DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERES OF ANTICONVULSANT DRUG BY 3² FULL FACTORIAL DESIGN

Short title: Gastroretentive drug delivery system

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ABSTRACT
The present study was undertaken to develop and evaluate gastroretentive microspheres by solvent evaporation technique. The preliminary batches of gabapentin microspheres were prepared and used for the development of factorial batches. Factorial batches showed the mean (FFMG1-FFMG9) particle size in the range of 185.63±0.13 to 510.04±0.09 μm for floating microsphere formulations. The percentage yields of formulations FFMG1 to FFMG9 for gabapentin range from 53.5±0.95 to 96.64± 0.42. The buoyancy proportion for all formulations was measured which displayed that all formulations float in the dissolution medium for 12 h. The drug loading in gabapentin microspheres was found 65.29 ± 0.46 to 84.3 ± 0.44. The swelling index was found 756.34± 1.48 to 890.46 ± 0.78 for gabapentin microspheres. Batch FFMG6 and FFMC2 showed better drug release 99.1% and 99.25% respectively. The optimized formulation FFMG6 for gabapentin shows an n value of 0.8474 and an R² value of 0.9965. Optimized formulation obeys Korsmeyer-Peppas release. SEM images showed microspheres were discrete, spherical as well as free-flowing. ANOVA for the given formulations showed P-value less than 0.0500. The stability study indicates no significant change in the microspheres properties. The radiographic images exhibited that floating microspheres were retained in the stomach of the rabbit for twelve hours.

Keywords: Gastroretentive, anticonvulsant, radiographic, microspheres, rabbit

1. INTRODUCTION
Microspheres are tiny spherical particles of micrometer diameters range (usually between 1 μm and 1000 μm). Often microspheres are called microparticles. Microspheres from different natural and synthetic materials could be produced. Commercially available are ceramic microspheres, polymer microspheres as well as glass microspheres. Microspheres with solid and hollow densities vary drastically and, therefore, are used in various usages. Hollow microspheres are normally utilized as antioxidants to reduce material density. Recent advances have resulted in the development of various types of microspheres (such as
floating, mucoadhesive, radio-active, double-walled, and magnetic) to serve different purposes. For example, floating/mucoadhesive microspheres have been developed as gastro-retentive delivery systems. [1]

**2. MATERIAL AND METHODS**

**Materials:** Gabapentin was obtained as a gift sample from Alkem Laboratories, Mumbai; the other excipients used were of analytical grade.

**Preparation of microspheres**

The solvent evaporation technique employed to prepare Gabapentin-loaded floating microspheres. HPMC K100 and Cellulose acetate phthalate were dissolved in various ratios at room temperature in a blend of ethanol and dichloromethane. Gabapentin was added to above solution and was agitated to create a homogeneous solution on a magnetic stirrer. The above solution containing gabapentin was squeezed into 100 ml of water containing 0.01% Tween 80 at room temperature and stirred for three hours. Finally, microspheres were filtered, separated and dried at room temperature. Formulation composition is provided in Table 1 and 2.

**Table 1: Formulation Composition of floating Microspheres of Gabapentin Preliminary Batches**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>FMG1</th>
<th>FMG2</th>
<th>FMG3</th>
<th>FMG4</th>
<th>FMG5</th>
<th>FMG6</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>HPMC K100: CAP</td>
<td>0.5:0.50</td>
<td>0.5:0.75</td>
<td>0.5:1.00</td>
<td>0.5:0.25</td>
<td>0.75:0.25</td>
<td>1.00:0.25</td>
</tr>
<tr>
<td>Solvent ratio Ethanol:Dichloromethane (%v/v)</td>
<td>1:1</td>
<td>1.5:1</td>
<td>2:1</td>
<td>1:1</td>
<td>1:1.5</td>
<td>1:2</td>
</tr>
</tbody>
</table>

**Table 2: Formulation Composition of floating Microspheres of Gabapentin Factorial Batches**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>FFMG1</th>
<th>FFMG2</th>
<th>FFMG3</th>
<th>FFMG4</th>
<th>FFMG5</th>
<th>FFMG6</th>
<th>FFMG7</th>
<th>FFMG8</th>
<th>FFMG9</th>
</tr>
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<tbody>
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<td>Gabapentin</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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</tr>
<tr>
<td>HPMC K100: CAP</td>
<td>0.5:0.5</td>
<td>0.37:0.75</td>
<td>0.25:0.75</td>
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<td>0.37:0.25</td>
<td>0.37:0.50</td>
<td>0.25:0.50</td>
<td></td>
</tr>
<tr>
<td>Solvent ratio Ethanol:Dichloromethane (%v/v)</td>
<td>1:1</td>
<td>1.5:1</td>
<td>2:1</td>
<td>1:1</td>
<td>1:1.5</td>
<td>1:2</td>
<td>1:1</td>
<td>1.5:1</td>
<td>2:1</td>
</tr>
</tbody>
</table>

**Characterization of floating Gastroretentive microspheres**

**Micromeritic evaluation**

- **Bulk density:** Bulk density= Bulk /Mass volume
- **Tapped density:** Tapped density= Tapped/Mass volume
- **Carr’s (compressibility) index:**
  \[ \% \text{ Compressibility index} = \frac{Tapped \text{ density} - Bulk \text{ density}}{Bulk \text{ density}} \times 100 \]
- **Tapped density**

\[ \text{Hausner ratio} = \frac{Bulk\text{ density}}{Tapped \text{ density}} \]
\textbf{Angle of repose:} \( \theta = \tan^{-1}\left(\frac{h}{r}\right) \)

Where \( h = \) pile height, \( r = \) pile radius, and \( \theta = \) angle of repose

\textbf{Particle size}

The size of a particle of the blank & gabapentin-loaded microsphere was determined by optical microscopy method using a compound microscope (Olympus India) equipped with ocular and calibrated stage micrometers. After the calibration of an ocular micrometer by placing the ocular lens after that the focusing on the object to be measured and determine the size in ocular units, then placing the samples on the slide and measuring the size of microspheres.\cite{4}

\[
\text{Length of one ocular unit} = \frac{\text{Divisions (mm)} \times \text{stage micrometer} \times 100 \mu \text{m/mm}}{\text{Ocular micrometer division}}
\]

\textbf{Percentage yield:}

The percentage yield of microsphere is ratio of weight of microspheres collected or recovered to the total weight of all solid contents taken. Dry microspheres collected were weighed to assess recovery.\cite{5}

\[
\% \text{ Yield} = \frac{\text{Mass of microspheres obtained (g)}}{\text{Theoretical mass of microspheres (g)}} \times 100
\]

\textbf{Measurement of microspheres hydration}

Hydration of the microsphere is described as the ratio among wet microspheres and dry microspheres weight. The recovered microspheres were immediately weighed and depicted at the end of each microencapsulation phase (M1). When the microsphere is dry to constant weight, it is again measured and shown as an (M2). It is expressed with the following equation: \cite{6}

\[
\% \text{ Microsphere's hydration} = \frac{M1}{M2} \times 100
\]

\textbf{Determination of Drug loading of microspheres}

20 mg of hollow loaded gabapentin microsphere samples are dissolved at room temperature by ultrasonication in 50 ml of ethanol for determining to load. The liquid was then purified by a Millipore (0.45 \( \mu \)m) filter. UV – visible sensor (UV1700–1800; “Shanghai Phoenix Optical Instrument Co., Ltd., Shanghai”, China) was used for determining drug concentration at 210 nm and 284 nm. The drug loading of gabapentin-loaded hollow microspheres was determined by the following equation \cite{7}

\[
\text{Drug loading amount} = \frac{\text{Amount of FD in hollow microspheres}}{\text{Amount of hollow microspheres containing}} \times 100
\]

\textbf{Drug entrapment efficiency}

The entrapment efficiency of microspheres was determined by extraction of drug from the microspheres. In a typical procedure, 50 mg of dried microspheres were grounded in a pestle and mortar, and the fine microspheres dissolved in a few ml of Ethanol and dilute with 50 ml of 0.1N HCL for 24h. After 24h, the solution was moved over a 0.45 \( \mu \)m filter. The gabapentin present in the filtrate was evaluated spectrophotometrically at 210 nm by using UV- Visible Spectrophotometer (Shimadzu, UV-1800, Japan) using 0.1N HCL as blank. \cite{8, 9}

\[
\text{Drug entrapment efficiency} = \frac{\text{Weight of drug in microspheres}}{\text{Weight of fed drug}} \times 100
\]

\textbf{Swelling measurement}

The dissolution apparatus USP type II was used for the swelling analysis. The vessels that comprise SGF were correctly weighed with gabapentin microsphere and allow to swell. The
speed of rotation was adjusted at 50 rpm. The microspheres were removed and blocked-in filter paper at a pre-determined time period to eliminate the excess water. The weight increases were calculated at various times before the full weight was increased. The index swelling was determined with the following equation \[^{[10]}\]

\[
Swelling\ index\ (S) = \frac{W_m - W_t}{W_t} \times 100
\]

Where \(W_m\) signifies the weight at equilibrium and \(W_t\) signifies the initial microspheres weight.

**In vitro buoyancy**

Gabapentin-equipped microspheres were assessed for in vitro floating properties on a USP dissolution device 2 (paddle type). 50 single microspheres were submerged in a vessel of 500 mL of SGF from each formulation. Rotation of the paddle at 50 rpm with maintaining the temperature at 37±0.5 °C. The number of microspheres floating was measured up to eight hours at hourly periods. In vitro buoyancy was represented as a percentage and the following equation was determined:\[^{[11]}\]

\[
F\% = \frac{\text{Weight of floating microspheres}}{\text{Weight of initial microspheres}} \times 100
\]

**In-vitro drug release**

Dose equivalent to 100 mg of floating microspheres of gabapentin was accurately weighed and dissolution studies were carried out using simulated gastric fluid (enzyme free) (900 ml) at temperature 37±0.5°C using USP type II apparatus. The rotation speed was maintained at 100 RPM. Aliquot of 5 ml of dissolution medium was removed at a fixed interval until a period of 12 h and substituted by a fresh medium. The content of gabapentin microspheres was determined by using a UV spectrophotometer (Spectro UV 2080, Double beam, Analytical Technologies, India) at 210 nm against SGF as blank.\[^{[12]}\]

**Scanning electron microscopy:**

Dry gabapentin microspheres have been mounted on a gold-coated electron microscope in the ion sputter. The random scan of a stub took a view of the microsphere. The microspheres study was performed with JEOL, JSM-670F Japan. In an accelerated voltage of 3.0, the microspheres were presented.\[^{[13]}\]

**Drug release kinetics**

The drug release from various controlled-release preparations are more often measured using four kinetic models. The data obtained from in vitro release of the drug were measured by 5 models to identify the most suitable model. The release of zero-order kinetics is a drug release mechanism that is not based on drug concentration. The zero-order release equation is; \[^{[6]}\]

\[
F_t = K_0t
\]

Here \(F\) indicates the drug fraction release in time \(t\) and \(K_0\) denotes the zero-order release constant.

**First-order kinetics:** “\(\ln (1 - F) = -K_1t\)”

Here \(F\) shows the drug release fraction in time \(t\) and \(K_1\) denotes the 1st order release constant.

**Higuchi model:** \(F = K_2 t^{1/2}\)

Here \(F\) signifies drug release fraction in period \(t\) & \(K_2\) denotes the “Higuchi constant”.

**Korsmeyer-Peppas model:** \(M_t/M_\infty = K_3 t^n\)

Here \(M_t\) denotes the drug amount released in time \(t\), \(M_\infty\) signifies the drug amount release at time infinity, \(K_3\) denotes the kinetic constant and \(n\) indicates the exponent defining the swelling mechanism.

**Stability study**\[^{[14]}\]

The optimized formulation was kept for accelerated stability study according to the
International Conference on Harmonization (ICH) guidelines for 3 months. Microspheres were packed in a laminated aluminum foil and kept in the stability chamber maintained at temperature of 40 ± 2 °C and 75 ± 5% RH. At the end of 0, 30, 60, 90 days, samples were withdrawn and examined for percentage buoyancy drug, entrapment efficiency and in vitro drug release.

In Vivo Study

The in vivo radiographic studies were conducted in young and healthy four male albino rabbits weighing 2.0 to 2.2 kg to monitor the in vivo transit behavior of the prepared floating hollow microspheres. The animals were fasted for 12 hrs before start of the experiment. The absence of radioopaque material in the GIT was confirmed by taking first radiographic image of the animal. The optimized formulations which showed good in vitro buoyancy and sustained-release behavior were selected for the study. The optimized formulation i.e. FFMG 6 batch was administered to rabbits.

RESULTS AND DISCUSSION

Micromeritic evaluation of Gabapentin microspheres

The designed formulations possessed average particulate size between 198.55±0.28 and 469.3±0.09 μm. Ci values range from 2.62±0.61 and 19.81±0.93 which indicate poor to excellent microspheres flow. All the formulations exhibited Hr values below 1.25 which indicate good flow characteristics. Besides, angle of repose value less than 25 indicates good flow properties.

Evaluation of preliminary batches of Gabapentin Microspheres

The percentage yield was 54.5±0.92 to 91.18±0.24 and invitro buoyancy 68.89±0.44 to 92.41±0.21 for preliminary batches prepared. Drug loading in all the formulation batches was good and ranges between 7.778±0.39 to 10.03±0.05. The swelling study revealed the swelling properties of the polymers used and the swelling index was found between 675.0 ± 2.37 to 856.3 ± 0.19. Results are demonstrated in Table3.

Table 3: Evaluation of preliminary batches of Gabapentin Microspheres

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Percentage yield</th>
<th>Drug entrapment efficiency</th>
<th>In-vitro buoyancy</th>
<th>Drug loading of microspheres</th>
<th>Swelling measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMG1</td>
<td>54.5±0.92</td>
<td>73.4±0.07</td>
<td>80.22±0.21</td>
<td>8.242 ± 0.40</td>
<td>789.4 ± 3.86</td>
</tr>
<tr>
<td>FMG2</td>
<td>67.07±0.87</td>
<td>81.5±0.05</td>
<td>76.12±0.53</td>
<td>8.998 ± 0.34</td>
<td>840.0 ± 2.46</td>
</tr>
<tr>
<td>FMG3</td>
<td>91.18±0.24</td>
<td>92.3±0.04</td>
<td>92.41±0.21</td>
<td>9.674 ± 0.22</td>
<td>856.3 ± 0.19</td>
</tr>
<tr>
<td>FMG4</td>
<td>72.88±0.67</td>
<td>84.3±0.15</td>
<td>68.89±0.44</td>
<td>10.03 ± 0.05</td>
<td>810.2 ± 0.23</td>
</tr>
<tr>
<td>FMG5</td>
<td>84.2±0.36</td>
<td>88.7±0.09</td>
<td>70.17±0.37</td>
<td>7.936 ± 0.46</td>
<td>675.0 ± 2.37</td>
</tr>
<tr>
<td>FMG6</td>
<td>69.3± 0.46</td>
<td>76.15±0.11</td>
<td>72.21±0.77</td>
<td>7.778 ± 0.39</td>
<td>750.0 ± 0.70</td>
</tr>
</tbody>
</table>

In-vitro drug release

The simulated gastric fluid (pH 1.2) was used in vitro drug release experiments. The drug release for batch FMG3 was highest amongst all the preliminary batches 98.64%. The result is shown in Figure1.
Micromeritic evaluation of Gabapentin Factorial batches

The average particle size of the floating microsphere formulations (FFMG1-FFMG9) was from 185.63±0.13 to 510.04±0.09 μm. Formulations representing an increase in Cellulose acetate phthalate and HPMC k15 concentration demonstrated a rise in the size of the particle. This can be attributed to an increased relative viscosity of Cellulose acetate phthalate and HPMC k15, which takes great energy to cut droplets and is harder to spread by enhancing interfacial tension and reducing shearing ability, contributing to the forming of major droplets of floating microspheres when polymer solution is added. The bulk and tapped formulations densities were observed between 0.410±0.11 to 0.875±0.12 and 0.463±0.14 to 0.91±0.16 respectively. The Carr’s index indicates how microsphere bridges are formed. The values of all formulations ranged from 0.25±0.06 to 12.15±0.28, which showed excellent microsphere flow and compression, except formulation FFMG 7 which shows 35.21±0.15. The Hausner ratio for the cohesion of microspheres particles was calculated. All formulations had values below 1.54, which indicates strong flow characteristics with simple handling during processing. The angle of repose values of formulations was below 21, suggesting microspheres free-flow characteristics. The stronger microspheres flow means that the development of floating microspheres was non-aggregated. The improved flow can be attributed to change in particle shape and size of the prepared microspheres resulting in reduced friction.

Evaluation of designed floating microspheres batches

To assess the polymer impact on the formulations the percentage yield of the floating microsphere was studied. The result indicates that the FFMG1 to FFMG9 percentage yields, as seen in Table 4, vary from 53.5±0.95 to 96.64±0.42. The rise in polymer concentration contributed to an increase in percentage yield. This impact could be clarified by the fact that with the increasing concentration of alginate, the quantity of polymer is sufficient for Gabapentin particles.

Drug trapping was linked to the permeation features of used polymers that would simplify the dissemination of a section of a medium stuck in floating microsphere preparation. With the polymer concentration, drug entrapment effectiveness improved. Table 4 presents the results. This is because the content of polymers has increased and more Gabapentin particles are covered such that the encapsulation performance is improved.
The buoyancy percentage was studied and all formulations were observed to float for 12 h on the dissolution medium (0.1 N HCl, pH 1.2). The microspheres buoyancy percentage was observed to decline with a rise in cellulose acetate phthalate concentration. (Table 4) This is due to the high viscosity of the polymer solution which in turn leads to more dense microspheres and fewer pores besides cavities during preparation.

The drug loading in gabapentin microspheres was found to be 8.324 ± 0.23 to 11.843 ± 0.44. The swelling index was 756.34 ± 1.48 to 890.46 ± 0.78 indicating more swelling and hydration of microspheres. Besides, gastric residence time was also increased to a greater extent.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>“Percentage yield”</th>
<th>Drug entrapment efficiency</th>
<th>In vitro buoyancy</th>
<th>Drug loading</th>
<th>Swelling index</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFMG1</td>
<td>53.5±0.95</td>
<td>74.28±0.07</td>
<td>94.01±0.2</td>
<td>8.324 ± 0.23</td>
<td>756.34 ± 1.48</td>
</tr>
<tr>
<td>FFMG2</td>
<td>65.09±0.81</td>
<td>82.87±0.05</td>
<td>93.18±0.5</td>
<td>8.786 ± 0.56</td>
<td>855.23 ± 1.38</td>
</tr>
<tr>
<td>FFMG3</td>
<td>70.89±0.64</td>
<td>86.28±0.15</td>
<td>85.72±0.4</td>
<td>9.557 ± 0.12</td>
<td>787.57 ± 0.16</td>
</tr>
<tr>
<td>FFMG4</td>
<td>90.23±0.21</td>
<td>94.18±0.04</td>
<td>90.43±0.2</td>
<td>10.34 ± 0.10</td>
<td>816.49 ± 0.37</td>
</tr>
<tr>
<td>FFMG5</td>
<td>91.35±0.34</td>
<td>90.18±0.09</td>
<td>80.38±0.3</td>
<td>8.945 ± 0.46</td>
<td>756.83 ± 2.46</td>
</tr>
<tr>
<td>FFMG6</td>
<td>96.64±0.42</td>
<td>97.37±0.11</td>
<td>95.25±0.7</td>
<td>11.843 ± 0.44</td>
<td>890.46 ± 0.78</td>
</tr>
<tr>
<td>FFMG7</td>
<td>90.17±0.23</td>
<td>93.18±0.12</td>
<td>92.67±0.69</td>
<td>9.475 ± 0.48</td>
<td>779.90 ± 3.16</td>
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<td>FFMG8</td>
<td>89.27±0.12</td>
<td>94.87±0.36</td>
<td>90.89±0.18</td>
<td>9.734 ± 0.59</td>
<td>798.90 ± 2.15</td>
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<tr>
<td>FFMG9</td>
<td>93.19±0.44</td>
<td>92.81±0.67</td>
<td>94.78±0.16</td>
<td>9.285 ± 0.30</td>
<td>835.19 ± 0.23</td>
</tr>
</tbody>
</table>
In-Vitro Drug Release for Gabapentin Factorial Batches

The drug release was studied in simulated gastric fluid. The batch FFMG6 containing 0.5:0.75 polymer concentration exhibited maximum drug release (99.1%) relative to other batches. This indicates the batch FFMG6 contained optimum concentration of polymer required for desired drug release. The drug release profile of the designed batches presented in Figure 2.

SCANNING ELECTRON MICROSCOPY

The surface morphology of the microspheres was examined by SEM study. Figure 3 shows SEM images of microspheres taken in various magnifications. The SEM images showed the circular, isolated, and free-flowing microsphere. The surfaces were often slightly rough as well as drug crystals often existed on the microspheres surface. These drug crystals were liable for the explosion of the drug from the microspheres.
kinetic models were fitted (Zero order, First order, Korsmeyer-Peppas & Higuchi) for all the selected batches. When the release profile was compared with the square root of time, a linear connection with the regression coefficient was observed nearly one. When n takes 0.5, it suggests diffusion-controlled release and indicates swelling-controlled release of medicines for value 1. A value of n within 0.5 to 1 represents the release mechanism by diffusion as well as swelling (anomalous transport). The optimized formulation FFMG 6 shows an n value of 0.8474 and an R² value of 0.9965. Hence it can be concluded that the optimized formulation obeys the Korsmeyer-Peppas release kinetic model. The results obtained are demonstrated in fig. 4.

![Release Profile](image)

**Figure 4:** Drug release kinetics for Gabapentin microspheres for batch FFMG6

**Statistical analysis and response surface study of factorial batches**

The drug release and floating lag time were selected as dependent variable and the effect of independent variables was studied on these responses. The ANOVA study showed the selected independent variables HPMC K-100 and cellulose acetate phthalate significantly affected the responses (P<0.05).

**ANOVA for 2FI model**

**Table 5: Response 1: Drug Release**

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>E-value</th>
<th>P-value</th>
<th>significant</th>
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</thead>
<tbody>
<tr>
<td>Model</td>
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<td>23.88</td>
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<tr>
<td>A-HPMC K 100</td>
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<td>28.73</td>
<td>80.08</td>
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</tr>
<tr>
<td>B-Cellulose Acetate Phthalate</td>
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<td>82.29</td>
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<td>0.3588</td>
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<td></td>
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</tr>
</tbody>
</table>
Final Equation in Terms of Actual Factors

Drugs Release = 96.17 + 2.18833 HPMC K 100 + 2.21833 Cellulose Acetate Phthalate - 1.83000 HPMC K 100 * Cellulose Acetate Phthalate

ANOVA for Quadratic Model

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F-value</th>
<th>p-value</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5</td>
<td>192.36</td>
<td>31.69</td>
<td>0.0085</td>
<td>Significant</td>
</tr>
<tr>
<td>A - HPMC K 100</td>
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<td>1</td>
<td>39.17</td>
<td>6.45</td>
<td>0.0847</td>
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<tr>
<td>B - Cellulose Acetate Phthalate</td>
<td>594.21</td>
<td>1</td>
<td>594.21</td>
<td>97.90</td>
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<tr>
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Final Equation in Terms of Actual Factors

Floating Lag Time = 63.01111 + 2.55500 HPMC K 100 + 9.95167

Cellulose Acetate Phthalate - 1.61500 HPMC K 100 * Cellulose Acetate Phthalate + 12.08833 HPMC K 100² + 3.58833 Cellulose Acetate Phthalate²
The stability study was conducted as per ICH guidelines and indicated that developed microspheres were stable. This was evident from the unchanged properties of the microspheres after duration of the study.

In-vivo Study:
After oral dosing, it was obvious to the stomach clearly the hard gelatin capsules comprising BaSO4 loaded hollow floating microspheres. All microspheres were observed scattered inside the stomach in the radiographic image within an hour. Dense microsphere images were seen at first hours, but with time passing, the microsphere images become lighter. It may be due to the distribution as well as scattering in the GI area of the microsphere. The images showed that these floating hollow microspheres were successfully stored up to 12 hours in the stomach.

**CONCLUSION**
The floating microspheres of gabapentin were prepared and evaluated by $3^2$ factorial design by using HPMC K-100 and cellulose acetate phthalate as polymers. The Micromeritic study showed designed microsphere formulation display better bulk and flow properties with
optimum particle size. Moreover, FFMG 6 batch was optimized based on the maximum drug release (99.1%). The developed microsphere formulations possessed optimum evaluation parameters as evident from the study. The optimized formulation obeyed Korsmeyer-Peppas release kinetic model and SEM images showed spherical, discrete, and freely floating microspheres. Besides, floating hollow microspheres were successfully stored up to twelve hours in the stomach. The gastroretentive microspheres were stable under appropriate storage conditions. Therefore, the designed floating microspheres can be used for the delivery of the drugs like gabapentin.

REFERENCES