Preparation and Evaluation of a Gas Formation-based Multiple-Unit Gastro-Retentive Floating Delivery System of Dipyridamole


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ABSTRACT

The aim of this study was to prepare mini tablets to be filled into a capsule that is designed to float on the gastric contents based on gas formation technique. The drug-containing core mini-tablets were prepared by wet granulation method followed by a coating of the core units with seal coating, an effervescent layer and a gas-entrapping polymeric membrane (Eudragit RS30D, RL30D). Dipyridamole, which is predominantly absorbed in the upper part of GI tract and unabsorbed/insoluble at the lower intestine, was used as a model drug. The effect of the preparative parameters like amount of the effervescent agent layered onto the seal coated units, type and coating level of the gas-entrapping polymeric membrane, floating ability and drug release properties of the multiple-unit FDDS were evaluated. The formulations were evaluated for pharmacopoeial quality control tests. Physical parameters were found to be within the acceptable limits. The system using Eudragit® RL30D as a gas-entrapping polymeric membrane exhibited floating properties. The time to float decreased as amount of the effervescent agent increased and coating level of gas-entrapping polymeric membrane decreased. The optimum system exhibited complete floating within 3 minutes and maintained that buoyancy over a period of 8 hours. The drug release was sustained and linear with the square root of time. Increasing the coating level of the gas-entrapping polymeric membrane decreased drug release. Both the rapid-floating and sustained-release properties were achieved in the multiple-unit floating delivery system developed in this study. The in vivo gastric residence time was examined by radiograms and it was found that the units remained in the stomach for about 6 hours. The analysis of the dissolution data after storage at 40°C and 75% RH for 6 months showed no significant change indicating good stability.

KEYWORDS: Floating delivery system; mini-tablets; effervescent agent; polymeric membrane; controlled release.

Introduction

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 (Streubel et al., 2003; Talukder and Fassihi, 2004). On the other hand, 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 lower the possibility of dose dumping (Bechgaard and Ladefoged, 1978). Various multiple-unit floating systems have been developed in different forms and principles such as air compartment multiple-unit systems (Vervaet et al., 1995), hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method (Sato et al., 2003), microparticles based on low-density foam powder (Streubel et al.,2002), and beads prepared by the emulsion-gelation method (Soppimath et al., 2001). The use of swellable polymers and effervescent compounds is another approach for preparing multiple-unit FDDS. A floating system using ion exchange resin loaded with bicarbonate and then coated by a semipermeable membrane was also proposed (Atyabi et al., 1996). Recently, Choi et al. prepared floating alginate beads using gas-forming agents (calcium carbonate and sodium bicarbonate).

The purpose of designing multiple-unit dosage forms is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high a loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine and polylalkylcyanoacrylate. Spherical polymeric microsponges, also referred to as “microballoons,” have been prepared. Microspheres have a characteristic internal hollow structure and show excellent in vitro floatability. In carbon dioxide-generating multiple-unit
oral formulations, several devices with features that extend, unfold, or are inflated by carbon dioxide generated in devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12-18 mm in their expanded state is exceeded.

Dipyridamole is a platelet inhibitor (Chakrabarti et al., 2008) that is primarily recognized as an antithrombotic agent. This binding of adenosine with the adenosine receptor stimulates adenylate cyclase activity and production of cyclic AMP (cAMP). Elevated cAMP impair platelet aggregation and cause arteriolar smooth muscle relaxation. Because of its short biological half-life of 2-3 hours, it should be frequently administered. In the recent statement from the American Heart Association and American Stroke Association Council on Stroke, extended release dipyridamole is considered safe. The solubility of dipyridamole is rather high in acidic solution, but poor in neutral or alkaline media (Kong et al., 2003). Dipyridamole is absorbed mainly in the first part of the GI tract, and therefore it is a suitable candidate for a floating dosage form (Patel and Patel, 2007).

The aim of this study was to prepare mini tablets to be filled into a capsule that is designed to float on gastric contents based on the gas formation technique. Dipyridamole-containing core mini-tablets were prepared by the wet granulation method followed by a coating of the core units with seal coating, an effervescent layer and a gas-entrapping polymeric membrane (Eudragit RS30D, RL30D). The formulation system was evaluated using in vitro and in vivo gastric residence time profiles.

**Materials and Methods**

**Chemicals and Drugs**

Dipyridamole and Microcrystalline cellulose (MCC) (Avicel PH102) were gift samples from AET laboratories Pvt. Ltd., Hyderabad, India. Methocel K4M CR (4000 mPa.s), Methocel K15M CR (15 000 mPa.s) and Methocel K100M LV CR (100 000 mPa.s) were received as gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Sodium bicarbonate (Merk, India) was used as an effervescent agent with HPMC (Methocel E15LV), plasticized with polyethylene glycol 6000 (PEG 6000 Merck, India) as a binder. The gas-entrapping 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 Mini-tablets**

Core mini-tablets were prepared with the wet granulation technique. Dipyridamole, Microcrystalline cellulose, and HPMC (K100LV) (quantities shown in Table 1) were weighed and sifted through number 40 mesh (ASTM) and mixed well. The mixture was granulated with granulation fluid, the wet mass passed through 10 mesh and wet granules were dried at 60°C for 30 minutes. The % LOD of the dried granules was less than 2%/W/W and dried granules were passed through the 30 mesh, and lubricated with magnesium stearate, were weighed and sifted through no.40 mesh (ASTM) then added to above blend and mixed well in a polybag. Final blend was compressed into mini tablets using 3.00 mm size round concave punches and corresponding dies on a 16-station rotary compression machine (Riddhi, India).

**TABLE 1**

Composition of Core Mini tablets.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (mg/Capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-A (Dry mix)</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>200.00</td>
</tr>
<tr>
<td>Methocel K100 LV</td>
<td>100.00</td>
</tr>
<tr>
<td>Avicel PH 101</td>
<td>32.00</td>
</tr>
<tr>
<td>Stage-B (Binder solution)</td>
<td></td>
</tr>
<tr>
<td>Water, Purified /IPA (30:70)</td>
<td>q.s</td>
</tr>
<tr>
<td>Stage-D (Blending &amp; Lubrication)</td>
<td></td>
</tr>
<tr>
<td>Methocel K100 LV</td>
<td>20.00</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>8.00</td>
</tr>
<tr>
<td>Total weight</td>
<td>360.00</td>
</tr>
<tr>
<td>mini tablet weight (mg) 3 mm tablets</td>
<td>30.00</td>
</tr>
</tbody>
</table>

**TABLE 2**

Particle size distribution by sieve analyser (Retsch).

<table>
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<th>Sieve No.</th>
<th>Cumulative % retained</th>
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</thead>
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<tr>
<td># 40</td>
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<tr>
<td># 60</td>
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<tr>
<td># 80</td>
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<tr>
<td># 120</td>
<td>49.10</td>
</tr>
<tr>
<td># 230</td>
<td>76.20</td>
</tr>
<tr>
<td>Receiver</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Physical Properties of the Final Blend**

Physical properties of the final blend such as bulk density, tapped density, compressibility index, Hausner ratio and the angle of repose were determined. Tapped density was determined by using a tapped density tester (Electrolab, Model ETB-1020). Percent compressibility and Hausner ratios were calculated using equations 1 and 2:

\[
\text{Percent compressibility} = \left( \frac{\rho_{\text{tap}} - \rho_b}{\rho_{\text{tap}}} \right) \times 100 \quad \ldots(1)
\]

Where
\[
\rho_b = \text{Bulk Density} \quad \rho_{\text{tap}} = \text{Tapped Density}
\]

\[
\text{Hausner’s ratio} = \frac{\rho_{\text{tap}}}{\rho_b} \quad \ldots(2)
\]

**Coating of the Core Mini tablets**

The core units were coated with three successive layers; first with the seal coat (HPMC), followed by the effervescent substance (sodium bicarbonate) as an inner
effervescent layer and polymethacrylate (Eudragit RS30D, RL30D, and RS30D: RL30D) as an outer gas-entrapping polymeric membrane. The HPMC solution plasticized with PEG 6000 (10-15% 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 the HPMC solution (10-12% 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 the effervescent layer was 12% (optimized) weight gain and the solid content of coating solution was kept constant at 8% (W/W).

The coating solution was sprayed onto the core units in a coating machine (Palm mini glatt). The conditions for coating are shown as follows: tablets charge 50 g; preheating temperature 40°C ± 5°C; preheating time 20 minutes; inlet air temperature 50°C ± 5°C; spray rate 8-10 ml/min. The seal-coated and NaHCO3-layered units were dried in the coating chamber for 60 minutes at 40°C ± 5°C. The prepared units were then removed from the coating pan and stored in a closed container for further processing. The NaHCO3-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 solid content of the coating dispersions was 10% W/W. The coating conditions were as follows: tablets charge 50 g; preheating temperature, 40°C ± 5°C; preheating time 20 minutes; inlet air temperature 45°C ± 5°C; spray rate 3-5 ml/min. The units were further dried in the coating chamber for 60 minutes 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 mini-tablets was determined as the percentage of weight lost after 100 revolutions of 10 g in a friability test apparatus Make: Electrolab; Model EF-2 Friabilator (USP).

Differential Scanning Calorimetry

For thermal analysis of drug and drug–excipient mixtures, a differential scanning calorimeter (DSC 823e, Mettler Toledo) was used. Individual samples (drug and excipients) as well as mixtures of drug and selected excipients were taken in a pierced DSC aluminum pan and scanned in the temperature range of 25-250°C (at the heating rate of 5°C min⁻¹) under an atmosphere of dry nitrogen (Mura et al., 1995).

Floating Behavior

The floating abilities of the effervescent-layered units and the coated effervescent-layered units (complete multiple unit FDDS) were determined using a USP II apparatus (50 rpm, 37°C ± 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

Dipyridamole release from different formulations was determined using a USP apparatus I. The dissolution medium was 0.1 N HCl 900 ml (pH 1.2) at 37°C ± 0.5°C. One capsule was placed in each dissolution vessel and the basket rotational speed was set at 100 rpm. All experiments were done in triplicate and average values were taken. The formulations prepared were subjected to dissolution for 8 hours. A sample (5 ml) was withdrawn at predetermined time intervals, filtered through filter paper (0.45 μ) and replaced by an equal volume of fresh dissolution medium. Drug content in the dissolution sample was determined by HPLC (Malan et al., 1997).

HPLC Analysis

Quantitative determination of dipyridamole was performed by HPLC. A waters alliance HPLC system with quarternary-2699 pumps, an 2489 UV-Visible detector, and Intersil ODS C18 (250 mm × 4.6 mm I.D., particle size 5 μ) was used. The HPLC system was equipped with the Empower software. A new method was developed for quantitation of dipyridamole. The mobile phase consisted of buffer pH 2.2, methanol and acetonitrile (50:35:15). The filtered mobile phase was pumped at a flow rate of 1.5 ml per minute. A 10 ml sample was injected into the column and the retention time of dipyridamole was found to be 2.2 minutes. The elute was detected by UV at 237 nm. The drug release was calculated using the equation generated from the standard curve. The percent cumulative drug release was calculated.

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 Qₘ (drug released up to 8 hours) excluding the lag time for all models except the Korsmeyer–Peppas model. This Peppas diffusion model was expected to be valid only up to approximately 60% cumulative drug released (Costa and Sousa Lobo, 2002), thus FDDS with up to 60% cumulative drug release was considered. The data was evaluated according to the following equations (J. W. Moore and H. H. Flanner 1996).

Zero-order equation:

\[ Q_t = Q_0 + k_0 t \quad \text{……(3)} \]
Where, $Q_t$ is the amount of drug released in time $t$, $Q_0$ is the initial amount of drug in the solution (most times, $Q_b = 0$) and $k_0$ is the zero-order release rate.

First-order equation:

$$\ln Q_t = \ln Q_0 = k_1 t \quad \ldots (4)$$

Where, $Q_t$ is the amount of drug released in time $t$, $Q_0$ is the initial amount of drug in the solution and $k_1$ is the first-order release rate constant.

Higuchi's equation:

$$Q = k_H t^{1/2} \quad \ldots (5)$$

Where, $Q$ is the amount of drug release at time $t$, and $k_H$ is the Higuchi diffusion rate constant.

Koremsayer's equation:

$$M_t / M_\infty = k t^n \quad \ldots (6)$$

Where, $M_t$ is the amount of drug released at time $t$, $M_\infty$ is the amount of drug released after infinite time, $k$ is a kinetic constant incorporating structural and geometric characteristics of the tablet, and $n$ is the diffusional exponent indicative of the drug release mechanism (Korsmeyer et al., 1977). 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 $n = 0.89$ (indicate 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.

**In Vivo X-ray Studies**

The *In vivo* tests discussed below were performed on six healthy male volunteers whose ages were between 25 and 32 years and weighed between 60 and 71 kg (approval for the study was taken from University Ethical Committee, UCPSc, Kakatiya University, Warangal, AP, India); 20% of BaSO$_4$ was added to the part of the final formulation (the amount of BaSO$_4$ that allows visibility by X-ray, but does not preclude the floating of tablets, was experimentally determined). Labelled Floating MUDF (Placebo) was given to subjects with 250 ml of water after a light, 308 kcal breakfast. Following ingestion, gastric radiography was undertaken at 0.5, 1, 3, 4 and 6 hours, and the duration of the mini-tablets stayed in the stomach was observed.

**Stability Studies**

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines (Mathews, 2003). The optimized formulation was kept in a humidity chamber (Lab Top, India) maintained at 40°C and 75% relative humidity for 6 months. At the end of the study, samples were analyzed for physicochemical parameters.

**Results and Discussion**

The final blend of all the batches showed good flowability (angle of repose < 30°) and compressibility and particle size distribution (Table II). The final blend had a bulk density of 0.414 g/cm$^3$, tapped density of 0.606 g/cm$^3$, compressibility index at 31.579% and Hausner ratio of 1.461.

**Design of Multiple-Unit FDDS**

Figure 1 shows the design of multiple-unit FDDS. The system consisted of drug-containing core mini tablets coated with seal coat (to prevent direct contact of core with effervescent layer), effervescent layer and gas-entrapping 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. Regarding their mechanical properties, the polymeric coatings should be sufficiently flexible in a wet state to be able to withstand the pressure of the generated gas and avoid rupturing. Higher flexibility polymers, polymethacrylates (Eudragit RS30D, RL30D, and RS30D:RL30D) were chosen and investigated as a gas-entrapping 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 mini tablets with a density less than 1.0 g/ml floated and maintained the buoyancy; therefore, the drug was released from the system for a long time. To develop the multi-unit FDDS based on the gas formation technique, several studies were necessary to identify the formulation variables providing the desired system properties, rapid expansion and formation of a 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 onto the seal coated mini-tablets, type and coating level of the polymeric membrane, floating ability and drug release of the multiple-unit FDDS were evaluated.

**Mini-Tablet Characterization**

The core mini tablets were prepared by direct compression using release rate-controlling polymers. The formulations were evaluated for pharmacopoeial quality control tests and all physical parameters evaluated for
quality control were within the acceptable limits of Pharmacopoeia (data 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.

The DSC trace of dipyridamole showed a sharp endothermic peak at 163.27°C (Figure: 2a). HPMC (Figure: 2g) shows a broad endothermic effect due to their dehydration in the 35°C-100°C temperature range. DSC scan of microcrystalline cellulose (Figure: 2b) 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. In case of magnesium stearate (Figure: 2c), 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. In case of NaHCO₃ (Figure: 2e), an endothermic peak was observed at 80.89°C. In the case of Eudragit RL30D (Figure: 2d) and RS30D (Figure: 2f), there is no interaction between dipyridamole and Eudragits observed by overlaying figure. All individual excipient DSC thermograms compared with mixture of dipyridamole. In the case of protective, effervescent and protective coated thermograms (Figure: 2h) there is no peak change compared with dipyridamole API. 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. 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. Thus, it was concluded that dipyridamole is compatible with all the excipients used in the formulation.

Fig. 1. Design of mini tablets with different coating layers.

![Diagram of mini tablets](image)

2(a) – DIP_WS

2(b) – DIP_MCC_Overlay
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 with respect to the amount of effervescent agent coated, 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. The percent coating level of the effervescent layer was evaluated and found to be 10-12% for floating. The effervescent layered units floated within 5-10 seconds after placement in 0.1 N HCl (Figure 3). The floating time of the effervescent-layered units was quite short (less than 3 hours) because HPMC dissolved and there was no polymeric membrane which could entrap the generated CO₂ gas. Therefore, the complete multiple-unit FDDS (effervescent layered units coated with polymeric membrane) were prepared and evaluated for floating ability.

Eudragit RL30D, RS30D and a combination of both were used as polymeric membranes. The multiple-unit FDDS using Eudragit RL30D and Eudragit RS: RL30D as polymeric membranes floated completely within 3
minutes. The time to float of the systems decreased with increasing amount of effervescent agent and increased with an increasing level of polymeric membrane coating (Figure 4). The higher amounts of effervescent agent caused faster and higher CO\textsubscript{2} generation. With increasing levels of Eudragit RL30D, the floating was delayed due to slowly water penetration through the thicker coating. The duration of floating was longer than 8 hours. It was found that the Eudragit RL30D and RS:RL combination polymeric membrane was impermeable to the generated CO\textsubscript{2} and could maintain the floatation. The multiple-unit FDDS systems coated with Eudragit RS30D as polymeric membranes did not float within 20 minutes even when 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\textsubscript{2} to make the units float. Eudragit RL30D is a highly water permeable polymer according to its hydrophilic quaternary ammonium groups in the structure. It has twice as many quaternary ammonium groups and is more hydrophilic than Eudragit RS. Faster and higher CO\textsubscript{2} generation caused by increasing the level of effervescence resulted in higher swelling of the polymeric membrane and subsequent floating. It is therefore hydrated faster and resulted in a shorter time to float. Based on these results, Eudragit RL30D and combination of RS: RL30D were used as the polymers of choice for the gas-entrapping membrane in this multiple-unit FDDS.

**In vitro Release Studies**

The release of dipyridamole from the core units, the effervescent layered units and the effervescent-layered units coated with Eudragit RL30D and RS: RL30D as the polymeric membrane was shown in (Figure 5). 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 levels, the effects of the polymer type and coating level on drug release were also investigated. Since only the multiple-unit FDDS using Eudragit RL30D or a combination of RS: RL as a gas-entrapping polymeric membrane could float, the drug release of this system was investigated for further study. The drug release decreased with an increasing level of polymeric coating from 5-10%. Higher membrane thickness retarded water penetration, resulting in decreased drug release. The drug release from the system using Eudragit RL30D and RS: RL combinations as gas-entrapping polymeric membrane was found to be linear with time.

![Effect of effervescent layer level on floating lag time](image)

**Fig. 3.** Effect of effervescent layer level on floating lag time.

![Effect of polymer coatings on floating lag time at a 12% of effervescent coating levels](image)

**Fig. 4.** Effect of polymer coatings on floating lag time at a 12% of effervescent coating level.
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 Equation 6 or comparing the fitting of the models of pure diffusion Equation 5 and of relaxational polymer and matrix erosion Equation 4. The results (Table 3) reveal that all formulations of FDDS were best fitted in the Higuchi model. The mechanism of drug release from these mini tablets was found to be diffusion controlled as seen from $r^2$ values of Higuchi model. The $n$ values of Peppas equation for these systems between 0.5121–0.8012, indicates a both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation) commonly called anomalous non-Fickian transport.

In view of the potential utility of the formulation, stability studies were carried out at 40°C and 75% RH for 1, 2, 3 and 6 months (for accelerated testing) to assess their long-term stability. After storage, the formulation was subjected to drug assay, floating behavior and in vitro dissolution studies. The dissolution data (Figure 6) after storage at 40±2°C / 75±5%RH for 6 months showed no significant change following the ingestion of the final formulation prepared by the addition of BaSO₄ to the release layer, the gastric residence time of mini-tablets was examined by radiogram, and it was observed that the units remained in the stomach for about 6 hours (Figure 7).

![Graph 1: Comparative Dissolution Profiles of Dipyridamole mini tablets (ACC stability) 200 mg in 0.1 N HCl with marketed product](image1)

**Fig. 5.** Comparative Release profiles of Dipyridamole mini tablets 200 mg in 0.1 N HCl with different levels of Eudragit RL30D and RS30D.

![Graph 2: Graph 2](image2)

**Fig. 6.** Dissolution profiles after storage at 40°C ± 2°C/75% RH ± 5% RH for 6 months [Batch: Eudragit RL: RS 30D (3:1) 5% coating].
Fig. 7. Typical chromatogram obtained from dipyridamole mini tablets solution.

Fig. 8. *In vivo* gastric residence time of floating mini tablets as evaluated by X-ray studies.

### TABLE 3
The correlation coefficient values ($r^2$) for different formulations.

<table>
<thead>
<tr>
<th>RS:RL (1:3) 10%</th>
<th>Release Models</th>
<th>Core</th>
<th>Effervescent Coated</th>
<th>RL 5%</th>
<th>RS:RL (1:1) 5%</th>
<th>RS:RL (1:3) 5%</th>
<th>RS:RL (1:1) 7.5%</th>
<th>RS:RL (1:3) 7.5%</th>
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</thead>
<tbody>
<tr>
<td>0.9853</td>
<td>Zero Order</td>
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<td></td>
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Conclusions

The systems using Eudragit RL30D and a combination of them as a gas-entrapping polymeric membrane could float. The time to float decreased as amount of the effervescent agent increased and coating level of gas-entrapping polymeric membrane decreased. The optimum system could float completely within 3 minutes and maintained the buoyancy over a period of 8 hours. The drug release was controlled and linear with the square root of time. Increasing the coating level of the gas entrapping 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 to access the bioavailability of the drug.

References


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