The gastric emptying time (GET) and the variation in the pH in the different segments of gastrointestinal tract (GIT) are the major challenging tasks for the development of oral controlled release drug delivery systems. Various attempts have been made to enhance the residence time of the dosage form within the stomach (1). Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drug in the GIT (2). The prolongation of gastric residence time (GRT) of delivery systems could be achieved by the mechanism of mucoadhesion (3, 4), flotation (5), sedimentation (6, 7), expansion (8, 9), modified shape system (10, 11), or by the simultaneous administration of pharmacological agents (12, 13) that delay the gastric emptying.

In the present study, enhancement of GRT is based on the mechanism of flotation. Floating drug delivery systems are less dense than the gastric fluid. Floating single unit dosage forms, also called hydrodynamically balanced systems (HBS), have been extensively studied (14). These single unit dosage forms have the disadvantage of a release all-or-nothing emptying process (15). However, the multiple unit particulate dosage forms pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly, which results in more reproducible drug absorption and reduced risk of local irritation than the use of single unit dosage form (16).

Acrylic polymers were selected for this study since they have been approved by FDA and are widely used in pharmaceutical industry. Indomethacin, a non steroidal anti-inflammatoy drug (NSAID) with analgesic and antipyretic properties, is used to treat moderate to severe rheumatoid arthritis including acute flares of chronic disease, ankylosing spondylitis, osteoarthritis, acute painful shoulder (bursitis and/or tendinitis) and acute gouty arthritis.

Indomethacin works by reducing the production of prostaglandins. Prostaglandins are chemicals that the body uses to cause fever, pain and inflammation. IND blocks the enzymes that make prostaglandins (cyclooxygenase 1 and 2) thereby reducing the level of prostaglandins. As a result, fever, pain and inflammation are reduced (17).

**FORMULATION AND IN-VITRO EVALUATION OF FLOATING MICROBALLOONS OF INDOMETHACIN**

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**Abstract:** Objective of present study involves preparation and evaluation of floating microballoons of indomethacin as a model drug, to increase its residence time in the stomach without contact with the mucosa. The microballoons were prepared by the emulsion solvent diffusion technique using different ratio of acrylic polymers (Eudragit RS100 and Eudragit S100) as carriers. The yield of microballoons was up to 91.02 ± 1.65%. Microballoons showed passable flow properties. On the basis of optical microscopy, particle size range was found to be ranging from 130.90 ± 12.10 to 170.58 ± 17.50 µm. Scanning electron microscopy (SEM) confirmed their spherical size, perforated smooth surface and a hollow cavity in them. Microballoons exhibited floating properties for more than 10 h. In vitro drug studies were performed in 0.1 M HCl with 0.1% SLS and phosphate buffer (pH 6.2). Different drug release kinetics models were applied for selected batches.

**Keywords:** floating microballoons, indomethacin, floating drug delivery system, emulsion solvent diffusion method, acrylic polymers

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MATERIALS AND METHODS

Indomethacin (batch no. 041206) was obtained as a gift sample from Wintac Ltd., (Bangalore). Eudragit S100 and Eudragit RS100 (Rohm Pharma GmbH, Germany) were used as polymers. Polyvinyl alcohol (Central Drug House Pvt. Ltd., New Delhi) served as dispersing agent. Dichloromethane (DCM), Tween 80 and Tween 20 were also obtained from CDH, New Delhi. All other chemicals/reagents were of analytical grade and were used without further purification.

Preparation method of hollow microballoons

Floating microballoons were prepared by the emulsion solvent diffusion method established by Kawashima et al. (18). Indomethacin, Eudragit RS100 and Eudragit S100 (Rohm Pharma GmbH, Germany) were dissolved in a mixture of ethanol and dichloromethane (Table 1). The resulting solution was added slowly to stirred 250 mL of aqueous solution of 0.50% (w/v) PVA at room temperature. The stirring was done for 2 h at 1000-1200 rpm by mechanical stirrer equipped with four bladed propellers, to evaporate the volatile solvent. After evaporation of solvent, microballoons were collected by filtration, washed with water and dried at room temperature in a desiccator for 24 h.

Characterization of floating microballoons

Micromeritic study

The prepared microballoons were characterized by their micromeritic properties such as particle size, true density, tapped density, % compressibility index and flow properties like angle of repose (θ).

The size of microballoons was determined using an optical microscope (Magnus MLX-DX, Olympus, India) fitted with an ocular micrometer and stage micrometer. The mean particle size was calculated by measuring 200-300 particles.

The tapping method was used to calculate tapped densities and % compressibility index, as follows (equation 1 and 2):

\[
\text{Tapped density} = \frac{\text{Mass of microballoons}}{\text{Volume of microballoons after tapping}} \quad (1)
\]

\[
\% \text{ Compressibility index} = \left(1 - \frac{V}{V_0}\right) \times 100 \quad (2)
\]

Here, \( V \) and \( V_0 \) are the volumes of the samples after and before the standard tapping, respectively.

True densities of hollow microballoons were determined by immersing the microparticles in 0.02% Tween 80 solution for three days in a metal mesh basket. The microparticles that were sunk after that process were used for density measurement as carried out by the displacement method (19).

The angle of repose, (θ) of the microballoons, which measures the resistance to particle flow, was determined by fixed funnel method (20) and calculated as follows (equation 3):

\[
\tan \theta = \frac{h}{r} \quad (3)
\]

where, \( h \) = height of pile, \( r \) = radius of the base of pile on the graph paper.

Morphology

Scanning electron microscopy (SEM) was done to study morphology of microballoons. The samples for SEM were prepared by sprinkling the powder on a both side adhesive tape stuck to a stub. Gold palladium coating on the prepared stub was carried out by using Sputter coater (POLARON model SC-76430). The thickness of coating was about 200 Å. The coated stubs were randomly scanned under electron microscope (LEO-430, UK).

Yield of microballoons

The prepared microballoons were collected and weighted. The actual weight of obtained microballoons divided by the total amount of all non-volatile material that was used for the preparation of the microballoons multiplied by 100 gives the % yield of microballoons (equation 4) (21):

\[
\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100 \quad (4)
\]

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Drug : Polymer ratio*</th>
<th>Solvent ratio** (EtOH : DCM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFM-1</td>
<td>1 : 1 : 1</td>
<td>1 : 1</td>
</tr>
<tr>
<td>EFM-2</td>
<td>1 : 1 : 2</td>
<td>1 : 1</td>
</tr>
<tr>
<td>EFM-3</td>
<td>1 : 1 : 3</td>
<td>1 : 1</td>
</tr>
<tr>
<td>EFM-4</td>
<td>1 : 2 : 1</td>
<td>1 : 1</td>
</tr>
<tr>
<td>EFM-5</td>
<td>1 : 2 : 2</td>
<td>1 : 1</td>
</tr>
<tr>
<td>EFM-6</td>
<td>1 : 2 : 3</td>
<td>1 : 1</td>
</tr>
<tr>
<td>EFM-7</td>
<td>1 : 1 : 3</td>
<td>2 : 1</td>
</tr>
<tr>
<td>EFM-8</td>
<td>1 : 1 : 3</td>
<td>1 : 2</td>
</tr>
<tr>
<td>EFM-9</td>
<td>1 : 2 : 2</td>
<td>2 : 1</td>
</tr>
<tr>
<td>EFM-10</td>
<td>1 : 2 : 2</td>
<td>1 : 2</td>
</tr>
</tbody>
</table>

*Indomethacin (model drug) : Eudragit RS 100 : Eudragit S100.

**Ethanol : dichloromethane
Incorporation efficiency

To determine the incorporation efficiency, 50 mg of microballoons were taken and dissolved in 25 mL of methanol. Then, the solution was filtered to separate shell fragments. The estimation of drug was carried out using a UV double-beam spectrophotometer (Shimadzu UV-1700 series) at the $\lambda_{\text{max}}$ of 318 nm. The incorporation efficiency was calculated as follows (equation 5):

\[
\text{Incorporation efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100 \quad (5)
\]

In vitro floating ability

Fifty mg of floating microballoons were placed in 50 mL beakers and 20 mL of 0.1 M HCl containing 0.02% Tween 20 was added. The beakers were shaken horizontally in a water bath at 37 ± 0.1°C (1). Floated particles were collected after 10 h and dried in a desiccator to constant weight. The percentage of floating microballoons was calculated as (equation 6):

\[
\text{% Floating ability} = \frac{\text{Weight of floating microballoons}}{\text{Initial weight of microballoons}} \times 100 \quad (6)
\]

In vitro drug release

The drug release rate from floating microballoons was determined using USP XXIII basket type dissolution apparatus. A weighted amount of floating microballoons equivalent to 75 mg of drug was placed in a non-reacting muslin cloth that had a smaller mesh size than the microballoons. The mesh was tied with a nylon thread to avoid the escape of any microballoons and a glass bead was used in the mesh to induce the sinking of microballoons in the dissolution medium (19). The dissolution test was performed in 900 mL of 0.1 M HCl with 0.1% SLS at 100 rpm and 750 mL of phosphate buffer (pH 6.2) at 75 rpm, according to the USP XXIII drug release test prescribed for indomethacin extended release capsules (22).

At specified time intervals, 5 mL aliquots were withdrawn, filtered, diluted with the same medium and assayed at 318 nm for indomethacin using a UV double-beam spectrophotometer (Shimadzu UV-1700 series). Samples withdrawn were replaced with equal volume of the same dissolution medium. All the experiments as specified above were conducted in triplicate.

Statistical analysis

In this study the results are given as the mean ± SD. Student’s t-test and one-way analysis of variance (ANOVA) were applied to find out the significant difference in drug release from different batches by using GraphPad-Instat Software Program (GraphPad-Instat Software Inc., San Diego). Considered statistically significant difference was at $p < 0.05$.

Kinetics of drug release

The zero-order rate (equation 7) (23) describes systems where drug release is independent of its concentration and this is applicable to the dosage forms like transdermal system, coated forms, osmotic system as well as matrix tablets with low soluble drugs. The first-order equation (equation 8) (24) describes systems in which the release is dependent on its concentration (generally seen for water-soluble drugs in porous matrix). The Higuchi model (25) describes the release of the drug from an insoluble matrix to be linearly related to the square root of time and is based on Fickian diffusion (equation 9). The Hixon-Crowell cube root law (26) (equation 10) describes the release of drug from systems where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in the case of systems that dissolve or erode over time. In order to authenticate the release model, dissolution data can further be analyzed by Korsmeyer and Peppas equation (equation 11) (27).

\[
\begin{align*}
Q_t &= K_0 t \quad (7) \\
\ln Q_t &= \ln Q_0 - K_1 t \quad (8) \\
Q_t &= K_H t^{1/2} \quad (9) \\
Q_0^{1/3} - Q_t^{1/3} &= K_{HC} t \quad (10) \\
M_t/M_\infty &= k t^n \quad (11)
\end{align*}
\]

where $Q_t$ is the amount of drug released at time $t$; $Q_0$ is the initial amount of the drug in the formulation; $k_0$, $k_1$, $k_H$, and $k_{HC}$ are release rate constants for zero-order, first-order, Higuchi model and Hixon-Crowell rate equations. In equation 11, $M_t$ is the amount of drug released at time $t$, and $M_\infty$ is the amount released at time $\infty$; $k$ is the kinetic constant, and $n$ is a release exponent value in order to characterize different release mechanisms i.e., Fickian or non-Fickian.

RESULTS AND DISCUSSION

The formulations of indomethacin-loaded microballoons were prepared using different ratio of acrylic polymers (Eudragit S 100 and Eudragit RS100) and solvent (ethanol and dichloromethane) by emulsion solvent diffusion technique.

The formulation mechanism of acrylic polymer hollow microspheres is reported in the literature (28, 29). According to this mechanism, the acrylic poly-
mer and drug were dissolved in solvent mixture such as dichloromethane : ethanol (1:1, v/v). Then, the polymer solution was emulsified in aqueous solution of PVA. Then, the ethanol diffused out of the embryonic microspheres into aqueous phase. On the other hand, dichloromethane, which could not diffuse, retained in the microspheres as core material. On keeping these microspheres at 40°C, the vapors of dichloromethane were generated, which escaped them, leaving the microspheres as a hollow spheres.

Micromeretic study
The mean particle size of the floating microballoons was found to be ranging from 130.89 ± 12.11 µm to 173.21 ± 21.62 µm. It was observed that, on increasing the polymer amount, the average particle size increased. This may be due to diminished shearing efficiency at higher concentration of the polymer (higher viscosity) (30). It was also observed that on increasing the volume of dichloromethane, average particle size was found to be increased.

The measured tapped density was in the range of 0.151 ± 0.009 to 0.293 ± 0.005 g/cm³. Compressibility index ranged from 31.33 ± 7.02 to 10.66 ± 2.31.

The true density of these acrylic hollow spheres was found to be 0.71 ± 0.04 to 0.95 ± 0.05 g/cm³. The angle of repose was found to be in the range of 25.03 ± 0.47 to 38.95 ± 2.40°, except for batch EFM-7 (40.92 ± 0.60°), which showed its passable flow properties (20) (Table 2).

Table 2. Micromeritic properties of different floating microballoons.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Mean particle size (µm)</th>
<th>True density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Compressibility index (%)</th>
<th>Angle of repose (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFM-1</td>
<td>130.90 ± 12.10</td>
<td>0.74 ± 0.04</td>
<td>0.152 ± 0.009</td>
<td>31.33 ± 7.02</td>
<td>38.95 ± 2.40</td>
</tr>
<tr>
<td>EFM-2</td>
<td>141.30 ± 14.16</td>
<td>0.86 ± 0.06</td>
<td>0.220 ± 0.008</td>
<td>22.66 ± 3.05</td>
<td>36.80 ± 1.46</td>
</tr>
<tr>
<td>EFM-3</td>
<td>167.18 ± 18.36</td>
<td>0.94 ± 0.06</td>
<td>0.231 ± 0.013</td>
<td>16.00 ± 6.00</td>
<td>35.69 ± 2.12</td>
</tr>
<tr>
<td>EFM-4</td>
<td>139.21 ± 10.85</td>
<td>0.79 ± 0.03</td>
<td>0.166 ± 0.001</td>
<td>30.66 ± 6.43</td>
<td>36.82 ± 1.58</td>
</tr>
<tr>
<td>EFM-5</td>
<td>164.21 ± 20.96</td>
<td>0.84 ± 0.04</td>
<td>0.230 ± 0.008</td>
<td>12.66 ± 5.03</td>
<td>35.47 ± 0.81</td>
</tr>
<tr>
<td>EFM-6</td>
<td>173.21 ± 21.62</td>
<td>0.92 ± 0.02</td>
<td>0.225 ± 0.004</td>
<td>10.66 ± 2.31</td>
<td>25.03 ± 0.48</td>
</tr>
<tr>
<td>EFM-7</td>
<td>157.57 ± 19.18</td>
<td>0.94 ± 0.04</td>
<td>0.286 ± 0.016</td>
<td>23.33 ± 2.30</td>
<td>40.92 ± 0.60</td>
</tr>
<tr>
<td>EFM-8</td>
<td>170.58 ± 17.50</td>
<td>0.86 ± 0.04</td>
<td>0.201 ± 0.013</td>
<td>14.00 ± 2.00</td>
<td>35.39 ± 1.48</td>
</tr>
<tr>
<td>EFM-9</td>
<td>156.51 ± 18.18</td>
<td>0.95 ± 0.05</td>
<td>0.294 ± 0.007</td>
<td>23.33 ± 2.31</td>
<td>36.60 ± 1.56</td>
</tr>
<tr>
<td>EFM-10</td>
<td>167.69 ± 18.53</td>
<td>0.83 ± 0.08</td>
<td>0.201 ± 0.009</td>
<td>11.33 ± 1.15</td>
<td>31.31 ± 0.58</td>
</tr>
</tbody>
</table>

*a The mean ± SD, n = 200–300. b The mean ± SD, n = 3. EFM = Eudragit floating microspheres.

Table 3. Various formulation parameters for microballoons.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Yield (%)</th>
<th>Incorporation efficiency (%)</th>
<th>Buoyancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFM-1</td>
<td>78.41 ± 4.68</td>
<td>77.28 ± 3.75</td>
<td>69.20 ± 1.71</td>
</tr>
<tr>
<td>EFM-2</td>
<td>83.35 ± 4.74</td>
<td>85.00 ± 4.00</td>
<td>74.73 ± 1.81</td>
</tr>
<tr>
<td>EFM-3</td>
<td>70.22 ± 4.70</td>
<td>86.67 ± 4.39</td>
<td>81.80 ± 3.07</td>
</tr>
<tr>
<td>EFM-4</td>
<td>91.02 ± 1.65</td>
<td>79.66 ± 3.51</td>
<td>65.87 ± 2.65</td>
</tr>
<tr>
<td>EFM-5</td>
<td>83.12 ± 3.02</td>
<td>87.08 ± 5.63</td>
<td>76.13 ± 1.85</td>
</tr>
<tr>
<td>EFM-6</td>
<td>82.11 ± 2.34</td>
<td>89.53 ± 4.58</td>
<td>79.93 ± 2.85</td>
</tr>
<tr>
<td>EFM-7</td>
<td>74.91 ± 2.85</td>
<td>80.03 ± 5.63</td>
<td>73.13 ± 5.43</td>
</tr>
<tr>
<td>EFM-8</td>
<td>69.53 ± 2.00</td>
<td>87.91 ± 5.05</td>
<td>83.53 ± 3.75</td>
</tr>
<tr>
<td>EFM-9</td>
<td>84.85 ± 3.97</td>
<td>84.58 ± 4.38</td>
<td>73.20 ± 4.46</td>
</tr>
<tr>
<td>EFM-10</td>
<td>82.39 ± 3.58</td>
<td>90.41 ± 5.05</td>
<td>78.53 ± 2.91</td>
</tr>
</tbody>
</table>

*a The mean ± SD, n = 3
Table 4. Kinetics model applied on EFM-3, EFM-6, EFM-8, and EFM-10 at pH 1.2

<table>
<thead>
<tr>
<th>Kinetic model</th>
<th>Parameters</th>
<th>EFM-3</th>
<th>EFM-6</th>
<th>EFM-8</th>
<th>EFM-10</th>
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<tr>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
<td>Zero-order</td>
<td>R</td>
<td>0.7492</td>
<td>0.7689</td>
<td>0.6712</td>
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<tr>
<td></td>
<td>RSS*</td>
<td>77</td>
<td>52</td>
<td>83</td>
<td>97</td>
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<tr>
<td></td>
<td>K_0</td>
<td>0.8369</td>
<td>0.6914</td>
<td>0.7835</td>
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</tr>
<tr>
<td>First order</td>
<td>R</td>
<td>0.7972</td>
<td>0.8031</td>
<td>0.7255</td>
<td>0.7221</td>
</tr>
<tr>
<td></td>
<td>RSS</td>
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<td>45</td>
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<tr>
<td></td>
<td>K_1</td>
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<tr>
<td>Higuchi</td>
<td>R</td>
<td>0.9949</td>
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<td>0.9959</td>
<td>0.9909</td>
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<tr>
<td></td>
<td>RSS</td>
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<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>k_H</td>
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<td>2.7740</td>
<td>3.1896</td>
<td>3.4254</td>
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<tr>
<td>Hixon-Crowell</td>
<td>R</td>
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<td>0.7921</td>
<td>0.7083</td>
<td>0.7041</td>
</tr>
<tr>
<td></td>
<td>RSS</td>
<td>69</td>
<td>47</td>
<td>76</td>
<td>88</td>
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<tr>
<td></td>
<td>k_HC</td>
<td>-0.0029</td>
<td>-0.0024</td>
<td>-0.0027</td>
<td>-0.0029</td>
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<td>Korsmeyer – Peppas</td>
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<td>0.9920</td>
<td>0.9975</td>
<td>0.9895</td>
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<tr>
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<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>k</td>
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<tr>
<td></td>
<td>n</td>
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<td>0.5520</td>
<td>0.4739</td>
<td>0.4858</td>
</tr>
</tbody>
</table>

*RSS = residual sum of squares

Figure 1. Scanning electron micrograph of microballoons. (A – population of spherical microballoons, B – spherical microballoons with perforated smooth surface, C – section of microballoons showing hollow cavity, D – ruptured microballoon due to rapid solvent evaporation)
Morphology

SEM micrograph confirmed that prepared microballoons were hollow with smooth perforated surface. The perforation may be due to evaporation of dichloromethane form embryonic microballoons. These images also confirmed that rapid evaporation of dichloromethane causes rapture of microballoons (Fig. 1).

The maximum and minimum % yield was 91.02 ± 1.65 and 69.53 ± 2.00 in batch EFM-4 and EFM-8, respectively (Table 3).

Drug entrapment efficiency

The drug entrapment efficiency of microballoons was found to be good (77.28 ± 3.75 to 90.41 ± 3.75)
5.05%). This may be due to insolubility of drug in water (Table 3).

**In vitro floating ability**

All microballoons showed good floating ability (69.20 ± 1.71 to 83.53 ± 3.75%) for 10 h. Such floating performance was due to insolubility of acrylic polymers in the gastric fluid. It was observed that the floating ability increased with increasing average particle size.

It was also observed that the formulation prepared with higher volume of dichloromethane (batch EFM-8 and EFM-10) showed better floating ability than the batch EFM-7 and EFM-9 (with lower volume of dichloromethane). The reason behind this may be larger air core formation in the batch EFM-8 and EFM-10, which made them lesser dense than that of gastric fluid (Table 3). *In vitro* floating behavior is shown in Figure 2.

**In vitro drug release**

The release of indomethacin floating microballoons was studied in 0.1 M HCl with 0.1% SLS (pH 1.2) and phosphate buffer (pH 6.2). Since the acrylic polymers are insoluble in acidic medium, very little amount of drug was released at the pH 1.2 compared to that in phosphate buffer (Table 4 and 5). Another cause of low drug release in the acidic medium is that the drug is a weak acid (pKₐ 4.5) and therefore, it will remain unionized in the same medium. On increasing the amount of polymers there was a significant decrease (p < 0.05) in the cumulative drug release in both dissolution media (Fig. 3 and 5).
There was not any significant effect of solvent ratio (dichloromethane : ethanol) on cumulative drug release (Fig. 4 and 6). No significant increase in cumulative drug release was observed on increasing the ratio of polymer – eudragit RS 100, since the total amount of polymer was the same (EFM-3, EFM-5 and EFM-2, EFM-4).

**Kinetics of drug release**

All release kinetics models were applied on EFM-3, EFM-6, EFM-8, and EFM-10 because of their good floating ability (Table 4). The best-fit model was found to be Higuchi (for EFM-3, EFM-6, and EFM-10), and Korsmeyer-Peppas (for EFM-8). The selection criteria for the best model were based on goodness of fit and residual sum of squares.

**CONCLUSION**

Novel floating microballoons were successfully prepared by emulsion solvent diffusion method for prolonged as well as controlled action of indomethacin. Due to their low densities, this multiparticulate drug delivery system showed good floating ability (more than 10 h). From *in vitro* drug release studies, it is concluded that by changing the ratio of polymers (RS100 and S100) and solvent (DCM and EtOH), indomethacin release can be controlled. These microballoons could be dispensed by filling them in the empty capsule shell.

**Acknowledgments**

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