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Formulation and Evaluation of Rapidly Disintegrating Fenoverine Tablets: Effect of Superdisintegrants

Sunil Kumar Battu
Department of Pharmaceutics, School of Pharmacy, The University of Mississippi, MS, USA

Michael A. Repka and Soumyajit Majumdar
Department of Pharmaceutics, School of Pharmacy, The University of Mississippi, MS, USA and The National Center for Natural Products Research, The University of Mississippi, MS, USA

Madhusudan Rao Y
Center for Biopharmaceutics and Pharmacokinetics, University College of Pharmaceutical Sciences, Katatiya University, Warangal (A.P.), India

The objective of this study was to formulate directly compressible rapidly disintegrating tablets of fenoverine with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration. Effect of varying concentrations of different superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time was studied. Tablets were evaluated for weight variation, thickness, hardness, friability, taste, drug content, in vitro and in vivo disintegration time, and in vitro drug release. Other parameters such as wetting time, water absorption ratio ('*R*'), and drug-excipient compatibility were also evaluated. The disintegration time of the best rapidly disintegrating tablet formulation among those tested was observed to be 15.9 sec in vitro and 37.16 sec in vivo. Good correlation was observed between disintegration time and '*R*' for each of the three superdisintegrants at the concentrations studied. Considering the '*R*' values and disintegration time, crospovidone was significantly superior ($p < 0.05$) compared to the other superdisintegrants tested. Release of drug was faster from formulations containing 6% crospovidone (CP 6) compared to the marketed fenoverine (Spasmopriv®) capsules. Similarity factor 'f_2' (51.5) between dissolution profiles of the rapidly disintegrating tablet formulation CP 6 and the marketed formulation indicated that the two dissolution profiles were similar. Differential scanning calorimetric studies did not indicate any excipient incompatibility, either during mixing or after compression. In conclusion, directly compressible rapidly disintegrating tablets of fenoverine with lower friability, acceptable taste, and shorter disintegration times were obtained using crospovidone and other excipients at optimum concentrations.

Address correspondence to Michael A. Repka, Department of Pharmaceutics, School of Pharmacy and The National Center for Natural Products Research, The University of Mississippi, University, MS 38677. E-mail: marepka@olemiss.edu

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INTRODUCTION

The elderly constitute a major portion of today's population mainly because of increased life expectancy of individuals. Physiological and neurological conditions, such as dysphagia, risk of choking, and hand tremors are leading causes for patient non-compliance in the self-administration of conventional solid oral dosage forms (Chang, Guo, Burnside, & Couch, 2000). Solid dosage forms also present significant administration challenges in other patient groups such as children, mentally challenged and uncooperative patients and patients on reduced fluid diets. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control (Chang et al., 2000; Parakh & Gothoskar, 2003). Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules (Hanawa et al., 1995).

Several fast dissolving drug delivery systems have been investigated in an attempt to overcome the above limitations of conventional solid dosage forms. Scientists at Wyeth Laboratories in the UK pioneered fast dissolving drug delivery during the late 1970s (Suresh, David, & James, 2003). During the last decade, rapidly disintegrating tablet (RDT) technology has drawn a great deal of attention (Fu, Yang, Jeong, Kimura, & Park, 2004). RDTs are also known as fast disintegrating, fast dispersing, rapid dissolving, and rapid melting, and/or orodisperse tablets. The *European Pharmacopoeia* defines the term *orodisperse* as a tablet that can be placed in the mouth where it disperses or disintegrates rapidly before swallowing

(Pharmeuropa, 1998). RDTs approved by United States Food and Drug Administration is classified as orally disintegrating tablets. The advantages of this dosage form over conventional tablets or capsules include ease of administration, patient compliance, and palatability. The fast disintegration of tablets inside the mouth renders possibly a certain degree of absorption throughout the sublingual or the buccal mucosa. Moreover, drug candidates that undergo pre-gastric absorption when formulated as RDTs may show increased oral bioavailability (Virely & Yarwood, 1990). From the perspective of the pharmaceutical industry, RDTs may provide new business opportunities in the form of product differentiation, line extension and life cycle management, exclusivity, uniqueness, and patent life extension. At the present time a significant limitation of RDT formulations is product cost since manufacturing involves use of novel excipients and technologies. In addition, specialized packaging is necessary to withstand handling and transportation mechanics.

The key parameters that are to be considered in the process of formulating a RDT are taste and the disintegration time. Both of these are related either directly or indirectly to the oral cavity. The mucosa in the oral cavity presents a surface area of about 100 cm^2 and three different types of oral mucosa are recognized: the masticatory mucosa, the lining mucosa, and the specialized mucosa. Of the total oral mucosa, 15% of it consists of specialized mucosa, which is present on the dorsum of the tongue. It is mainly involved in identifying the taste of the formulation (Song, Wang, Thakur, Meidan, & Michniak, 2004). The saliva plays an important role in disintegration of RDTs and primarily secreted in the oral cavity by parotid, submandibular (sub maxillary), sublingual glands, and also by numerous minor glands. Saliva is mainly constituted by water (99.5% w/v) and the remaining 0.5% w/v is constituted by dissolved compounds (Saracco, 1993). The principal components of saliva are inorganic electrolytes (0.2% w/v), gases (CO2, N2, and O_2), nitrogen products, such as urea and ammonia, vitamin C, creatinine, and mucins (glycoprotein with high molecular weight which renders the saliva viscous and adhesive). The accepted range of normal salivary flow is comprised from about 0.1 to 0.2 mL/min and reaches 7 mL/min upon stimulation (Rossi, Sandri, & Caramella, 2005; Smart, 2004).

Fenoverine is a novel, potent anti-spasmodic agent that restores smooth muscle motility and relieves the distressing symptoms associated with irritable bowel syndrome (IBS) and primary dysmenorrhoea (Spasmopriv, 2006). IBS is a functional disorder associated with cramping and abdominal pain, which can affect people of any age group. It is estimated that one in five Americans or as many as 20% of the adult population are affected by IBS (IBS, 2006). In addition, it is reported that approximately 75% of those suffering from this disorder are women (Wrong-diagnosis, 2006). The objectives of this study were to assist various patient subpopulations who have difficulty in swallowing conventional dosage forms, by formulating fenoverine containing RDTs with sufficient mechanical integrity, good content uniformity, and acceptable palatability. Drug release profiles were also studied on the RDTs containing the model drug.

EXPERIMENTAL

Materials

Fenoverine, aspartame, and peppermint flavor were gifts from Euro Drug Laboratories (Hyderabad, India); Pearlitol® SD 200, a directly compressible vehicle, was obtained from Signet Chemical Corporation (Mumbai, India); crospovidone, croscarmellose sodium, sodium starch glycolate, and sodium stearyl fumarate were obtained from Zydus Cadila (Ahmedabad, India); microcrystalline cellulose [Avicel PH 102]; and colloidal silicon dioxide [Aerosil®] were purchased from Span Pharma Private Limited (Hyderabad, India); and nigrosine RM 247, a water soluble dye, was purchased from Hi Media Laboratories Private Limited (Mumbai, India). All chemicals were of analytical or pharmacopoeial grade and were used as supplied.

Methods

Assignment of Formulation Codes

Various formulations of fenoverine rapidly disintegrating tablets (RDTs) were designed utilizing three superdisintegrants, crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG) each varied at three different levels (4, 6, and 8%). All of the other ingredients were kept constant. A total of such nine formulations prepared were designated with their codes and will be referred with the same in further sections. The assigned formulation codes were as follows: CP 4, CP 6, and CP 8 for formulations containing CP as the superdisintegrant with concentrations of 4, 6, and 8%, respectively. Similarly, CCS 4, 6, 8, and SSG 4, 6, 8 were the assigned codes for the formulations prepared with these respective superdisintegrants at the percentage levels provided for CP above.

Preparation of Rapidly Disintegrating Tablets

All of the formulation components other than the lubricant and glidant were accurately weighed passed through a 40-mesh sieve and mixed in a V-blender for 15 min. The obtained blend was lubricated with sodium stearyl fumarate and Aerosil® for another 5 min and the resultant mixture was directly compressed into tablets. The amount of all the tablet components other than superdisintegrants and Pearlitol® SD 200 (filler) were kept constant. Round biconvex tablets of 250 mg in weight and 8 mm in diameter were prepared one at a time utilizing a 16-station single rotary tabletting machine (STD model RDD3, Riddhi, Ahmedabad, India). Tablet thickness and hardness were maintained at 5.5 ± 0.1 mm and 2.5 ± 0.5 kg, respectively for all of the formulations. Table 1 outlines the compositions of various RDT formulations studied.

TABLE 1
Quantitative Composition of Fenoverine Rapidly Disintegrating Tablets (mg/Tablet)

Ingredients	Super Disintegrants Concentration (%) of CP/CCS/SSG		
	4% w/w	6% w/w	8% w/w
Fenoverine	100	100	100
Pearlitol® SD 200	93.75	88.75	83.75
Avicel pH 102 (15%)	37.5	37.5	37.5
Super disintegrants	10	15	20
Aspartame (1%)	2.5	2.5	2.5
Peppermint flavor (1%)	2.5	2.5	2.5
Aerosil® (1%)	2.5	2.5	2.5
Sodium stearyl fumarate (0.5%)	1.25	1.25	1.25

RDT Evaluation

Weight Variation

Twenty tablets from a batch size of 500 were randomly selected from each formulation and weighed using a Shimadzu digital balance. The mean ± standard deviation (*SD*) and relative standard deviation (*RSD*) were recorded.

Thickness Variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer (Digimatic micrometer, Mitutoyo, Japan). The mean ± *SD* and *RSD* values were calculated.

Hardness and Friability

Hardness or crushing strength of the tested RDT formulations was measured using the Monsanto hardness tester (Pharmalab, Ahmedabad, India).

The friability of a sample of 20 RDTs was measured utilizing a USP-type Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss (friability) was calculated.

Assay

The RDT formulations were assayed for drug content. Ten tablets were randomly selected from each formulation and pulverized to a fine powder. Weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate and assayed for the drug content utilizing a UV-VIS spectrophotometer (Model SL-150, Elico Pvt. Ltd., Hyderabad, India) at a wavelength of 261 nm.

Taste Evaluation

The taste characteristic of fenoverine RDT formulations with and without peppermint (flavor) and aspartame (sweetener) at varying concentrations (0.5, 1.0, 1.5, and 2.0%) was compared in healthy human volunteers as per the protocol (Ethics permit # 16EC/pharm/ku/2005). Optimum concentrations of flavor and sweetener were determined in preliminary studies based on the taste perception. The evaluation was based on the extent to which subjects liked the taste of each RDT. Formulations were rated on a scale of 1 through 5. A '5' was considered to be "extremely desirable" while a '1' was considered as "extremely undesirable" or "no taste." The volunteers' spontaneous verbal judgments, immediately after the tablet was placed in their mouth and also after 3–4 min, were recorded.

Wetting Time

Five circular tissue papers were placed in a petri dish of 10 cm diameter as depicted (Figure 1). Ten milliliters of water containing 0.5% nigrosine, a water-soluble dye, was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petri dish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time (Bi et al., 1996). These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch.

Water Absorption Ratio (R)

The weight of the tablet prior to placement in the petri dish was noted (w_b) utilizing a Shimadzu digital balance. The wetted tablet was removed and reweighed (w_a). Water absorption ratio, *R*, was then determined according to the following equation.

$$R = 100 \times (w_a - w_b) / w_b \quad (1)$$

where w_b and w_a were tablet weights before and after water absorption, respectively.

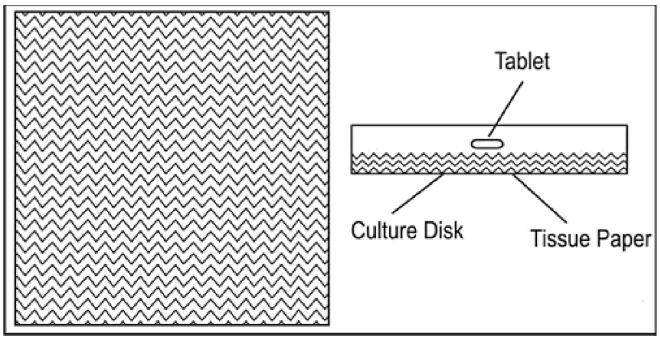

FIGURE 1. A simple method for measurement of both wetting time and water absorption ratio.

In Vitro Disintegration Time

In vitro disintegration time (DT) of the RDTs was determined following the procedure described by Gohel et al. (2004). Briefly, 10 mL of water at 25°C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted (Gohel et al., 2004). Measurements were carried out in replicates ($n=6$) and mean ± *SD* values were recorded.

In Vitro Release Studies

Release studies of fenoverine from different formulations were performed according to USP XVIII apparatus II, paddle method utilizing a dissolution system (Disso 2000, Lab India, Thane, India) equipped with an auto sampler and fraction collector. Paddle speed was maintained at 50 rpm and 900 mL of 0.1N HCl was used as the dissolution medium. Samples (5 mL) were collected at predetermined time intervals (5, 10, 15, 30, and 45 min) and replaced with equal volume of fresh medium, filtered through a 0.22 μm filter and analyzed with a UV—Visible spectrophotometer (λ = 261 nm). Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved. The release studies were performed in replicates of six.

In Vivo Disintegration Time

Oral DT of the optimized RDT formulation (determined based on its in vitro DT and drug release) was assessed in six healthy male human volunteers according to the procedure described by Abdelbary et al. (2005). The subjects were informed of the purpose and protocol of the study. The institutional ethics committee approved the in vivo study protocol and each subject gave his written consent to participate. As per the protocol (Ethics permit # 17EC/pharm/ku/2005), all volunteers were asked to rinse their mouth with distilled water prior to the test. Tablets were placed on the tongue and a stopwatch was started immediately. Volunteers were allowed to move the tablet against the upper palate of the mouth with their tongue and cause a gentle tumbling action on the tablet without chewing it. Time taken for the volunteer to feel that the last noticeable granule had disintegrated in the oral cavity was considered as the in vivo DT. Swallowing of saliva was prohibited during the test, and the mouth was rinsed after each measurement. This experiment was conducted in all six subjects and the mean ± *SD* were calculated for each.

Differential Scanning Calorimetry (DSC)

DSC was used to characterize the thermal properties of the drug, bulking agent, physical mixture, and the compressed RDT formulation. The DSC thermograms were recorded using a differential scanning calorimeter (Perkin-Elmer Pyris 1 DSC). Ultrahigh pure nitrogen was used at a flow rate of 20 mL/min. Samples were analyzed in crimped aluminum pans and heated from 50–300°C at a linear heating rate of 10°C min^{-1}.

Statistical Analysis

To compare between different formulations, in all of the studies statistical analysis was determined utilizing one-way analysis of variance (ANOVA). A statistically significant difference was considered when $p < 0.05$.

RESULTS AND DISCUSSION

Taste Evaluation

Preliminary studies were performed to optimize the concentrations of all the excipients used in the formulation other than the superdisintegrants. A single blind study was conducted in healthy male human volunteers (Ethics permit # 16EC/pharm/ku/2005) to optimize the taste of the RDT formulations. Formulations containing different concentrations of sweetener and flavor were given to subjects who were asked to rate them on a scale of 1 through 5. In this study, formulations without aspartame and peppermint received ratings of '1,' as the formulations were perceived as "no taste" or "undesirable." Formulations with 0.5% of sweetener and flavor were rated as '4,' which was "slightly sweet" while those with 1% and above were rated as '5,' suggesting that these formulations were "extremely desirable." Therefore, a formulation containing 1% sweetener and flavor was determined to be optimum for a palatable fenoverine RDT formulation.

Formulation Rationale

An objective of a directly compressible rapidly disintegrating tablet is that it disintegrates or disperses in the saliva within a matter of seconds. To achieve such a formulation most of the excipients selected are inherently required to be water-soluble. Pearlitol® SD 200 utilized in the formulation is a directly compressible grade of mannitol with good flow properties and provides a refreshing or cooling mouth feel due to its negative heat of solution (Rowe, Sheskey, & Weller, 2003). Pearlitol® SD 200 was thus used as a bulking agent to achieve the desired tablet weight. Avicel 102 was included in the formulation as a disintegrant and a diluent. This grade of microcrystalline cellulose is granular in nature and thus displays excellent flow properties. To impart pleasant taste and improve mouth feel, aspartame and peppermint were included as sweetening and flavoring agents, respectively. Sodium-stearylfumarate was employed as a lubricant instead of magnesium stearate not only because of the metallic taste of the latter, but also due to its water solubility and directly compressible features. Colloidal silicon dioxide (Aerosil®), which acts both as a glidant and lubricant, also helps in appreciably decreasing tablet friability. This may be due to Aerosil® helping in restoring the bonding properties of the excipients (Shasaku, 1999).

The above considerations must be made for many solid dosage forms. However, superdisintegrants form the core of RDT formulations. Crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG) are three of the most commonly used and highly effective superdisintegrants currently included in solid dosage formulations. In this study, effectiveness of CP, CCS, and SSG in the fenoverine RDT formulations was evaluated at three different concentrations. Other formulation components were kept constant.

CP polymers are densely cross-linked homopolymers of *N*-vinyl 2-pyrrolidones. Their porous particle morphology enables them to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration (ISP, 2006b). As Yen et al. reported, in addition to its unique particle size and morphology, disintegrant properties of CP are not affected by pH and consequently being non-ionic does not bind to ionic drug moieties (Yen, Chen, Lee, & Chen, 1997). In addition, CP can also be used as a solubility enhancer to improve dissolution and, unlike other superdisintegrants, does not form a gel at higher concentrations.

CCS is cross-linked carboxymethyl cellulose sodium, and is generally used at concentrations of up to 5% w/w as a disintegrant in both wet granulation and direct compression processes (Gorman, Rhodes, & Rudnic, 1982). Its unique fibrous nature imparts excellent water wicking properties and cross-linking makes it a hydrophilic and highly absorbent material resulting in excellent swelling properties. CCS swells rapidly up to 4–8 times its original volume on contact with water. Similar to CP, it is also used as a dissolution aid.

SSG, a sodium salt of carboxymethyl ether of starch, is usually employed at concentrations between 2–8% w/w and a concentration of 4% may be optimum in most cases (Khan & Rhodes, 1975). Disintegration occurs as a result of rapid uptake of water followed by rapid and enormous swelling, which is its primary mechanism of action (Wan & Prasad, 1989; Yen et al., 1997). SSG may swell up to 300 times its original volume in water.

Quality Control Tests

A number of formulations containing these three superdisintegrants at different concentrations were investigated. In all of the formulations, tablet weight and thickness were within mean ± 7.5% and mean ± 5%, respectively. Friability values were less than 1% in all cases. Tablet hardness was maintained at 2.5 ± 0.5 kg for all of the RDT formulations. Fenoverine formulations demonstrated uniform assay and content uniformity, with a mean drug content of 99.0% and relative standard deviation of 3.0%.

Wetting Time

Wetting time was determined for all of the formulations (data not presented). A correlation between wetting time and superdisintegrant concentrations, '*R*' or DT was not evident. Wetting time of formulations containing CP was less compared to formulations containing CCS or SSG at equivalent concentrations. Faster wetting of tablets containing CP might be due to its rapid water absorbing nature involving both capillary and swelling mechanisms (Kornblum & Stoopak, 1973).

Water Absorption Ratio

Water absorption ratio, '*R*,' of formulations containing SSG and CCS were greater than that of CP containing formulations and SSG demonstrated greater '*R*' values compared to CCS. These results are consistent with reports describing broad differences in swelling capacity of the superdisintegrants [SSG > CCS > CP] (Zhao & Augsburger, 2005). Water absorption ratio '*R*' increased with an increase in superdisintegrants' concentrations from 4–8 % (Figure 2). A linear relationship was observed for each of the superdisintegrant types. The increase in '*R*' was most likely due to increased water uptake capacity of the superdisintegrants at higher concentrations.

In Vitro Disintegration Time

Disintegration time is an important criterion for selecting an optimum RDT formulation. Several methods have been described for evaluating in vitro and in vivo DT of RDT formulations. In vitro DT was determined following the procedure described in a previous section (Gohel et al., 2004). It was observed that increasing the superdisintegrant concentration from 4 to 8% resulted in a decrease in DT as depicted in Figure 3. However, in the case of formulations containing CP and SSG, an increase in superdisintegrant concentration from 6 to 8% did not demonstrate a change in DT. Also, DT of formulations containing CP was lower than those containing SSG at the same concentration which might be attributed due to its rapid water absorbing nature involving both capillary and swelling mechanisms (Kornblum & Stoopak,

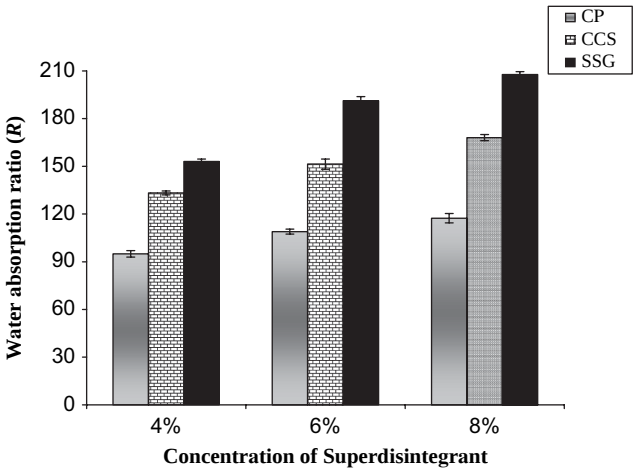

FIGURE 2. Water absorption ratios '*R*' of different fenoverine rapidly disintegrating tablet formulations. Values represent Mean ± *SD* (*n* = 6).

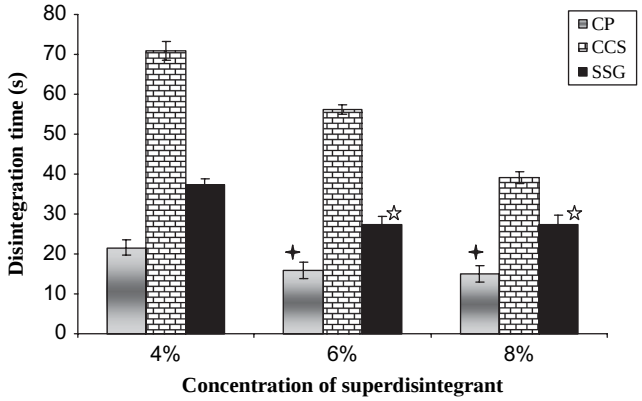

FIGURE 3. Disintegration times of different fenoverine rapidly disintegrating tablet formulations. Values represent Mean ± *SD* (n = 6).
+ RDT formulations CP 6 and CP 8 were not significantly different ($p > 0.05$).
☆ RDT formulations SSG 6 and SSG 8 were not significantly different ($p > 0.05$).

1973), building up the pressure internally leading to the faster disintegration.

Correlation Between 'R' and 'DT'

An inverse relationship was observed between the two parameters: '*R*' and *DT*, when '*R*' values of the different RDT formulations were plotted against their respective *DT*s as a function of the concentrations of different superdisintegrants (Figure 4). As the superdisintegrant concentration was increased, '*R*' value increased and *DT* decreased. The more the amount of superdisintegrant in the formulation, the greater the volume of water being absorbed (increased '*R*' value), which is an inherent property of each superdisintegrant. Also, this volume expansion of each formulation led to faster disintegration of the same due to increased hydrostatic pressure inside the tablet (ISP, 2006b).

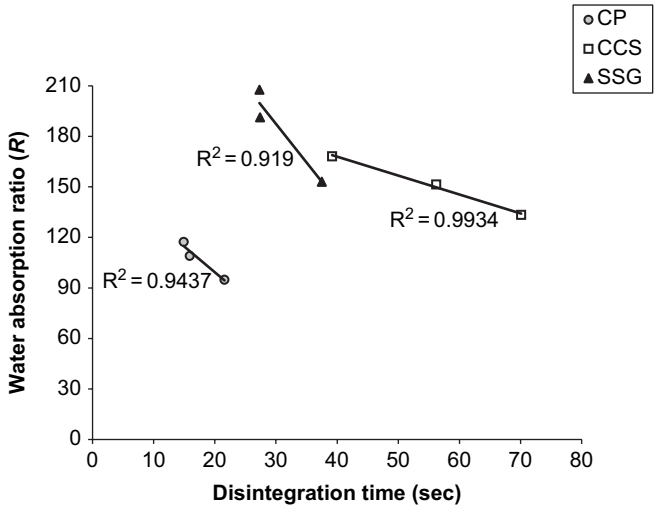

FIGURE 4. Correlation between water absorption ratio and disintegration time. Mean values represented (n = 6).

In Vitro Release Studies

Dissolution methods for RDTs are similar to approaches taken for conventional tablets, unless taste masking is required, and USP XVIII apparatus II with a paddle speed of 50 rpm is commonly used for in vitro release studies of these formulations. Lower paddle speeds yield more discriminating dissolution profiles since RDT formulations disintegrate rapidly (James, 2003).

An increase in superdisintegrant concentration resulted in increased cumulative % drug released in the first 5 min and all of the RDT formulations released 99.0% of the drug within 15 min (Figure 5). CP 6 released 99.9% drug within 15 min whereas the marketed fenoverine formulation (Spasmopriv® capsules) released 88.5% in the same period and 99.9% in

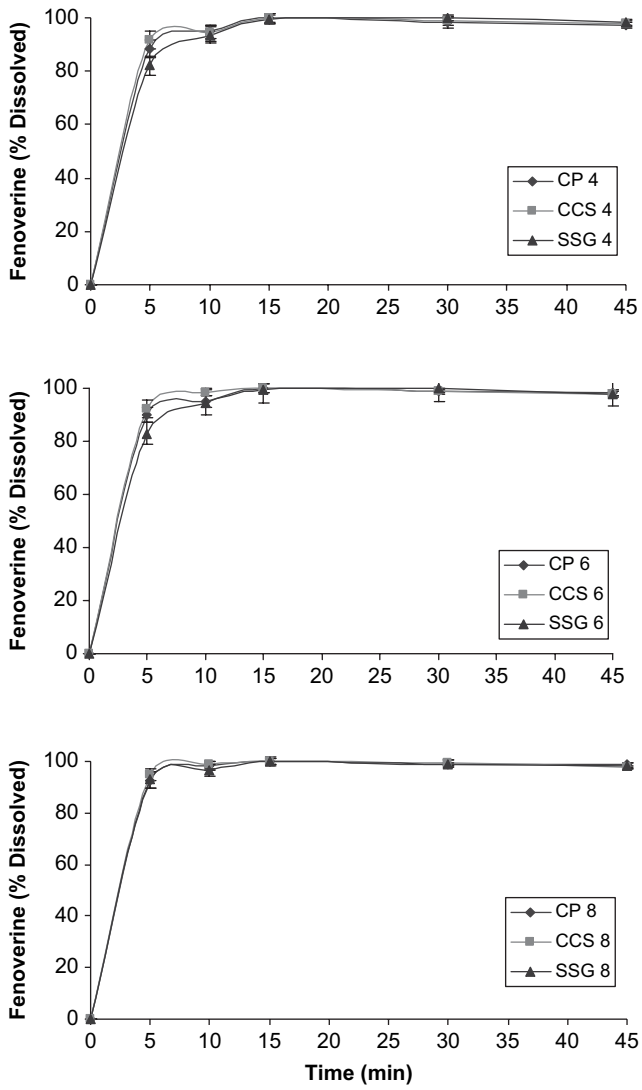

FIGURE 5. Dissolution of fenoverine from rapidly disintegrating tablets with different concentrations of superdisintegrants. Values represent Mean ± *SD* (n = 6).

30 min (Figure 6). Similarity factor 'f_2' between dissolution profiles of CP 6 and Spasmopriv® capsules was calculated using Equation (2), where 'n' is the total number of sampling intervals and 'R_t' and 'T_t' are cumulative % drug released from reference and test at any time interval 't.'

$$f_2 = 50 \times \log\{[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\} \qquad (2)$$

The calculated value of similarity factor (f_2 = 51.5) obtained between dissolution profiles of the optimized RDT formulation CP 6 and Spasmopriv® indicated that the two dissolution profiles were similar.

These results may, however, have clinical significance. The fenoverine RDTs disintegrated in the mouth undergo rapid dissolution in situ and the drug solution is formed instantaneously. If drug undergoes any pre-gastric absorption, it bypasses first pass metabolism to a certain extent, which ultimately results in an increase in the bioavailability of the drug

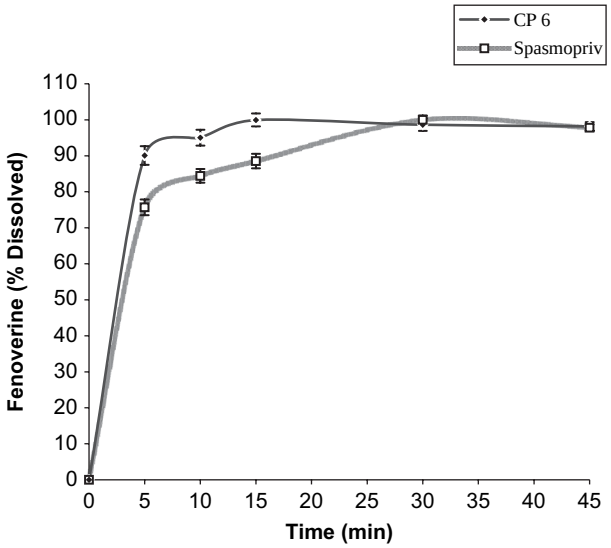

FIGURE 6. Drug release profiles of CP 6 rapidly disintegrating tablet and marketed Spasmopriv® capsule formulations (USP XVIII apparatus II paddle method). Values represent Mean ± *SD* (n = 6).

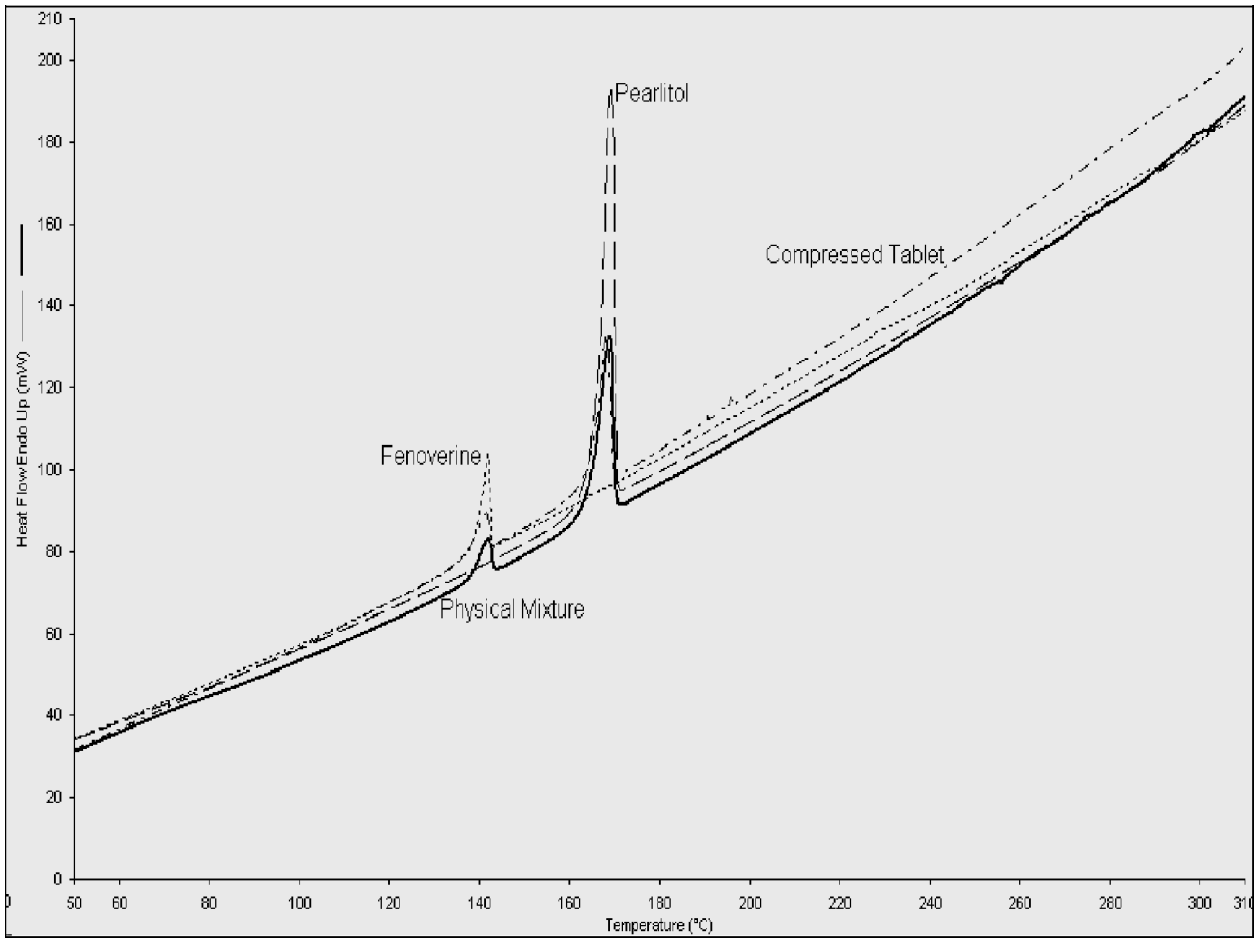

FIGURE 7. DSC endotherms (a) Fenoverine-dotted line; (b) Pearlitol SD 200-dashed line; (c) Physical mixture (of all components)-solid line and (d) Compressed formulation-dash dot line.

in contrast to those of capsule formulations, which release the drug directly into the gastric environment.

In Vivo Disintegration Time

Considering wetting time, '*R*' value, in vitro DT, and cumulative % drug released, formulations containing CP was considered to be better than those containing CCS and SSG. Since a significant difference in DT between formulations CP 6 and CP 8 was not observed, CP 6 was considered as the optimal RDT formulation among all of the 9 formulations tested in this study and selected for in vivo DT studies. The test was performed as discussed in an earlier section (Abdelbary et al., 2005).

The disintegration time of RDTs containing 6% CP was measured in the mouths of six healthy male human volunteers as per the protocol (Ethics permit # 17EC/pharm/ku/2005). Complete disintegration was achieved at 38.5, 31.7, 37.2, 36.6, 38.1, and 40.9 sec, respectively (mean and *SD*, 37.16 and 3.05 sec). The same formulation was administered thrice to each individual and the average of triplicate measurements represents an individual oral DT. Based on these data, this in vivo study demonstrates the applicability of the formulated RDT for potential commercial use.

Differential Scanning Calorimetry (DSC)

Drug-excipients compatibility was evaluated using a differential scanning calorimeter. Samples were collected prior to mixing, during mixing and after compression. The endotherms of pure drug and excipients were recorded separately, as a physical mixture and in the compressed form. No shifts in the melting endotherms were noted (Figure 7). These results indicate that the drug is compatible with the excipients used and does not undergo any change during processing.

CONCLUSION

In this study, directly compressible RDT formulations of fenoverine with desirable taste, sufficient mechanical strength, and shorter *DT*s were obtained using CP and other excipients at tested concentrations. CP 6 was determined to be optimal of all of the fenoverine RDT formulations studied as it exhibited the lowest *DT* and a similar or better dissolution profile compared to that of the marketed Spasmopriv® capsule. These results demonstrate that these formulations afford high utility as an oral drug delivery system.

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