDA was 200:1, and the molar ratio of acrylic acid to ammonium persulfate (initiator) and to TMED was 100:1. After being milled and screened by a series of sieves, SPH microparticles of various size ranges were obtained.

Swelling of SPH microparticles

Poly(acrylic acid) SPH microparticles swelled to approximately 80-times of their dried state in distilled water and approximately 50-times in pH 6.8 phosphate buffer (Table 2). The swelling values increased slightly as the microparticle size increased. However, the swelling values of various microparticle sizes were not significantly different ($P > 0.05$). For SPH in large blocks, it has been reported that the swelling ratio was up to 300-times. The pores inside the SPH were connected to each other to form extensive capillary channels; this helped the dried gel swell in water to near equilibrium in a matter of minutes (Chen et al 1999). The superpores were destroyed during grounding of the SPH blocks into microparticles. Thus, the swelling value of SPH microparticles was lower compared with

Table 2 Swelling values of poly(acrylic acid) superporous hydrogel microparticles with various sizes.

Size (μm)	Swelling value ($cm^3 g^{-1}$)	
	Distilled water	Phosphate buffer
25–44	77.5 ± 2.5	47.5 ± 2.5
44–106	78.0 ± 2.0	48.0 ± 2.0
106–150	80.0 ± 2.5	50.0 ± 2.5
150–250	82.5 ± 2.5	52.5 ± 2.5

Swelling data represent mean ± s.d. (n = 3).

the same SPH in blocks. The swelling values of sodium starch glycolate were approximately 20-times (Ferrari et al 2000; Edge et al 2002) and croscarmellose sodium rapidly swelled to approximately 10-times on contact with distilled water (Ferrari et al 2000). Compared with these commercially available super-disintegrants, the SPH microparticles showed the highest swelling values for a better disintegrant efficiency in tablets.

Crystallinity of poly(acrylic acid) SPH microparticles

The X-ray diffraction diagrams of microparticles of poly (acrylic acid) SPH, poly(acrylic acid) hydrogel and poly (acrylic acid) are shown in Figure 1. There was no sharp peak in the X-ray diffraction diagrams, indicating that the three polymers existed in an amorphous state. Poly(acrylic acid) SPH was different from poly(acrylic acid) hydrogel and poly(acrylic acid) in the diagrams. This difference may have been due to the existence of sodium in the crosslinked amorphous network of poly(acrylic acid) SPH, since SPH particles were not washed with water to remove the salts.

Moisture sorption isotherm curve of poly (acrylic acid) SPH microparticles

Absorption and desorption of moisture by poly(acrylic acid) SPH microparticles were measured with the sorption balance at 25 °C as shown in Figure 2. The moisture absorption increased with the increase of relative humidity. Absorption of water was as high as 150% of the dry mass at the relative humidity 90%, which may have been due to the high hygroscopic property and high porosity of the SPH. Absorption and desorption behaviour of the SPH microparticles were similar in the range of 35–90% relative humidity. However, the water content at desorption was higher than the corresponding values at absorption when the relative humidity was below 35%. The difference may have been due to the fact that desorption of moisture from SPH needed a longer time than the predetermined time of 3 h at 25 °C.

Compressibility and compactability study of SPH microparticles

The compressibility and compactability has a direct relationship with the tableting performance of the particulate solids. The compactability of SPH microparticles was measured by plotting the SPH tablet tensile strength as a function of compaction pressure. The tablet tensile strength increased in a sigmoid shape following the pressure increase. As the pressure increased higher than 400 MPa, the tablet tensile strength did not increase any further.

The compressibility behaviour of poly(acrylic acid) SPH microparticles was analysed by measuring the relationship between compression pressure and the relative volume decrease of the microparticles using the Kawakita equation (Figure 3). When the pressure was lower than 63 MPa, a curvature appeared for various ranges of microparticle sizes. Straight lines ($r^2 > 0.9900$) were observed at the pressure higher than 63 MPa for various particle sizes. In the

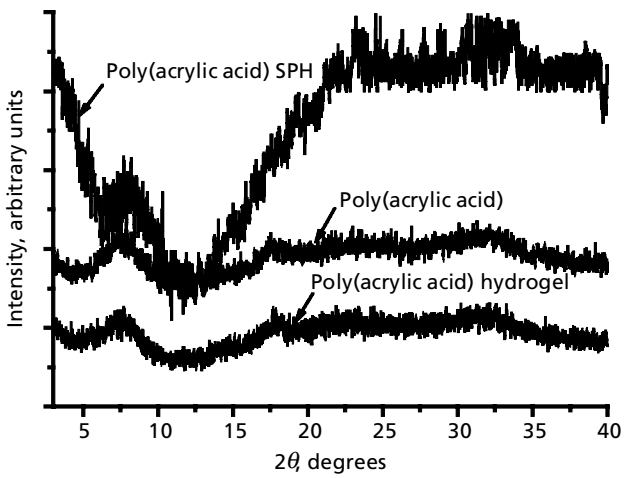

Figure 1 X-ray diffraction diagrams of poly(acrylic acid), poly (acrylic acid) hydrogel, and poly(acrylic acid) superporous hydrogel microparticles.

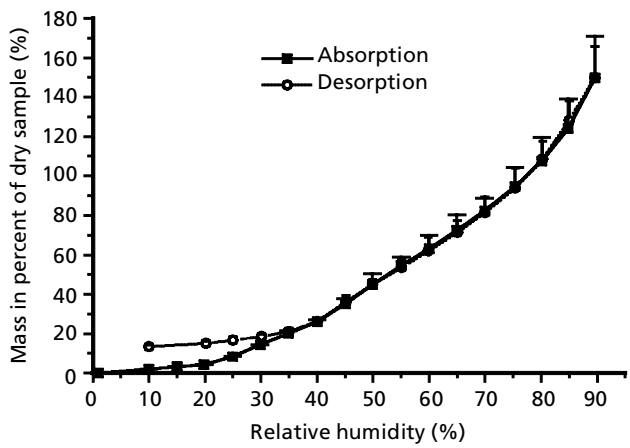

Figure 2 The absorption and desorption of moisture by poly (acrylic acid) superporous hydrogel microparticles as measured by a sorption balance at 25 °C. Mean value ± s.d. (n = 3).

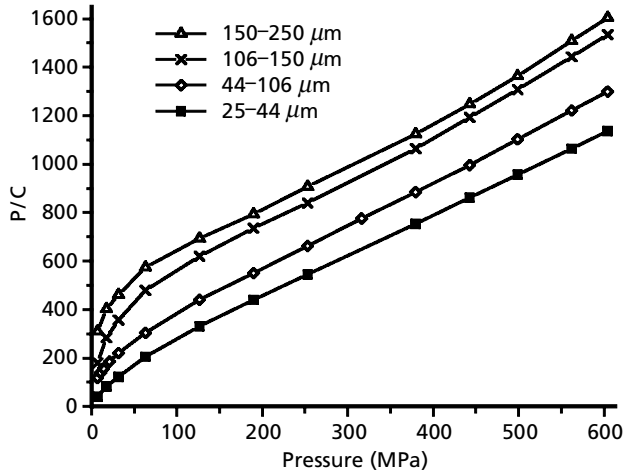

Figure 3 Kawakita plots for poly(acrylic acid) superporous hydrogel microparticles.

Kawakita equation, the constant, a, gives an indication of the maximum volume reduction available and is considered to describe the compressibility of the particle. The constant a for poly(acrylic acid) SPH microparticles decreased significantly from 0.59 ± 0.04 ($n = 3$) for 25–44 μm to 0.53 ± 0.03 ($n = 3$) for 150–250 μm. The constant b is considered to describe an inclination toward volume reduction, and has the dimension of the reciprocal of stress. The stress of SPH microparticles increased significantly from 65.3 ± 2.5 ($n = 3$) for 25–44 μm to 236.1 ± 6.8 ($n = 3$) for 150–250 μm. Kawakita & Ludde (1971) stated that this equation holds best for soft fluffy pharmaceutical particles. It is now generally accepted that the Kawakita equation is best used for low pressure and high porosities (Kawakita & Ludde 1971; Denny 2002). The SPH microparticles possessed a high porosity, and so the Kawakita equation was suitable to evaluate the compressibility of SPH microparticles.

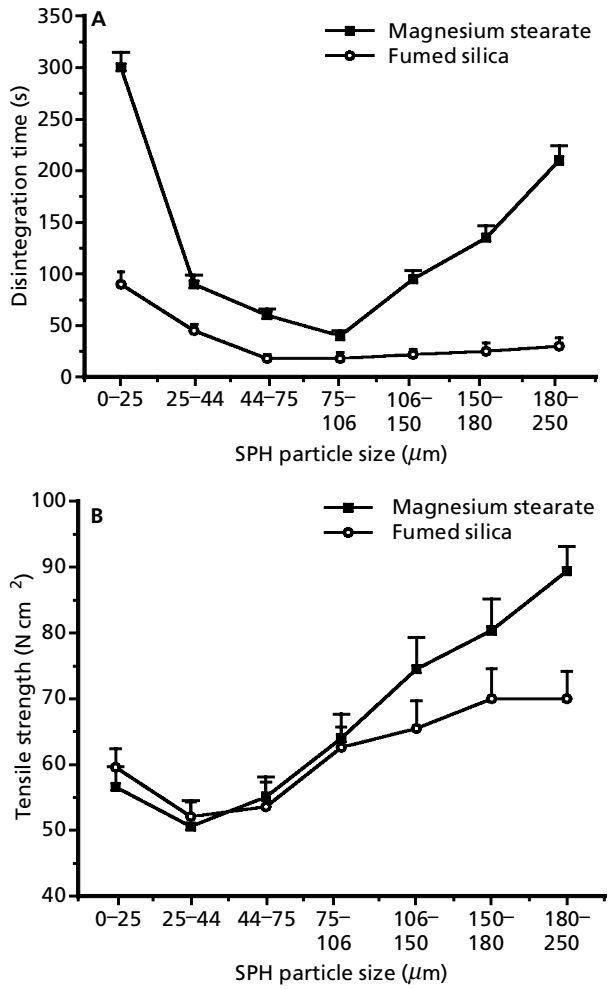

Figure 4 The effects of poly(acrylic acid) superporous hydrogel microparticle sizes on the disintegration time (A) and tensile strength (B) of ketoprofen fast disintegration tablets. Mean value ± s.d. ($n = 3$).

Fast disintegrating tablets

The FDTs containing SPH microparticles and water soluble carbohydrates were evaluated using ketoprofen as a model drug. Ketoprofen is a hydrophobic drug and has poor compaction properties. If ketoprofen could be successfully formulated in FDTs containing SPH microparticles, this study could be easily extended to other drugs. To mask the unpleasant taste of ketoprofen, all the formulations contained 1.5% w/w citric acid, 2.0% w/w aspartame.

Effect of SPH microparticle size on the disintegration time and tensile strength

The ketoprofen FDT formulations containing 2.5% w/w SPH microparticles with different sizes were prepared at 63 MPa pressure. Figure 4 shows the effect of microparticle size on the disintegration time and tensile strength of ketoprofen FDTs. The minimum disintegration time was observed when the microparticle size was in the range of 75–106 μm. Tensile strength of the tablets decreased as the SPH microparticle sizes decreased from 180–250 μm to 25–44 μm. However, when the microparticle size was smaller than 25 μm, the tensile strength of resultant tablets increased as the size decreased. According to the results, the optimal microparticle size should be in the range of 75–106 μm. From Figure 4, the glidants and/or lubricants had a significant effect on the disintegration time of the tablets. The disintegration time of ketoprofen FDTs significantly increased after the addition of hydrophobic magnesium stearate as compared with the addition of silicon dioxide. For the tablets containing a swelling disintegrant, a negative effect of magnesium stearate on the disintegration time was observed (Smallenbroek et al 1981). Different particle sizes of disintegrants might result in different swelling pressure in the process of tablet disintegration (List & Mauzzam 1979). The effect of disintegrants on tablet disintegration time and hardness depends on the physicochemical properties of the disintegrants themselves and formulation composition (Asker et al 1975).

Experimental design of ketoprofen FDTs

The disintegration time and tensile strength of ketoprofen FDTs prepared according to the fractional factorial design are shown in Table 3. The analysis of variance results of disintegration time indicated that the three factors SPH ($P < 0.01$), pressure ($P < 0.05$) and ketoprofen content ($P < 0.05$) had significant effects on the disintegration time of ketoprofen FDTs. The proportion of dextrates to mannitol had little effect on the disintegration time of ketoprofen FDTs.

SPH microparticles, which acted as a super-disintegrant in the tablets, was a key factor to tablet disintegration time. With 2.5% w/w of SPH microparticles (75–106 μm), the disintegration time of ketoprofen FDTs decreased with the increase of SPH content in tablet formulation. However, the disintegration time did not decrease with the increase of SPH content when it was higher than 2.5% w/w. The maximum disintegration force developed in a tablet depended on the quality and quantity of the disintegrating agent and was related to the amount of water absorbed by the tablet. Water penetration rate, rather than the amount of water absorbed, influenced the disintegration time (Colombo et al 1981). The swelling materials make pore walls hydrophilic, providing enough swelling force to produce interparticle bond disruption (Caramella et al 1984). The time taken for the tablets to disintegrate was generally reduced by the addition of a super-disintegrant; the effectiveness of the super-disintegrant was dependent on the nature of the compound and excipients used (Mattsson et al 2001).

Porosity depended on the pressure at which tablets were compressed as well as on the nature of the materials used. A high compression force led to tablets with a lower porosity. Penetration of water into the tablet was hindered, and thus the disintegration time increased. Fast dispersible ibuprofen tablets with the optimal porosity of approximately 13% had the shortest disintegration time of 36 s (Schiermeier & Schmidt 2002). Ketoprofen is a hydrophobic drug that can increase the wetting time of tablets as the content in the formulation increases, and thus increase the disintegration time of ketoprofen FDTs. The analysis of variance results for tensile strength of ketoprofen FDTs showed that the three factors tableting pressure ($P < 0.01$), SPH microparticles ($P < 0.01$) and ketoprofen ($P < 0.05$) had significant effect on the tensile strength of ketoprofen FDTs. The filler had little effect on the tensile strength of resultant tablets. The tensile strength of the FDTs greatly increased as the pressure increased. The tensile strength of tablets or compacts is governed by the sum of the bonding forces of all individual interparticulate bonds in the failure plane of the compact, and the sum increases with the compaction pressure through rearrangement of particles, particle deformation and fragmentation (Eriksson & Alderborn 1995; Rankell & Higuchi 1968). However, the tensile strength of tablets decreased as the amount of SPH microparticles increased in the formulation, which may have been due to the high stress of SPH microparticles.

Selection of the optimum setting

An ideal FDT should possess both short disintegration time and high mechanical strength. The mechanical strength of a tablet is of great importance with regard to the subsequent packaging process and transportation. The optimal ketoprofen FDT should have a disintegration time of less than

Table 3 Factors and responses of the 19-run fractional factorial design.

Run	Ketoprofen (A) (% w/w)	SPH (B) (% w/w)	Dextrates: mannitol (C)	Pressure (D) (MPa)	Disintegration time (s)	Tensile strength ($N\,cm^{-2}$)
1	10	5	3:2	84	96.8 ± 19.0	110.6 ± 9.9
2	10	5	4:1	42	16.0 ± 1.2	36.5 ± 2.0
3	10	5	1:0	63	15.0 ± 0.5	66.4 ± 4.6
4	10	2.5	3:2	84	99.8 ± 17.3	120.1 ± 10.9
5	10	2.5	4:1	42	14.0 ± 0.4	39.7 ± 4.4
6	10	0	4:1	84	308.5 ± 19.5	152.5 ± 4.9
7	10	0	1:0	63	207.5 ± 18.6	119.1 ± 9.8
8	20	5	4:1	84	219.5 ± 7.9	110.1 ± 9.4
9	20	5	4:1	63	44.8 ± 8.8	70.3 ± 12.8
10	20	2.5	1:0	84	145.0 ± 16.3	104.0 ± 14.7
11	20	2.5	1:0	42	18.3 ± 1.8	36.4 ± 0.8
12	20	0	3:2	63	339.5 ± 36.4	90.6 ± 5.3
13	20	0	3:2	42	101.3 ± 13.6	37.4 ± 4.5
14	0	5	3:2	42	11.5 ± 1.5	30.2 ± 2.3
15	0	5	1:0	84	25.0 ± 1.2	99.9 ± 8.9
16	0	2.5	3:2	63	18.0 ± 1.2	86.6 ± 18.3
17	0	2.5	4:1	63	20.5 ± 1.9	87.8 ± 21.5
18	0	0	4:1	84	82.0 ± 12.4	146.1 ± 16.0
19	0	0	1:0	42	52.5 ± 2.1	58.7 ± 3.6

Response data represent mean ± s.d. (n = 4).

30 s with a tensile strength of the tablet no less than 75 N cm^{-2}. Ketoprofen could increase the disintegration time and decrease the tensile strength of tablets. For the formulation ketoprofen was chosen as 10% w/w. From the analysis of variance results of disintegration time and tensile strength, the SPH microparticle and tableting pressure had significant effects on the resultant FDTs. When the amount of SPH microparticles in the formulations increased from 2.5 to 5.0% w/w, the disintegration time did not decrease any further. On the other hand, the microparticles had an adverse effect on the resultant tablet tensile strength. The amount of SPH microparticles in the formulation was chosen as 2.5% w/w, which was high enough to decrease the disintegration time but did not result in a great decrease in the tensile strength of the tablets. High pressure can increase the tensile strength, but significantly prolong the disintegration time of the resulting tablets. When the pressure was higher than 63 MPa, the disintegration time was too long to be acceptable for FDTs. However, when the pressure was lower than 63 MPa, the resultant tablets were too weak to be packaged as conventional tablets. Optimum pressure was considered to be 63 MPa. The filler had no significant effect on either disintegration or tensile strength of resultant tablets. Dextrates is sweeter and cheaper than mannitol, and thus dextrates was selected as a water soluble filler in the ketoprofen FDTs. The optimum setting of ketoprofen FDTs was: A2 (ketoprofen, 10% w/w), B2 (SPH microparticles, 2.5% w/w), C1 (dextrates:mannitol = 1:0) and D2 (pressure, 63 MPa). The optimum formulation contained 10% w/w ketoprofen, 2.5% w/w SPH microparticles (75–106 μm), 83.5% w/w dextrates, 1.5% w/w citric acid, 2.0% w/w aspartame, and 0.5% w/w fumed silica. The optimal setting was performed six times, and the disintegration time and tensile strength of optimal FDTs were 15.0 ± 2.0 s and 84.4 ± 4.1 N cm^{-2}, respectively. The results indicated that the ketoprofen FDTs produced according to these optimal settings had an excellent response of the disintegration time and tensile strength.

Conclusions

Poly(acrylic acid) SPH was synthesized using PEGDA as a crosslinker. Poly(acrylic acid) SPH microparticles showed a high swelling property in various aqueous media, and had a high compressibility and good compactability. The microparticle size of SPH had a great effect on the disintegration time of FDTs. The optimal microparticle size for disintegration time was in the range 75–106 μm. A fractional factorial experiment with 19 runs was conducted to evaluate the effects of ketoprofen, SPH, filler and tableting pressure on disintegration time and tensile strength of FDTs. The addition of SPH microparticles significantly decreased the disintegration time of FDTs, but had a negative impact on tensile strength. The optimum ketoprofen FDT consisting of 2.5% w/w SPH microparticles, 10% w/w ketoprofen prepared under 63 MPa pressure, demonstrated 15 s disintegration time and 85 N cm^{-2} tensile strength. The results indicated that poly(acrylic acid) SPH microparticles were a promising super-disintegrant for making FDTs.

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