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Research Article

Preparation of a Matrix Type Multiple-Unit Gastro Retentive Floating Drug Delivery System for Captopril Based on Gas Formation Technique: *In Vitro* Evaluation

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Abstract. A gastro retentive floating drug delivery system with multiple-unit minitab's based on gas formation technique was developed in order to prolong the gastric residence time and to increase the overall bioavailability of the drug. The system consists of the drug-containing core units prepared by direct compression process, which are coated with three successive layers of an inner seal coat, effervescent layer (sodium bicarbonate) and an outer gas-entrapped polymeric membrane of an polymethacrylates (Eudragit RL30D, RS30D, and combinations of them). Only the system using Eudragit RL30D and combination of them as a gas-entrapped polymeric membrane could float. The time to float decreased as amount of the effervescent agent increased and coating level of gas-entrapped polymeric membrane decreased. The optimum system floated completely within 3 min and maintained the buoyancy over a period of 12 h. The drug release was controlled and linear with the square root of time. Increasing coating level of gas-entrapped polymeric membrane decreased the drug release. Both the rapid floating and the controlled release properties were achieved in the multiple-unit floating drug delivery system developed in this present study. The analysis of the parameter dissolution data after storage at 40 °C and 75% RH for 3 months showed, no significant change indicating the two dissolution profiles were considered to be similar (*f*2 value is more than 50).

KEY WORDS: captopril; controlled release; gastroretentive; minitablets.

INTRODUCTION

It is widely known that gastric residence time (GRT) is one of the important factors affecting the drug bioavailability of pharmaceutical dosage forms (1).Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system (DDS) above the absorption zone (stomach or upper part of small intestine), leading to a diminished efficacy of the administered dose (2,3).Floating drug delivery system (FDDS) is one of gastroretentive dosage forms which could prolong gastric residence time to obtain sufficient drug bioavailability (4–7). The system basically floats in the gastric fluid because of its lower bulk density compared to that of the aqueous medium. FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine (8,9). It is also useful for drugs that act locally in the proximal part of gastrointestinal (GI) tract such as antibiotic administration for *Helicobacter pylori* eradication in the treatment of peptic ulcer (10–12,7), and for drugs that are poorly soluble or unstable in the intestinal fluid (5,13). Most of the floating systems previously reported are single unit systems. A drawback of these systems is the high variability of the GI transit time due to their all-or-nothing emptying processes (14–17,12,13). On the other hand, the multiple-unit dosage forms may be an attractive alternative since they have been shown to reduce the inter- and intra-subject variabilities in drug absorption as well as to lower the possibility of dose dumping (18–20).Various multiple-unit floating systems have been developed in different forms and principles such as air compartment multiple-unit system (3), hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method (13,21),microparticles based on low-density foam powder (22), beads prepared by emulsion–gelation method (17,23).Use of swellable polymers and effervescent compounds is another approach for preparing multiple-unit FDDS. Ichigawa *et al.* (14) developed FDDS by coating the sustained release pills or granules with tartaric acid layer, sodium bicarbonate layer and polymeric film consisting of polyvinyl acetate and shellac. The floating system using ion exchange resin loaded with bicarbonate and then coated by a semipermeable membrane was also proposed (24).Recently, Choi *et al.* (25) prepared floating alginate beads using gas forming agents (calcium carbonate and sodium bicarbonate).

Captopril, (1-[(2S)-3-mercapto-2-methyl propionyl]-l-proline),an angiotensin-converting enzyme inhibitor, has been used widely for the treatment of hypertension and

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congestive heart failure (26).The drug is freely water soluble and has elimination half-life after an oral dose of 1.7 h (27). It is stable at pH 1.2 and as the pH increases, the drug becomes unstable and undergoes a degradation reaction (28). Benefits of the controlled release dosage form of the drug have been reported (29,30). Various attempts have been made to develop floating systems to control drug release; among them is the so called hydrodynamically balanced system (31,32).Such a system is useful for drugs acting locally in the proximal gastrointestinal (GI) tract or for drugs that degrade in the intestinal fluid.

In this study, a new approach with minitablets filled into capsules based on gas formation technique was developed. The drug-containing core minitablets was prepared by direct compression method followed by coating of the units with seal coating, effervescent layer and gas-entrapped polymeric membrane (Eudragit RS30D, RL30D). Captopril which is predominantly absorbed in the upper part of GI tract and unstable in intestine was used as a model compound. The effect of the preparative parameters like, amount of the effervescent agent layered onto the seal coated units, and type and coating level of the gas-entrapped polymeric membrane, on the floating ability and drug release properties of the multiple-unit FDDS were evaluated.

MATERIALS AND METHODS

Materials

Captopril was gift sample from Nicholas Piramal, India. Microcrystalline cellulose (MCC) (Avicel PH102), Hydroxy propyl methyl cellulose (HPMC K100), Ethyl cellulose 7 cps were procured from Dr. Reddy's Labs India. Sodium bicarbonate (Merk, India) was used as an effervescent agent with HPMC (Methocel E15LV), plasticized with polyethylene glycol 6000 (PEG 6000 Sd fines, India) as a binder. The gas-entrapped polymeric membrane used was polymethacrylates (Eudragit RL and RS, Rohm Pharma, Germany) plasticized with triethyl citrate (Himedia), a water soluble plasticizer. All other reagents were of analytical grade.

Preparation of the Multiple-Unit FDDS

Preparation of Core Minitabs

Core minitabs were prepared with direct compression technique. Captopril, Microcrystalline cellulose, HPMC (K100), Ethyl cellulose (quantities shown in Table I) were weighed and sifted through no. 40 mesh (ASTM) and mixed well. Magnesium stearate was weighed and sifted through no. 60 mesh (ASTM) then added to above blend and mixed well in polybag. Final blend was compressed into minitabs using 6.0 mm size round concave punches and corresponding dies on 16 station rotary compression machine (Riddhi, India).

Table I. Composition of Core Containing Minitabs

Core formula	mg/cap
Captopril	50.0
Microcrystalline Cellulose	46.0
HPMC K100	200.0
Ethyl cellulose 7 cps	100.0
Magnesium stearate	4.0
Total weight	400.0

Four minitablets in one capsule (each core minitabs wt 100 mg×4 minitabs=400 mg)

Physical Properties of the Final Blend

Physical properties such as bulk density, tapped density, compressibility index, Hausner ratio and the angle of repose of blend were determined, tapped density was determined by using a tapped density tester (Campbell, India).Percent compressibility and Hausner ratio were calculated using Eqs. 1 and 2:

$$\text{Percent compressibility} = \left\{\frac{D_t - D_b}{D_t}\right\} \times 100 \qquad (1)$$

$$\text{Hausner ratio} = \frac{D_t}{D_b} \qquad (2)$$

Where, D_t and D_b are tapped and bulk densities.

Coating of the Core Minitabs

The core units were coated with three successive layers; first with seal coat (HPMC), followed by effervescent substance (sodium bicarbonate) as an inner effervescent layer and polymethacrylate (Eudragit RS30D, RL30D, and RS30D: RL30D) as an outer gas-entrapped polymeric membrane. HPMC solution plasticized with PEG 6000 (10%, *w*/*w* based on the solids content) was layered onto the core units. The coating level of seal coat layer was 2–3% weight gain and the solid content of coating solution was kept constant at 8% (*w*/*w*). An effervescent agent was incorporated into HPMC solution plasticized with PEG 6000 (10%, *w*/*w* based on the solids content) and then layered onto the seal coated units. On a dry solid basis, the ratio of sodium bicarbonate to HPMC was 6:2 *w*/*w*. The coating level of effervescent layer was 12% (optimized) weight gain and the solids content of coating solution was kept constant at 8% (*w*/*w*).

The coating solution was sprayed onto the core units in a coating pan (Allegro, India). The conditions for coating were shown as follows: tablets charge 100 g; preheating temperature 40±5 °C; preheating time 20 min; inlet air temperature 50±5 °C; spray rate 8–10 ml/min. The seal coated and $NaHCO_3$-layered units were dried in the coating chamber for 60 min at 40±5 °C. The prepared units were then removed from the coating pan and stored in a closed container for further processing. The $NaHCO_3$-layered units were subsequently coated with polymethacrylates dispersions (Eudragit RS30D, RL30D, or RS30D:RL30D) to achieve a weight gain of 5% and 10% (*w*/*w*) to obtain the complete multiple-unit FDDS. A plasticizer (triethylcitrate 10% *w*/*w* based on polymer solids content) was added into the polymer dispersion then the whole dispersion was stirred throughout the coating process. The solids content of the coating dispersions was 10% (*w*/*w*). The coating conditions were as follows: tablets charge 100 g; preheating temperature, 40±5 °C; preheating time 20 min; inlet air temperature 45±5 °C; spray

rate 3–5 ml/min. The units were further dried in the coating chamber for 60 min after the coating was finished to evaporate the residual moisture. The prepared units were then removed from the coating chamber and stored in a closed container for further experiments.

Evaluation of the Core and Multiple-Unit FDDS

Friability

The friability of the core minitabs was determined as the percentage of weight loss after 100 revolutions of 10 g of the core minitabs in a friability test apparatus (Thermonic, India).

Differential Scanning Calorimetry

For thermal analysis of drug and drug–excipient mixtures, a differential scanning calorimeter (DSC 821, Mettler Toledo, Switzerland) was used. Individual samples (drug and excipients) as well as mixtures of drug and selected excipients were taken in the pierced DSC aluminum pan and scanned in the temperature range of 25–300 °C (at the heating rate of 10 °C min^{-1}) under an atmosphere of dry nitrogen.

Scanning Electron Microscopy (SEM)

The core, effervescent layered and final coated minitabs were mounted onto the stages after coating with gold under vacuum. The surface morphology for checking the uniform coating of the units was observed under SEM.

Floating Behavior

The floating abilities of the effervescent-layered units and the coated effervescent-layered units (complete multiple-unit FDDS) were determined using USP II apparatus (50 rpm, 37±0.5 °C, 900 ml, 0.1 N HCl). Units were placed in the medium; the time required to float was measured by visual observation.

In Vitro Dissolution

The captopril release from different formulations was determined using a USP 24 paddle apparatus 2. The dissolution medium was 900 ml (pH 1.2, no enzyme) at 37± 0.5 °C; paddle speed 50 rpm. All experiments were done in triplicate and average values were taken. The formulation prepared was subjected to dissolution tests for 12 h. Sample (5 ml) was withdrawn at predetermined time intervals, filtered through filter paper (0.45 μ) and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined by HPLC.

HPLC Analysis

Quantitative determination of captopril was performed by HPLC. A isocratic HPLC system (Shimadzu, Japan) with LC 10AT VP pumps, with SPD-10A VP UV-Vis detector, a system controller SCL-10AVP and RPC-18 column (250 mm×4.6 mm I.D., particle size 5 μ, Phenomenex, Germany) was used. The HPLC system was equipped with the winchrom software. Quantitation was performed according to the earlier reported method with a slight modification (33). The mobile phase consisted of *n*-propanol/phosphate buffer (pH 3.0, 0.4% triethylamine) 20:80 (*V*/*V*). The filtered mobile phase was pumped at a flow rate of 1.0 ml min^{-1}. Twenty microliters of sample was injected into the column and the retention time of captopril was found to be 4.1 min. The elute was detected by UV at 240 nm.

Kinetic Modeling of Drug Release

The suitability of several equations, which are reported in the literature to identify the mechanism for the release of drug, was tested with respect to the release data. The data for analysis was taken to Q_{10} (drug released up to 10 h) excluding the lag time for all models except (Korsmeyer–Peppas) model. This Peppas diffusion model expected to be valid only up to approximately 60% cumulative drug released (34), thus FDDS with up to 60% cumulative drug release was considered. The data were evaluated according to the following equations (35).

– First order model:

$$lnM_t = lnM_0 + K_1 t \tag{3}$$

– Zero-order model

$$M_t = M_0 + K_0 t \tag{4}$$

– Higuchi model

$$M_t = M_0 + K_H t^{0.5} \tag{5}$$

– Korsmeyer–Peppas model

$$M_t = M_0 + K_K t^n \tag{6}$$

Where M_t is the amount of drug released in time t, M_0 the initial amount of drug, K is respective release constant and n is the release exponent, which characterizes the mechanism of drug release. The magnitude of the exponent n indicates the release mechanism as Fickian diffusion, as case II transport, or as anomalous transport. In the present study (cylindrical shape) the limits considered were n=0.45 (indicates a classical Fickian diffusion-controlled drug release) and n=0.89 (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of n between 0.45 and 0.89 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation) commonly called anomalous non-Fickian transport. Values of n greater than 0.89 indicates a super case II transport, in which a pronounced acceleration in solute release by a film occurs toward the latter stages of release experiments, resulting in a more rapid relaxation-controlled transport (36).

Table II. Physical Properties of Final Blend (n=3)

Property	Values
Angle of repose (degrees)	28.01±1.44
Bulk density (g/cm^3)	0.49±0.36
Tapped density (g/cm^3)	0.58±0.19
% Compressibility	14.43±0.30
Hausner ratio	1.17±0.14

Stability Studies

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines (34,37). Optimized formulation kept in the humidity chamber (LabTop, India) maintained at 40 °C and 75% Relative Humidity for 3 months. At the end of studies, samples were analyzed for physicochemical parameters. For the comparison of release profiles of initial and stability samples, "difference factor" $f1$ and "similarity factor" $f2$, were calculated (38). The difference factor ($f1$) measures the percent error between the two curves over all time points and was calculated as follows

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad (7)$$

where n is the number of sampling points, R_j and T_j are the percent dissolved of the reference and test products at each time point j. The two release profiles are considered to be similar, if $f1$ value is lower than 15 (between 0 and 15). The similarity factor ($f2$) is a logarithmic transformation of the sum of squared error of differences between the test T_j and the reference products R_j over all time points. It was calculated using the following equation:

$$f_2 = 50 \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n} w_j |R_j - T_j|^2\right]\right\}^{-0.5} \times 100 \quad (8)$$

Where w_j is an optional weight factor and other terms are as defined earlier. The two dissolution profiles are considered to be similar, if $f2$ value is more than 50 (between 50 and 100).

RESULTS AND DISCUSSION

Physical Properties of the Final Blend

The final blend of all the batches showed good flowability (angle of repose <30°) and compressibility (Table II)

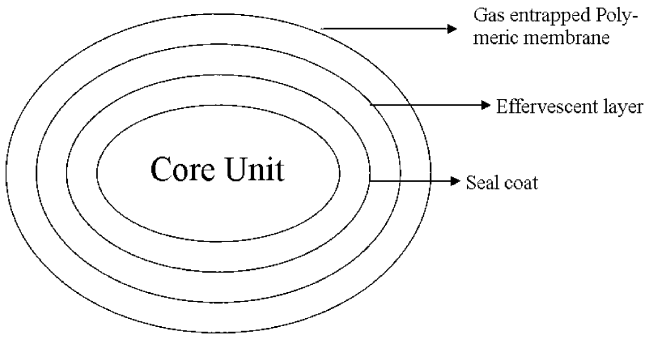

Fig. 1. Design of minitablets with different coating layers

Design of Multiple-Unit FDDS

Figure 1 shows the design of multiple-unit FDDS. The system consisted of drug-containing core minitabs coated with seal coat (to prevent direct contact of core with effervescent layer), effervescent layer and gas-entrapped polymeric membrane, respectively. Since sodium bicarbonate itself could not adhere to the units, HPMC was used as a binder in the inner effervescent layer. An ideal coating material for a floating system should be highly water permeable in order to initiate the effervescent reaction and the floating process rapidly. However, the wet or hydrated coatings should also be impermeable to the generated CO_2 so as to promote and maintain floatation (39). Regarding their mechanical properties, the polymeric coatings should be sufficiently flexible in wet state to be able to withstand the pressure of the generated gas and to avoid rupturing. Krögel and Bodmeier (39) reported that the cellulosic polymers were not suitable candidates for FDDS. Cellulose acetate was too rigid and did not expand sufficiently when in contact with dissolution media, while ethyl cellulose was not flexible and ruptured easily upon CO_2 formation. Gas bubbles were released rapidly after the burst of coating. According to these reasons, the higher flexibility polymer, polymethacrylates (Eudragit RS30D, RL30D, and RS30D:RL30D) were chosen and investigated as a gas-entrapped polymeric membrane in this study. Upon contact with the gastric fluid, the fluid permeated into the effervescent layer through the outer polymeric membrane. Carbon dioxide was liberated via neutralization reaction and was entrapped in the polymeric membrane. After that, the swollen minitabs with a density less than 1.0 g/ml floated and maintained the buoyancy; therefore, the drug

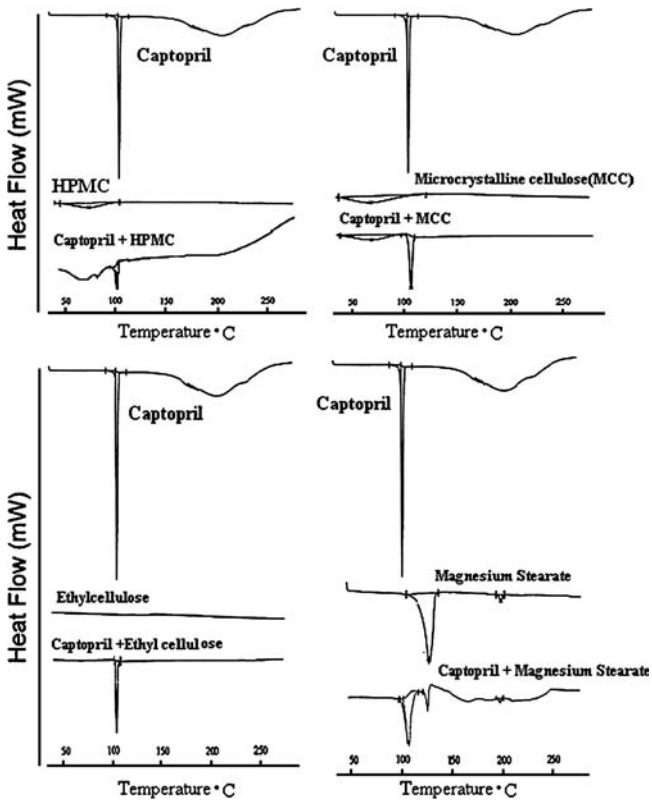

Fig. 2. DSC thermograms of captopril, excipients and their combinations

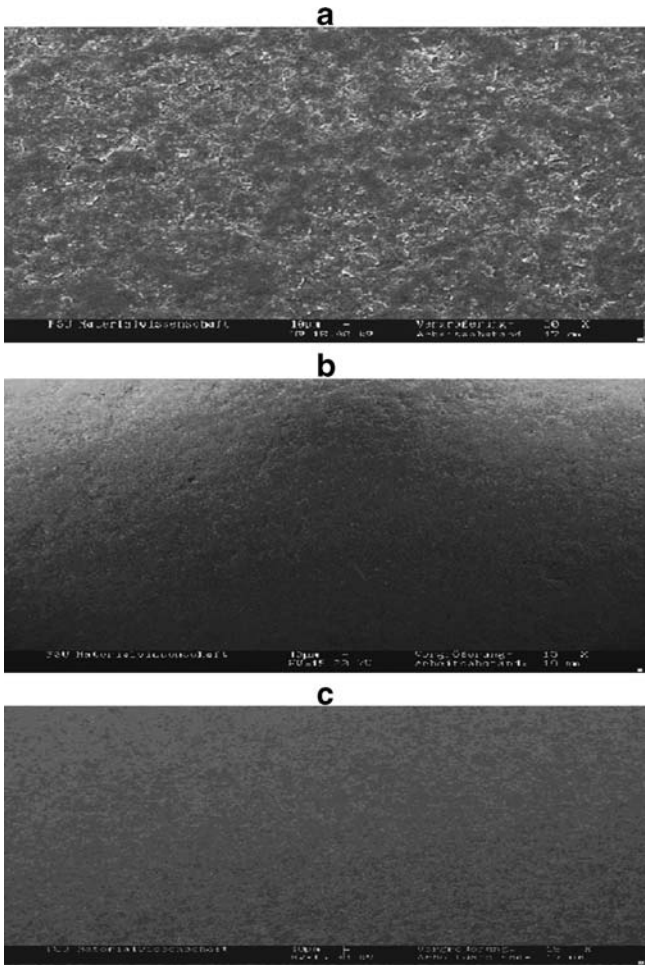

Fig. 3. SEM of **a** core units, **b** effervescent layered units and **c** complete final coated units

was released from the system for a long time. To develop the multi-unit FDDS based on gas formation technique, several studies were necessary to identify the formulation variables providing the desired system properties, rapid expansion and formation of low-density system within minutes after contact with gastric fluids and maintaining the buoyancy in stomach with controlled release. The effect of the preparative parameters such as amount of the effervescent agent layered

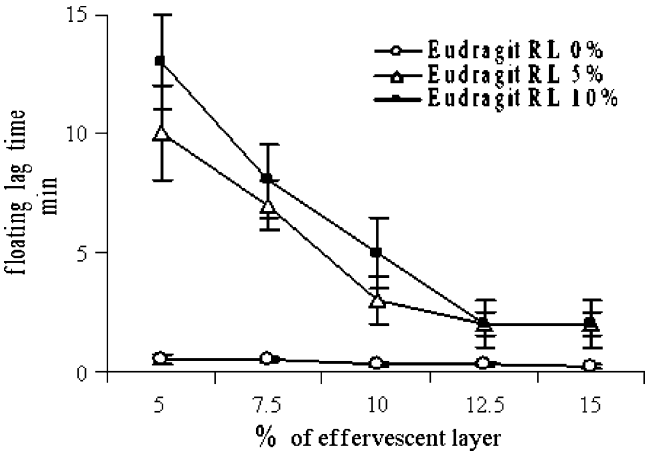

Fig. 4. Effect of effervescent layer level on floating lag time

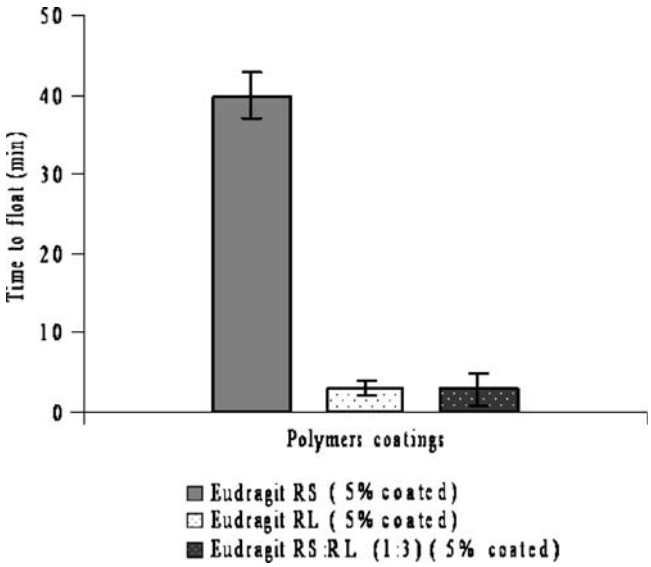

Fig. 5. Effect of polymer coatings on floating lag time at a 12% of effervescent coating levels

onto the seal coated minitabs, type and coating level of the polymeric membrane, on the floating ability and drug release of the multiple-unit FDDS were evaluated.

Minitab's Characterization

The core minitabs were prepared by direct compression using release rate controlling polymers. The formulations were evaluated for pharmacopoeial quality control tests and all the physical parameters evaluated for quality control were within the acceptable limits of Pharmacopoeia (data were not shown). Friability of the formulation was 0.4±0.08%. This indicated that the core units were quite hard and able to withstand the mechanical stresses of the subsequent coating process.

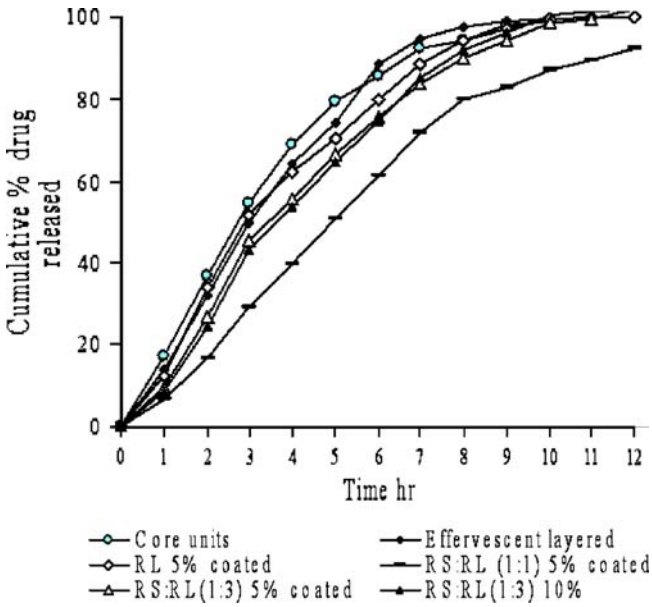

Fig. 6. Cumulative percentage of drug released with different polymer coating levels

Table III. The Correlation Coefficient (r^2) Values for Different Formulations

	R^2					
Release models	Core	Effervescent layered	RL 5%	RS:RL (1:1) 5%	RS:RL (1:3) 5%	RS:RL (1:3) 10%
First order	0.7344	0.7547	0.7319	0.8261	0.7553	0.7681
Zero order	0.8958	0.9006	0.9243	0.9788	0.9485	0.9606
Higuchi	0.9586	0.9642	0.9817	0.9905	0.9925	0.9947

The DSC trace of captopril showed a sharp endothermic peak at 107.07 °C. HPMC shows a broad endotherm effect due to their dehydration in the 35–100 °C temperature range (40). DSC scan of microcrystalline cellulose showed a broad endotherm at 63.29 °C (starting from 28.98 °C and ending at 104.76 °C), which may be attributed to the loss of adsorbed water (41,42). In case of ethyl cellulose, there was no peak in the region of 25–300 °C and in case of magnesium stearate, an endothermic peak was observed at 121.11 °C,a small peak was also present at 203.83 °C, which might be due to palmitate impurity (41,43) (Fig. 2).In the mixture of drug and excipients melting endotherm of drug was well preserved with slight changes in terms of broadening or shifting towards the lower temperature. It has been reported that the quantity of material used, especially in drug–excipient mixtures, affects the peak shape and enthalpy (44,41). Thus, these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility (42,45,46).Thus, it was concluded that captopril is compatible with all the excipients used in the formulation.

Figure 3a shows the appearance of the external morphology of the core units under SEM. The core units were with a slightly rough surface. The surface of the effervescent-layered units was slightly smoother (Fig. 3b) and the smoothest was the surface of effervescent-layered units coated with polymeric membrane (Eudragit RL30D/RS30D) (Fig. 3c).

Floating Ability

The floating ability of the effervescent-layered units and the effervescent-layered units coated with polymeric membrane (complete multiple-unit FDDS) were investigated respected to amount of the effervescent agent coated, and type and level of the polymeric coating. The system should float within a few minutes after contact with gastric fluid to prevent the dosage form from transiting into the small intestine together with food (3).The percent coating level of effervescent layer was evaluated and found that 10–12% of effervescent layer is required for floating the units within minutes. The effervescent layered units floated within 5–10 s after placed in 0.1 N HCl (Fig. 4). The floating time of the effervescent-layered units was quite short (less than 3 h) because HPMC dissolved and there was no polymeric membrane which could entrap the generated CO_2 gas. Therefore, the complete multiple-unit FDDS (effervescent-layered units coated with polymeric membrane) was prepared and evaluated for floating ability. Eudragit RL30D, RS30D and in combination were used as polymeric membrane. The multiple-unit FDDS using Eudragit RL30D and Eudragit RS:RL30D as polymeric membranes floated completely within 3 min. The time to float of the systems decreased with increasing amount of effervescent agent and increased with increasing level of polymeric membrane coating (Fig. 5). The higher amount of effervescent agent caused faster and higher CO_2 generation (39). With increasing level of Eudragit RL30D, the floating started later due to the delayed water penetration through the thicker coating. The duration of floating was longer than 12 h. It was indicated that Eudragit RL30D and RS:RL combinations polymeric membrane was impermeable to the generated CO_2 and could maintain the floatation. The multiple-unit FDDS systems coated with Eudragit RS30D as polymeric membranes did not floated within 20 min even used high effervescent coating level (15% w/w weight gain). Eudragit RS30D might not be permeable enough for dissolution medium to induce the effervescent reaction and generate sufficient amount of CO_2 to make the units floated. Eudragit RL30D is a highly water permeable polymer according to its hydrophilic content, quaternary ammonium groups in the structure (47,48). It has twice as many quaternary ammonium groups and is more hydrophilic than Eudragit RS. A faster and higher CO_2 generation caused by increasing the level of effervescent resulted in higher swelling of polymeric membrane and subsequent floating. It is therefore hydrated faster and resulted in a shorter time to float (39). Based on these results, Eudragit RL30D and combination of RS:RL30D were the polymers of choice as gas-entrapped membrane in this multiple-unit FDDS.

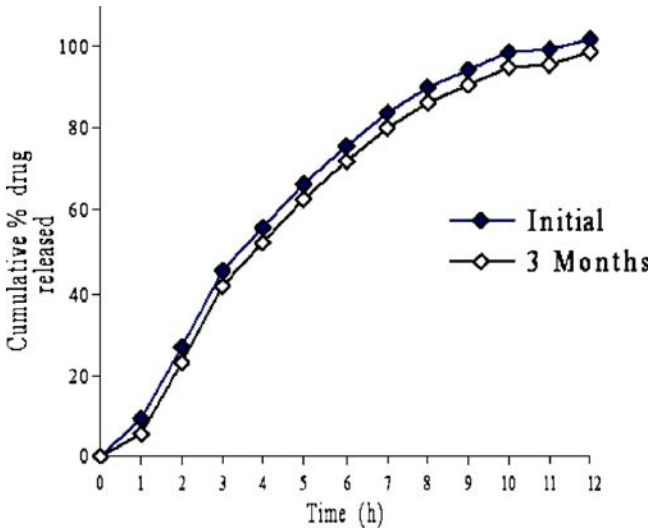

Fig. 7. Dissolution profiles after storage at 40 °C and 75% RH for 3 months [batch: Eudragit RS:RL30D (1:3) 5% coating]

In Vitro Release Studies

The release of captopril from the core units, the effervescent-layered units and the effervescent-layered units coated with Eudragit RL30D and RS:RL30D as polymeric membrane was shown in Fig. 6. There is no significant difference in drug release between the core units and the effervescent layered units. The drug release of the effervescent-layered units coated with Eudragit RL30D and combinations was slower than that of the uncoated effervescent layered units because the polymeric membrane retarded the water penetration through the effervescent-layered cores. Besides the effect of effervescent level, the effects of polymer type and coating level on drug release were also investigated. Since only the multiple-unit FDDS using Eudragit RL30D and combination of RS:RL as a gas-entrapped polymeric membrane could float, the drug release of this system was investigated for further study. The drug release decreased with increasing level of polymeric coating from 5% to 10%. The higher membrane thickness retarded water penetration, resulting in decreasing drug release (14,39). The drug release from the system using Eudragit RL30D and RS:RL combinations as gas-entrapped polymeric membrane was found to be linear with time.

Drug Release Pattern from the Systems

The correlation coefficient (r^2) was used as indicator of the best fitting, for the models considered. Some release mechanisms can be better elucidated indirectly, on basis of exponent n, in Eq. 6 or comparing the fitting of the models of pure diffusion Eq. 5 and of relaxational polymer and matrix erosion Eq. 4. The results (Table III) reveal that all formulations of FDDS were best fitted in the Higuchi model. The mechanism of drug release from these minitablets was found to be diffusion controlled as seen from r^2 values of Higuchi model. The n values for these systems were in the range of 1.01–1.27, indicates a super case II transport, in which a pronounced acceleration in solute release by a film occurs toward the latter stages of release experiments, resulting in a more rapid relaxation-controlled transport.

In view of the potential utility of the formulation, stability studies were carried out at 40 °C and 75% RH for 3 months (for accelerated testing) to assess their long-term stability. After storage, the formulation was subjected to a drug assay, floating behavior and *in vitro* dissolution studies. The analysis of the parameter dissolution data (Fig. 7), after storage at 40 °C and 75% RH for 3 months showed, no significant change indicating the two dissolution profiles are considered to be similar ($f2$ value is more than 50).

CONCLUSION

The system using Eudragit RL30D and combination of them as a gas-entrapped polymeric membrane could float. The time to float decreased as amount of the effervescent agent increased and coating level of gas-entrapped polymeric membrane decreased. The optimum system could float completely within 3 min and maintained the buoyancy over a period of 12 h. The drug release was controlled and linear with the square root of time. Increasing coating level of gas-entrapped polymeric membrane decreased the drug release. Both the rapid floating and the controlled release properties were achieved in the multiple-unit floating drug delivery system developed in this present study. Further *in vivo* study has to be carried out in healthy human volunteers.

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