Performance Optimization of Buoyant Beads of Anti-Diabetic Drug Using Quality by Design (QbD)

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SUMMARY. The present study examined the formulation variables and resulted in successful optimization of buoyant beads of glipizide using combination of sodium alginate, light liquid paraffin and chitosan with a computer optimization technique and response surface methodology utilizing polynomial equations. Different concentration of light liquid paraffin and sodium alginate were used and selected as independent variables. The effects of independent variables were determined on properties like floating, bead size, drug entrapment efficiency and drug release rate. In vivo hypoglycemic activity of the optimized beads was determined. The optimized formulation showed a drug release 92.6%, entrapment efficiency 80.5%, floating lag time 22 s, floating time 12.2 h and bead size 2.15 mm. The drug release from the beads was sustained for more than 10 h and beads were also found stable. It was observed that the concentration of light liquid paraffin and sodium alginate had highly significant effects on dependent variables. In vivo study indicates significant hypoglycemic effect for optimized formulation.

INTRODUCTION

Quality by Design (QbD) helps in systemic development of drug product based on sound scientific principles, thus it refers to the successful achievement of predictable quality with desired predetermined specification 1. QbD paradigm of drug regulation necessitates very well understanding of the product to overcome future product failures 2. Design of Experiment (DoE) and RSM helps in finding the individual as well as combined effect of variables on product 3.

Gastro retentive drug delivery system is a novel approach to retain the dosage form in the stomach. This plays an important role in enhancing the bio-availability of the drug at desired site of absorption. Extended-release dosage forms having prolonged residence times in the stomach are useful for the drugs having narrow absorption windows, instability in the intestinal or colonic environments, locally acting in the stomach and poor solubility at pH of intestine 4. Newer approaches to improve the gastric residence time of drug delivery systems include floating devices 5-6, swelling devices that increase their size 7, low density devices 4, several floating drug delivery systems 8-10, high density systems 11,12, expandable systems, magnetic systems, super-porous, biodegradable hydrogel systems 8 and micro-particulate systems 6. Naturally occurring biodegradable polymers used to prepare microsphere have become a novel approach in developing sustained/ controlled drug delivery system. Dosage forms that can precisely control over their release and target drugs towards specific site in the body have a good impact in the formulation and development of novel drug delivery systems. Microsphere forms an important part of novel drug delivery systems 13-15.

KEY WORDS: Central composite design (CCD), Glipizide, Ionic-gelation, Response surface methodology (RSM).

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Glipizide is a well known oral hypoglycemic agent and a commonly prescribed drug for the treatment of patients with type II diabetes mellitus \(^{10}\). Glipizide is a weak acid with pKa value of 5.9, practically insoluble in water and in acidic environment but highly permeable (BCS class II). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 2-4 h \(^{17}\). Glipizide has a short biological half-life (3.4 ± 0.7 h) administered in two or three doses of 2.5-10 mg per day \(^{18}\) and it shows high peak to through fluctuations. Hence it is clear that the development of controlled release dosage forms of glipizide would be advantageous. A number of researchers have developed oral controlled release beads by various techniques \(^{19}\). Glipizide controlled delivery had been developed with conventional microencapsulation techniques \(^{20}\). Hence the study was aimed to develop optimized oil entrapped multiple-unit buoyant dosage form of glipizide and to determine the effect of light liquid paraffin (LP) on the physicochemical properties of formulated alginate beads. Ionotropic-gelation technique using sodium alginate (SA) was adopted to prepare oil-entrapped beads containing drug. The effect of the ratio of drug to polymer (w/w), ratio of LP to drug polymer solution (v/v) on the physicochemical properties, buoyancy and release were evaluated.

**MATERIALS AND METHODS**

**Materials**

Glipizide was received as gift sample from USV Ltd. (Daman, India). SA (low viscosity grade, 250 cp of 2% solution at 25 °C) and LP were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). Chitosan was purchased from M/S Sigma Aldrich (Germany). Calcium chloride di-hydrate and Hydrochloric acid (35% GR) were purchased from E. Merck India Ltd. (Mumbai, India). All other chemicals were of analytical grade and were used as such. Qualicaps capsule shells were supplied as gift sample from Qualicaps, Japan. Goat mucosa was taken from local slaughter house, Glynase XL 10 mg tablets were purchased from local market. Double distilled water was used throughout the study.

**Study design**

Preliminary studies were carried out to select the amounts of variables for further studies, with focus on the formation of beads and floating properties. Variables were studied by preparing all the batches as per \(3^2\) CCD with \(\alpha = 1\). This DoE is employed as most efficient design in estimating the influence of individual variables (main effects) and their interactions, using minimum experimentation centre point was repeated five times and mean of all five was used in further investigation. Floating, bead size, drug entrapment efficiency and drug release rate were selected as dependent variables. Various batches were prepared as listed in Table 1.

**Preparation method**

Emulsion Ionic gelation method was adopted for the preparation of oil entrapped buoyant beads of glipizide \(^{21,22}\). In this method solution of SA was prepared by the addition of required amount of SA in distilled water. Glipizide was dispersed in the formulated solution according to the Table 1. LP (10, 12.5 and 15%, v/v) was then added to the drug polymer mixture. The mixtures were homogenized at 10000 rpm using

<table>
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<th>Batch code</th>
<th>Coded Level</th>
<th>Actual Amount</th>
<th>Glipizide (mg)</th>
<th>Distilled water (to make)</th>
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<td>500</td>
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<td>500</td>
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<td>1:9</td>
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<td>500</td>
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<td>GF13</td>
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<td>1:7</td>
<td>12.5</td>
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</table>

Table 1: Different Batches with their Coded Level and Actual Amount of Variables.
a homogenizer (Remi motors, RQ-122, Vasai, India) for 20 min with addition of emulsifier Span 80 to ensure stabilization of emulsion. The bubble free drug loaded emulsion was extruded, using a 22 gauge syringe needle into 100 mL 0.45 mol/L calcium chloride solution with 0.5% chitosan, maintained under gentle agitation at room temperature. The emulsion gel beads were allowed to stand for 15 min before being separated and washed with distilled water. The beads were dried at 40 °C temperature and stored. The time of drying was optimized by weighing the beads repeatedly, until obtained a constant weight 23.

**Evaluation of glipizide loaded floating alginate beads**

**Estimation of glipizide**

Glipizide content was estimated by using UV spectrophotometer (Shimadzu 1800, Japan) at 275 nm in 7.4 ph phosphate buffer 4. The method was validated for linearity, accuracy and precision. The method obeyed Beer’s law in the concentration range of 5-50 µg/mL.

**Size, uniformity and swelling index of beads**

Various conditions such as viscosity, rate of falling of drops, stirring rate and distance between syringe and gelation media were kept constant during the course of preparation for uniform beads preparation. Variation in any of these parameters may result in production of non-homogenous and non-uniform beads, affecting the overall results to an appreciable extent 24.

All batches of beads were visually analyzed for oil leakage, shape and color. Particle size of the prepared beads was determined using a digital vernier (Mitutoyo Japan). Twenty dried beads were measured for calculating the mean diameter. The result is expressed as the mean diameter (mm) ± standard deviation. The swelling index (S) was determined using 0.1 N HCl. The beads of known weight were placed in 50 mL of 0.1 N HCl for 24h. At time intervals of 15m for first one hour, 30m for next two hours and one hour for next four hours, the beads were removed, excess surface liquid was removed by blotting paper and their weight was recorded and it was determined as 25

\[
S = \left( \frac{\text{weight of swollen microcarrier} - \text{weight of dry microcarrier}}{\text{weight of dry microcarrier}} \right) \times 100.
\]

**Surface morphology**

Surface morphology was studied by scanning electron microscopy of beads (Phillips 1500, scanning electron microscope). The beads were previously fixed on a brass stub using double sided adhesive tape and then were made electrically conductive by coating in vacuums, with a thin layer of gold (approximately 300 Å), for 30s and at 30 W. The pictures were taken at an excitation voltage of 15 Kv and at magnification of 22, 65 and 610 X.

**Drug entrapment efficiency**

Beads (50 mg) were crushed in a glass mortar-pestle and the powdered beads were suspended in 10 mL ethanol in a 100 mL volumetric flask and volume was made up with 0.1 N HCl. After sufficient dilution and filtration it was analyzed for the drug content. Entrapment efficiency (EE) was calculated by the following formula 26:

\[
EE (\%) = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100.
\]

**In vitro buoyancy of prepared beads**

The floating ability was determined using USP dissolution test apparatus-II. Fifty beads were kept in the vessel and the paddles were rotated at 50 rpm in 500 mL 0.1 N HCl solution maintained at 37 ± 0.5 °C for 18 h. The floating and the settled portion of beads were collected separately after test. Percentage buoyancy was calculated as the ratio of the number of beads that remained floating and total number. The floating ability of the beads was measured by visual observation and the results taken as the average of three determinations. The preparations were considered to have buoyancy, only when all beads floated on the test solution immediately or within a lag time, which did not exceed 2 m 27.

**In vitro glipizide release**

In vitro release studies were carried out using USP XXIV dissolution test apparatus-I. Weighed quantity of beads equivalent to 10 mg of glipizide were filled in “Qualicap” capsule shell and the capsule was placed into 900 mL of simulated gastric fluid (0.1 N HCl) maintained at 50 rpm and 37 ± 0.5 °C 28. Aliquots of 5 mL solution were withdrawn at a specific time interval and replaced with fresh dissolution medium. The samples withdrawn were analyzed for glipizide content spectrophotometrically (Shimadzu 1800, Japan) at 275 nm. The results of in vitro release data were fitted into various release equations for the following kinetic models (zero-order, first order 29, Higuchi 30, Korsemeyer and Peppas 31).
In vivo anti-diabetic study

Optimized beads were evaluated in normal healthy Wistar rats of weight range 250-300 g each. Institutional Animal Ethical Committee (IAEC) approval was taken before conduction of study. All the studies were conducted as per standard guidelines using 2 groups having 6 Wistar rats each, fasted with water at least 12 h before the start of the experiments. Blood sample (1 mL) was taken as control before administration of beads, from each rat from behind the eyeball through the angle of ocular cavity using small capillary tubes. Reduced blood glucose level was determined for both control and test samples. Pure drug suspension and beads of optimized batch were administered orally to each group using stomach intubations. A dose of 800 µg/kg of glipizide was administered. One mL of blood samples were collected at a specific time intervals at 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 h and plasma glucose levels were determined using one touch ACCU-Chek Active® and the percentage reduction in blood glucose level was determined.

Stability studies

Optimized beads were also subjected to accelerated stability studies to find the changes in release profile and floating on storage; stability studies were carried out at 40 ± 2°C/75 ± 5% RH for 3 months (zone II conditions as per ICH Q1 guidelines) in environment chamber (Jindal instrument, India). The samples were withdrawn periodically and evaluated.

RESULTS AND DISCUSSION

Pre-formulation trail batches of beads were prepared for setting up the range of SA and LP for study. These trials were also helpful in setting the manufacturing variables like stirring speed, and cross linking time. The stirring speed was varied from 50, 70, and 90 rpm and cross linking time 5, 10 and 15 min; 50 rpm and 15 min were found optimum revolution and cross linking time for the preparation of floating beads. Time of cross-linking did not shown significant effect on the entrapment efficiency. While bead size decreases with increased concentration of calcium chloride and increased curing time these causes shrinkage of beads.

Size, uniformity, swelling index and surface topography of beads

Emulsion gelation technique was used for preparing buoyant beads of glipizide using a natural polymer SA. Polymer concentration (drug: polymer) plays an important role, as the ratio changes the viscosity of polymer solution changes which effects the bead size. As previously consigned in Table 1, three different polymer concentrations were selected. Least concentration 2.5% [1:5 (drug: polymer)] showed least size, maximum sphericity and no oil leakage, with increase in concentration and hence, the viscosity of alginate solutions, beads with more surface area and less surface porosity were obtained, thus they cause slow drug release. Increased viscosity at a higher concentration of SA resulted in larger particles (2.00-2.25 mm, Table 2). Syringe

<table>
<thead>
<tr>
<th>Batch</th>
<th>Size (mm)</th>
<th>Mean Swelling (%)</th>
<th>Drug entrap Efficiency (%)</th>
<th>Mean Density (gm/cm3)</th>
<th>FLT (s)</th>
<th>TFT (h)</th>
<th>Oil leakage</th>
<th>Shape and color</th>
<th>Flowability</th>
</tr>
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<tr>
<td>GF1</td>
<td>2.02 ± 0.02</td>
<td>5.44</td>
<td>75.0 ± 2.4</td>
<td>0.87</td>
<td>0</td>
<td>&gt;12</td>
<td>NO SOW</td>
<td>Free flowing</td>
<td>Flowing</td>
</tr>
<tr>
<td>GF2</td>
<td>2.13 ± 0.01</td>
<td>5.23</td>
<td>81.5 ± 2.4</td>
<td>0.99</td>
<td>121</td>
<td>2.5</td>
<td>NO SOWT</td>
<td>Flowing</td>
<td>Flowing</td>
</tr>
<tr>
<td>GF3</td>
<td>2.13 ± 0.01</td>
<td>3.13</td>
<td>81.0 ± 2.1</td>
<td>0.67</td>
<td>0</td>
<td>&gt;18</td>
<td>NO SLY</td>
<td>Flowing</td>
<td>Flowing</td>
</tr>
<tr>
<td>GF4</td>
<td>2.24 ± 0.01</td>
<td>3.21</td>
<td>87.0 ± 2.2</td>
<td>0.97</td>
<td>50</td>
<td>&gt;12</td>
<td>YES SLYT</td>
<td>Sticky with oil</td>
<td>Flowing</td>
</tr>
<tr>
<td>GF5</td>
<td>2.14 ± 0.02</td>
<td>4.16</td>
<td>79.5 ± 3.2</td>
<td>0.74</td>
<td>0</td>
<td>&gt;12</td>
<td>NO SOW</td>
<td>Flowing</td>
<td>Flowing</td>
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<tr>
<td>GF6</td>
<td>2.15 ± 0.02</td>
<td>4.24</td>
<td>84.3 ± 1.8</td>
<td>0.98</td>
<td>110</td>
<td>&gt;12</td>
<td>NO SOWT</td>
<td>Flowing</td>
<td>Flowing</td>
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<tr>
<td>GF7</td>
<td>2.05 ± 0.01</td>
<td>4.87</td>
<td>78.5 ± 1.2</td>
<td>0.89</td>
<td>32</td>
<td>&gt;12</td>
<td>NO SOW</td>
<td>Free flowing</td>
<td>Flowing</td>
</tr>
<tr>
<td>GF8</td>
<td>2.16 ± 0.01</td>
<td>3.84</td>
<td>83.1 ± 3.2</td>
<td>0.88</td>
<td>18</td>
<td>&gt;12</td>
<td>YES ASLY</td>
<td>Flowing</td>
<td>Flowing</td>
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<tr>
<td>GF9</td>
<td>2.06 ± 0.02</td>
<td>4.36</td>
<td>80.5 ± 1.5</td>
<td>0.90</td>
<td>27</td>
<td>&gt;12</td>
<td>NO ASLY</td>
<td>Flowing</td>
<td>Flowing</td>
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<tr>
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<td>2.09 ± 0.03</td>
<td>4.78</td>
<td>80.6 ± 1.8</td>
<td>0.90</td>
<td>27</td>
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<td>Flowing</td>
<td>Flowing</td>
</tr>
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<td>4.35</td>
<td>80.5 ± 1.2</td>
<td>0.89</td>
<td>27</td>
<td>&gt;12</td>
<td>NO ASOW</td>
<td>Flowing</td>
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<tr>
<td>GF12</td>
<td>2.06 ± 0.02</td>
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<td>80.9 ± 1.7</td>
<td>0.90</td>
<td>26</td>
<td>&gt;12</td>
<td>NO ASOW</td>
<td>Flowing</td>
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<tr>
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<td>2.04 ± 0.02</td>
<td>3.43</td>
<td>80.7 ± 1.1</td>
<td>0.90</td>
<td>25</td>
<td>&gt;12</td>
<td>NO ASOW</td>
<td>Flowing</td>
<td>Flowing</td>
</tr>
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</table>

Table 2. Physicochemical properties of alginate beads. SOW = spherical off white, SOWT = spherical off white with tailing, SLY = spherical light yellow, SLYT = spherical light yellow with tailing, ASOW = almost spherical off white.
opening size was kept constant which also affects the bead size. More LP concentration in beads shows oil leakage and flowability decreases. Beads prepared were free flowing and of monolithic matrix type.

It was observed that concentration of calcium chloride and hardening time had a negative effect on the beads size. High calcium chloride concentration and hardening time results in more cross linking and thus causes shrinkage of beads and smaller particle. The negative effect of calcium chloride concentration and cross linking time on size was of less magnitude, but the more effect was on the morphology of the beads i.e. the surface became rougher and porous 34. Each batch beads were found uniform in size. Concentration of LP affects the swelling index, as with increased LP, swelling decreases (Table 2).

Scanning electron microscopy was used to study the surface topography of prepared beads and is shown in Fig. 1. Buoyant beads of glipizide were well-rounded spheres with rough surface because of sudden cross linking of alginate with calcium. These drug-loaded beads started becoming elongated with increase in LP concentration in emulsion. LP entrapped beads had an “orange peel” surface with corrugations because of surface coating with chitosan present in cross linking solvent.

**Drug Entrapment Efficiency**

Entrapment efficiency is an important variable used to assess the drug loading capacity of beads and their drug release profile. EE depends upon various parameters such as process used for preparation, physicochemical properties of the drug and various formulation variables.

All thirteen batches show entrapment efficiency ranging between 72.6-89.2% depending on the composition of alginate glipizide beads (Table 2). The curing time was kept to 15 min since drug is insoluble in water. EE of the beads increases with increase LP due to partitioning of the drug in the LP phase. Moreover, an increase in the amount of alginate increases EE due to increased space for drug molecules to be retained throughout a larger cross linked network of calcium alginate. It was also observed that cross-linking time did not affect over the drug EE.

**In-vitro buoyancy of prepared beads**

Effect of LP loadings over the buoyancy of the alginate beads is shown in Table 2. All LP loaded samples stayed afloat for ≥ 12 h in 18 h test cycle except GF2. The prepared beads also shows floating lag time depending on concentration of SA and LP in them, with increased SA inclusion FLT increases but at the same time the concentration of LP is also governing the FLT that is low concentration of LP was resulting in more FLT and with increase LP concentration FLT decreases. It may be due to the decreased density with increased LP.

**In vitro glipizide release**

Drug release study of alginate beads was performed in the simulated fasted state dissolution media of pH 1.2 for a period of 14 h (Table 3). As shown in Fig. 2 the release was first slow then it increases and again a decrease in the release was found during dissolution study. The batch with least SA and LP shows fastest release as it releases 23.65 ± 2.1% glipizide within one hour, followed by a tailing off sustained release profile for 14 h. rapid release in initial stage may be due to drug dissolution from the surface of beads. The drug release was found to be slower.

![Figure 1: Scanning Electron Micrograph of beads (A = single bead, B = multiple elongated beads with increased LP, C = enlarged surface view)](image-url)
in formulations with higher oil concentration. Slow release of drug from the beads may be due to the formation of drug-LP dispersion system in the oil pockets of the beads. Where, the drug has to firstly diffuse from the oil pockets into the polymeric matrix and followed by transportation of drug out of the polymeric matrix into the dissolution medium.

### Data Analysis and optimization

Various release kinetics models were used, to investigate the mechanism of drug release, like zero-order, first order, Higuchi’s square root of time model and Korsmeyer-Peppas model. First order gave $r^2$ value 0.9263-0.9911 describing the drug release rate relationship with concentration of drug. The best linearity was found in Higuchi’s equation plot, $r^2$ is between 0.9912-0.9950 indicating the release of drug from matrix as a square root of time dependent process. The diffusion exponent (n) value, as calculated from Korsmeyer-Peppas model, for glipizide loaded beads ranged from 0.4470 to 0.5170 (Table 3), showing anomalous (non-Fickian) diffusion involving a combination of swelling, diffusion and/or erosion of matrices, in most of batch except GF9. Hence polymer swelling and erosion as well as formation of hydrophobic diffusion barrier by the incorporated LP in the beads might be retarding the release of the drug from the beads. Various response surfaces were also plotted (Fig. 3) to find out the combined effect of various independent variables, on the dependent variables like $Q_{10}$, EE, FLT, TFT, BS and result of ANOVA for Response Surface Quadratic Model for dependent parameters are like:

#### Table 3. Drug Release Study ($Q_6$ = release in 6 h, $Q_{10}$ = release in 10 h, $Q_{14}$ = release in 14 h).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>$Q_6$</th>
<th>$Q_{10}$</th>
<th>$Q_{14}$</th>
<th>Korsmeyer $R^2$</th>
<th>Higuchi $R^2$</th>
<th>First Order $R^2$</th>
<th>Zero Order $R^2$</th>
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<td>69.33</td>
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<td>98.29</td>
<td>0.9752</td>
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<td>0.9263</td>
<td>0.9000</td>
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<td>91.13</td>
<td>94.55</td>
<td>0.9803</td>
<td>0.9930</td>
<td>0.9795</td>
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<td>94.11</td>
<td>95.05</td>
<td>0.9827</td>
<td>0.9944</td>
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<td>0.9950</td>
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<td>0.9760</td>
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<td>0.9476</td>
<td>0.8971</td>
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<td>0.9946</td>
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<td>0.9935</td>
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</table>

### Figure 2. Drug release study.

#### Figure 2. Drug release study.
Fig. 3A shows a nearly linear ascending pattern for the values of entrapment efficiency, as the content of LP increased, while the entrapment efficiency decreases with increasing SA. Maximum entrapment efficiency is observable at the highest levels of LP and lowest SA. Contour lines corroborate markedly significant influence of LP and SA on entrapment efficiency.

Fig. 3B portrays a nonlinear increase or decrease relationship of TFT with increasing and decreasing amounts of SA and LP. Nonlinear lines in contour plot shows the presence of any interaction between the polymer and LP for TFT as it increases with increasing LP and at high LP concentration with low SA it is maximum while with high SA it again decreases.

Fig. 3C shows that the FLT is almost zero at all concentration of LP with Lowest SA while the increasing concentration of SA increases FLT. Maximum FLT was found at highest SA and lowest LP combination.

Bead size according to Fig. 3D shows a nearly linear ascending pattern for the values, as the content of either SA or LP is increased, the effect being much more prominent with SA. Maximum bead size is observable at the highest levels of both SA and LP.

Fig. 3E reveals a sharp decline in the value of Q₁₀ with an increase in the amount of the polymers, i.e., SA while with increase in LP it decreases, the influence of SA is more pronounced. Nonlinear contour lines in figure further show that the variation in Q₁₀ is a complex function of the polymer SA and entrapped LP levels.

**Design validation and Selection of Optimum Formulation**

Upon comparison of the observed responses with those of the anticipated ones (Table 4), the prediction error varied between -6.33 and 5.35 % (mean ± SD = 0.39 ± 1.2 %). The linear correlation plots drawn between the predicted and observed responses, forcing the line through the origin, demonstrated high values of R (0.9114 to 0.9854, Fig. 4), indicating excellent goodness of fit (p < 0.005). The corresponding residual plots show nearly uniform and random scatter around the mean values of response variables. The optimum formulation was selected by trading off various response variables and adopting the following maximizing criteria: Q₁₀ > 92%; EE > 80%; FLT ≤ 40 s; TFT > 12 h and BS ≤ 2.15 mm. Upon comprehensive evaluation of feasibility and grid searches, the formulation (SA: 3.38 mg and LP: 12.3 mL) fulfilled the optimal criteria of best regulation of the release rate Q₁₀ = 92.6%; EE = 80.5%; FLT = 22 s; TFT = 12.2, and BS = 2.15 mm. So, this formulation was taken as optimized formulation.

**In-vivo evaluation**

The results show that when pure glipizide suspension was administered in normal healthy Wistar rats blood glucose levels was decreased rapidly and it was observed that maximum reduction (45.5 %) was found within 1 h after oral administration and within 6 h blood glucose level reaches rapidly to its normal level (Fig. 5). When optimized formulation was administered, the reduction in blood glucose levels was
reached to maximum value within 1 h after administration and percentage reduction in blood glucose levels was sustained over 10 h. Reduction in blood glucose levels by 25% is considered as a significant hypoglycemic effect which is maintained only up to 2 h after oral administration of the pure glipizide. In the case of glipizide beads with alginate, significant hypoglycemic effect was maintained for a period of 1 to 10 h. Thus glipizide floating beads are significantly more effective than immediate release formulation of glipizide in reducing fasting plasma glucose levels.

**Stability study of optimized formulation**

All the parameters viz., content, TFT, FLT, BS and drug release remained quite well within the desirable limits, showing negligible and random variation over three months of storage under accelerated conditions. Dissolution parameter (viz.
NANDA A., SINGH L., SHARMA S. & SHARMA V.

Q10), obtained during various time points of stability studies carried out at 40 ± 2 °C and 75 ± 5% RH, remained almost unaffected during the studies, suggesting the robustness of the optimized formulation with respect to dissolution characteristics.

Comparison of Optimized Formulation with Marketed Product

Table 5 shows all the drug release data of marketed Glynase XL 10 mg extended release glipizide tablet and its comparison with optimized formulation.

As the results shows the release of optimized batch for a prolonged duration, the studies conclude successful development of gastroretentive CR formulation of glipizide capable of maintaining the drug release profiles for a prolonged duration as observed with the marketed CR products while eliminating the disadvantages of single unit, maintaining almost constant level of drug and delivering the drug at its preferred site of absorption in the GI tract.

CONCLUSION

The centred task of maintaining and balancing the required buoyancy and required release profile of anti-diabetic drug was successfully meets in the present study using Quality by Design (QbD) with appropriate mix of alginate and light liquid paraffin supplemented with chitosan. Chitosan, have higher density and they are also considered unsuitable to impart buoyancy but useful for controlling drug release while lighter light liquid paraffin impart floatation and also influence drug release. Hence, the present work can be said as foundation for future development in the manufacture of gastroretentive optimized oil entrapped multiple-unit buoyant dosage form of glipizide using an approach which reduces time as well as achieves predictable quality with desired specification.

Technological transference potential

The technique used in the present work for preparation beads i.e. emulsion ionic-gelation of alginate with liquid paraffin may be easily transferred in to high scale manufacturing facility. Both technology consideration i.e. risk involved and high scale manufacturing facilities availability as well as commercial consideration i.e. potential commercial application and potential market of the product are abundantly available.

REFERENCES

Gastroretentive Drug Delivery System: An Overview

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ABSTRACT
Oral route is most preferable route of administration but it has certain limitations for those drugs which absorb from specific region of gastrointestinal tract. The bioavailability of drugs can be improved by increase their retention time in the stomach and several approaches are used to increase the gastric retention time of the dosage form are described.

INTRODUCTION
Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e., gastroretentive dosage forms (GRDFs), will provide us with new and important therapeutic options.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Gastroretentive Techniques
Several techniques, including floating, swelling, inflation, and adhesion have been explored to increase the gastroretention of dosage forms.

Floating systems
Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate which results in increased GRT and reduces fluctuation in plasma drug concentration.

The floating drug delivery system and bioadhesive drug delivery are widely used technique for gastroretention and floating systems in particular has been extensively researched, mainly because the floating system does not adversely effect the motility of GI tract.

Floating systems can also be classified as effervescent and noneffervescent systems.

Effervescent systems
Floatation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO₂ produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a predetermined amount of
time to permit the spontaneous ejection of the inflatable system from the stomach.

**Noneffervescent systems**

Noneffervescent systems incorporate a high level (20–75 % w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers, polysaccharides and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the dosage form. The following approaches used in designing intra-gastric floating systems\(^5\).

**Hydrodynamically balanced systems**

These are single unit dosage form, containing one or more gel forming hydrophilic polymers, HPMC is the most commonly used excipient, although HEC, HPC, NaCMC, agar and alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsules rapidly dissolve in the gastric fluid, and hydration and swelling of the surface polymer produce a floating mass. Drug release is controlled by the formation of hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layer, maintaining surface hydration and buoyancy. Incorporation of fatty excipients give low density formulations and reduce penetration of water, reducing the erosion. The main drawback is the passivity of operation. It depends on the air sealed in the dry mass centre following hydration of gelatinous surface layer and hence the characteristics and amount of polymer. Effective drug delivery depends on the balance of drug loading and effect of polymer on its release profile.

**Gas generating system**

Floatability can also be achieved by generation of gas bubbles. CO\(_2\) can be generated *in situ* by the incorporation of carbonates or bicarbonates, which react with acid- either the natural gastric acid or co-formulated as citric or tartaric acid. The optimum stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:

1. An alternative is to incorporate a matrix with entrapped of liquids, which forms a gas at body temperature. These approaches have been used for single and multiple unit system.

**Raft-forming System**

Here, a gel forming solution (e.g., Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO\(_2\) bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity. Because raft forming systems produce a layer on the top of gastric fluids, they are often used for the treatment of gastroesophageal reflux treatment.

**Low-Density Systems**

Gas-generating system inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density system (<1 g/cm\(^3\)) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called “microballoons” because of low-density core.

**Bio/mucoadhesive systems**

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The concept is based on the self-protecting mechanism of the GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Mucus is a viscoelastic, gel-like, stringy slime comprised mainly of glycoproteins. The thickness of the mucus layer decreases from the membrane surface to the GI lumen. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases. In addition, it serves as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses. The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/mucoadhesive polymers. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability. A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). The characteristics of these polymers are molecular flexibility, hydrophilic
functional groups, and specific molecular weight, chain length, and conformation. Furthermore, they must be nontoxic and nonabsorbable, form noncovalent bonds with the mucin–epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug, and offer no hindrance to drug release, have a specific site of attachment and be economical. The binding of polymers to the mucin–epithelial surface can be subdivided into three broad categories: hydration-mediated adhesion, bonding-mediated adhesion, and receptor-mediated adhesion. Materials commonly used for bioadhesion are poly(acrylic acid) (Carbopol, poly(carboxylic)), Chitosan, Gantrez (Poly(butyl vinyl ether/maleic anhydride copolymers), cholesterylamine, tragacanth, sodium alginate, saccharate, polyethylene glycol, dextran and poly( acrylic acid).

Hydration-mediated adhesion
Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties. The prolonged gastroretention of the bio/mucoadhesive drug delivery systems is further controlled by the dissolution rate of the polymer.

Bonding-mediated adhesion
The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical–mechanical bonding and chemical bonding. Physical–mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., van der Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

Receptor-mediated adhesion
Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

Swelling systems
After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical–chemical crosslinks in the hydrophilic polymer network. These crosslinks prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of the polymer. An optimum amount of cross linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration.

High-density systems
These systems, which have a density of ~3 g/cm³, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm³, such systems can be retained in the lower part of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50 %) and to achieve the required density of 2.4–2.8 g/cm³. Diluents such as barium sulphate (density = 4.9), zinc oxide, titanium dioxide, and iron powder may be used to manufacture such high-density formulations.

Superporous Hydrogels
Although these are swellable systems, they differ sufficiently from the conventional type to warrant separate classification. With pore size ranging between 10nm and 10μm, absorption of water by conventional hydrogels is very slow process and several hours may be needed to reach an equilibrium state during which pre mature evacuation of dosage form may occur. Superporous hydrogels, average pore size > 100μm, swell to equilibrium size within a
minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores.

**Magnetic System**
This system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach.

**Limitations**
GRDDS have great potential in improving the bioavailability of drugs that exhibit an absorption window, but with certain limitations. One of the major disadvantages of floating systems is the requirement of high levels of fluids in the stomach for the delivery system to float and work efficiently. These systems also require the presence of food to delay their gastric emptying.

In addition, there are limitations to the applicability of floating systems for drugs that have solubility or stability problems in the highly acidic gastric environment or that are irritants to the gastric mucosa. In the case of bioadhesive systems, which form electrostatic and hydrogen bonds with the mucus, the acidic environment and the thick mucus prevent bond formation at the mucus–polymer interface. The high turnover rate of mucus may further aggravate the problem and localized high drug concentration could lead to irritation or ulceration.

For swellable systems, the major limiting factor is that the system must maintain a size larger than the aperture of the resting pylorus for the required time period. Hydrodynamically balanced systems, designed using effervescent mixtures, have achieved commercial success but require a high drug: excipient ratio and may have unpredictable bioavailability and are unsuitable for the drugs degrading in basic pH due to the alkaline microenvironment.

**Rationale for Multiple Unit G. R. Drug Delivery Systems**
Large single-unit dosage forms undergo significant swelling after oral administration and the swollen matrix inhibits the gastric emptying even at an unconstructive state of the pyloric sphincter. But the swelling and expanding systems may show hazard of permanent retention. Bioadhesive systems may cause problems such as irritation of the mucous layer owing to high localized concentration of the drug. Hydrodynamically balanced systems, designed using effervescent mixtures, have achieved commercial success but require a high drug: excipient ratio and may have unpredictable bioavailability and are unsuitable for the drugs degrading in basic pH due to the alkaline microenvironment. The single-unit systems such as tablet or capsule may exhibit the all-or-none emptying phenomenon, which may be overcome by the design of multi-unit systems.

Most single unit floating drug delivery system are generally unreliable and non reproducible in prolonging the GRT. They also show higher inter and inter subject variability resulting from their unpredictable all-or-nothing emptying process. Disadvantages of floating drug delivery system based on gas generation include controlling of in situ acid base reaction and subsequent drug release.

Multiple unit floating delivery system show several advantages over monolithic ones, which include avoiding all or nothing emptying, absence or impairing of performance due to failure of few units, more predictable drug release kinetics, less chance of localized mucosal damage and administration of units with different release profiles and claim to reduce the intersubject variability in absorption and lower the probability of dose dumping.

**List of Drugs Formulated in Multiple Unit Forms of Floating Drug Delivery Systems**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
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<tr>
<td>Verapamil Hydrochloride</td>
<td>Floating Microparticles</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Floating Microparticles</td>
</tr>
<tr>
<td>Ranitidine Hydrochloride</td>
<td>Floating Granules</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Floating Beads</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Floating Micropellets</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Low density multiparticulate system</td>
</tr>
<tr>
<td>Diltiazem Hydrochloride, Theophylline and Verapamil Hydrochloride</td>
<td>Foam Based Floating Microparticles</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Hollow Microsphere</td>
</tr>
<tr>
<td>Acetylhydrazic Acid</td>
<td>Floating Microsphere</td>
</tr>
<tr>
<td>Piroxicam</td>
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</tr>
<tr>
<td>Residronate Sodium</td>
<td>Granules</td>
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<tr>
<td>Diltiazem Hydrochloride</td>
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**CONCLUSION**
Gastroretentive drug delivery system showed the potential to increase the gastric retention of drug and increase the bioavailability of drug with some limitations. These limitations can be reduced by formulating as multiple unit drug delivery system and by formulating the drug as floating bioadhesive tablets.

**REFERENCES**


INTRODUCTION

The challenge in developing controlled release system is not only in sustaining the release but also to prolong the retention of dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired time period [1, 2]. Approaches proposed to control the gastric residence of delivery systems in the upper gastrointestinal tract (GIT) include floating drug delivery systems (FDDS) [3-5], high-density [6, 7], mucoadhesive [8, 9], swelling and expanding [10], modified shape and other delayed gastric devices [2, 11, 12].

A minimum growth of 9% per year had been proposed for this market since 2003 [13], as these offers several advantages, including improved patient compliance, better therapeutic efficiency, potential for patentability, and extending the product life-cycle. Extended-release stomach retentive dosage forms are also

Original Research Article

Design Optimization and Evaluation of Gastric Floating Matrix Tablet of Glipizide

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Abstract

Purpose: To formulate an optimized gastric floating drug delivery system (GFDDS) containing glipizide with carboxomers and cellulosic polymers.

Method: Central composite design (CCD) was employed in formulating the GFDDS using hydroxypropyl methylcellulose K4M (HPMC K4M) (A) and Carbopol 934P (CP934P) (B), as independent variables. Floating lag time (FLT), total floating time (TFT) and time required to release 50% of the drug (T50) were selected as dependent variables. The dissolution data obtained were fitted to various release models and the floating profiles of the formulations analyzed.

Results: HPMC K4M loading clearly enhanced floating properties while CP934P showed negative effect on floating properties but was helpful in controlling drug release. The quadratic mathematical model developed was used to predict optimum formulations. The computer optimization process, contour plots and response surface plots predicted the concentration of independent variables A and B to be 47.32 and 8.4 mg, respectively, for maximum TFT and T50 at the same time for least FLT. Predicted concentration of independent variables showed the same results experimentally, with -0.75 - 1.47 percentage errors.

Conclusion: CCD demonstrated the role of the derived equations, contour plots and response surface plots in predicting the values of independent variables for the preparation and optimization of glipizide gastric floating matrix tablet.

Keywords: Effervescent, Floating tablet, Design of Experiment, Release kinetics, Central composite design, Optimization.
desirable for drugs with a narrow absorption window, stability and solubility problems in the intestinal or colonic environment, and drugs that are locally acting in the stomach [3]. A major drawback for this delivery device is that it cannot be employed in the formulation of drugs which cannot be well absorbed throughout the GIT [14-16]. Glipizide is an anti-diabetic drug [17] which is effective in the management of type- II diabetes mellitus. The recommended adult dose is 5 mg twice daily (or) 10 mg once daily. Absorption is in the stomach, and short biological half-life (ranging from 3.5 to 4 h) following oral administration. Further, its short half-life (3.5 h), low dose (5 - 20 mg), narrow absorption window (stomach), high physico-chemical stability etc. make glipizide an ideal drug for floating matrix formulation [18]. These gastro-retentive systems continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability [19].

EXPERIMENTAL

Materials

Glipizide was obtained as gift sample from USV Ltd (India). HPMC K4M, (ZydusCadila, India), CP934P (Noveon, India), sodium bicarbonate (Merck, Germany) magnesium stearate, talc and microcrystalline cellulose (SD Fine, India) were also used in the study. All other chemicals used were of analytical grade and used as received. Double distilled water was used in the study.

Central composite design (CCD)

CCD with $\alpha = 1$ was employed as per the standard protocol. In the study independent variables were concentration of HPMC K4M (A) and CP934P (B) and dependent variables included total floating time (TFT), floating lag time (FLT), and time for 50% release ($T_{50}$). Tables 1 summarize an account of the all experimental runs, coded and actual levels of independent variables.

Preparation of floating tablets

Tablets were formulated using HPMC K4M and CP934P polymers for floating and release rate control. Sodium bicarbonate was added as a gas-generating agent (CO$_2$) in the presence of gastric fluid. Glipizide was mixed with the required quantities of HPMC K4M, CP 934P and Sodium bicarbonate by geometric mixing then mixture was blended with microcrystalline cellulose (q.s. 200 mg), magnesium stearate 1 % and talc 2 %, and further mixed for additional 2-3 min. Then 200 mg tablets containing 10 mg glipizide were prepared by direct compression Minipress-I, 16 station rotatory tabletting machine (Rimek Karnawati, India) using 8-mm flat face punch. Compression force was adjusted for hardness in the range of 3.5 - 4.5 kg/cm$^2$. The batches of 25 tablets were prepared for each batch of all the experimental runs (Table 1).

Table 1: Central composite design and level of independent variables

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Coded value</th>
<th>Actual value</th>
</tr>
</thead>
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<td>Factor B</td>
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<td>F5</td>
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<td>0</td>
</tr>
<tr>
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</tbody>
</table>
Microcrystalline cellulose was used as a filler to adjust each tablet weight to 200 mg because it does not interfere with the floating property of the tablet due to its low bulk density [21].

**In-vitro buoyancy studies**

Buoyancy studies were done to determine FLT and TFT according to the method described by Rosa et al [22]. The tablets were placed in a 100 ml beaker containing 0.1 mol/L of HCl. The time required for the tablet to rise to the surface and float was taken as the FLT and TFT, the time during which tablet remains buoyant was recorded.

**In-vitro swelling ability**

Single tablet was weighed (W₁) and placed in a glass beaker with 200 ml of 0.1N HCl and maintained in a water bath at 37.0 ± 0.5 °C. At regular time intervals, the tablet was removed from beaker and the excess surface liquid was carefully removed with filter paper. The swollen tablet was weighed again (W₂) [23]. The swelling index (SI) was calculated using Eq 1.

\[
SI = \left( \frac{W₂ - W₁}{W₁} \right) \times 100
\] ………………………… (1)

**In-vitro dissolution studies**

The release rate of glipizide from floating matrix tablets (n = 6) was determined according to USP XXIV using type II apparatus (Electrolab, TDT-08L, India). The dissolution test was performed using 900 mL of 0.1 mol L⁻¹ HCl at 37 ± 0.5 °C and 50 rpm [24]. Samples (5 mL) were withdrawn from the dissolution apparatus and replaced with fresh medium. The samples were filtered through a 0.45 μm membrane and diluted to a suitable concentration with 0.1 mol L⁻¹ HCl. Absorbance of samples were measured at 274 nm (Shimadzu UV-1800, Japan) [25] and Cumulative drug release was calculated. The FLT and TFT of the tablets were measured during dissolution studies.

**Statistical analysis and optimization data**

Drug release data were subjected to various release models, including Higuchi model (Eq 2), which indicates whether the drug release mechanism deviates from Fick’s laws and shows anomalous behaviour [28].

\[
Q = Kt^{1/2}
\] ………………………… (2)

where, Q is the amount of drug release at time t, and \(K_t\) is the Higuchi rate constant.

The dissolution data was also fitted to Koresmeyer model which is used to describe drug release behaviour from polymer systems (Eqs 3 and 4) [29].

\[
\frac{M_t}{M_\alpha} = k.t^n
\] ………………………… (3)

\[
\log (\frac{M_t}{M_\alpha}) = \log K + n \log t
\] …………….. (4)

where, \(M_t\) is the amount of the drug release at time ‘t’, ‘\(M_\alpha\)’ is the amount of drug release after infinite time and ‘K’ is a release rate constant incorporating structural and geometric characteristic of the tablet and ‘n’ is the diffusion exponent indications for release mechanism.

For the studied design, the multiple linear regression analysis (MLRA) method was applied using Design Expert 6.0.6 (Stat-Ease, Minneapolis, USA) software to fit full second order polynomial equation (Eq 4) with added interaction terms to correlate the studied responses with the examined variables.

The polynomial regression results were demonstrated for the studied responses. Finally, the prognosis of optimum formulation was conducted using a two-stage brute force technique using MS-Excel spread sheet software. First, a feasible space was located and second, an exhaustive grid search was conducted to predict the possible solutions. Four formulations were selected as the confirmatory check-points to validate by response surface methodology (RSM). The observed and predicted responses were critically compared. Linear correlation plots were constructed for the chosen four optimized formulations, and the percent bias (prediction error) was calculated with respect to the observed responses.

**RESULTS**

Oral floating controlled drug delivery of glipizide was developed and optimized using mixture of HPMC K4M and CP934P which were found suitable for obtaining directly compressible matrix tablet with suitable technological properties and well reproducible drug release profiles. For optimization, preliminary trials were
carried out using different concentrations of HPMC K4M and CP934P to shortlist the levels.

Drug content and physical evaluation

The physical parameters of the compressed tablets were found within the specifications. As the assayed drug content in formulations ranges between 98.2% and 102.7%, weight variation between 198.22 mg and 201.1 mg. Hardness also has an effect on the floating and disintegration thus dissolution, it was ranging between 4.05 to 4.5 kg/cm². Friability of all batches was between 0.44 %w/w to 0.86 %w/w i.e. less than the limit of 1%w/w. The swelling index results of all batches were found between 0.45- 0.82 up to 6 h. All these results are shown in Table 2.

Table 2: Physicochemical characteristics of floating glipizide tablets (mean ± SD, n = 6)

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Mean tablet variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%w/w)</th>
<th>Assay (%)</th>
<th>Floating time (h)</th>
<th>Floating lag-time (s)</th>
<th>Swelling index after 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>200.15±1.04</td>
<td>4.3±0.2</td>
<td>0.6±0.029</td>
<td>99.9±1.04</td>
<td>11.2±0.28</td>
<td>23.7±0.6</td>
<td>0.45</td>
</tr>
<tr>
<td>F2</td>
<td>199.75±1.52</td>
<td>4.2±0.5</td>
<td>0.57±0.13</td>
<td>99.75±1.12</td>
<td>10.05±0.28</td>
<td>26.4±1.5</td>
<td>0.47</td>
</tr>
<tr>
<td>F3</td>
<td>200.75±1.36</td>
<td>4.2±0.4</td>
<td>0.69±0.04</td>
<td>100.0±1.00</td>
<td>9.0±0.28</td>
<td>33.2±2.0</td>
<td>0.50</td>
</tr>
<tr>
<td>F4</td>
<td>200.53±0.50</td>
<td>4.1±0.2</td>
<td>0.79±0.13</td>
<td>99.9±1.47</td>
<td>14.45±0.76</td>
<td>18.7±1.1</td>
<td>0.62</td>
</tr>
<tr>
<td>F5</td>
<td>199.66±0.90</td>
<td>4.1±0.15</td>
<td>0.76±0.07</td>
<td>99.9±1.00</td>
<td>13.1±0.28</td>
<td>20.4±1.5</td>
<td>0.65</td>
</tr>
<tr>
<td>F6</td>
<td>200.35±0.57</td>
<td>4.1±0.2</td>
<td>0.78±0.13</td>
<td>99.75±2.08</td>
<td>11.9±0.28</td>
<td>25.1±2.6</td>
<td>0.68</td>
</tr>
<tr>
<td>F7</td>
<td>199.85±1.26</td>
<td>4.0±0.2</td>
<td>0.75±0.15</td>
<td>99.45±1.25</td>
<td>20.15±0.50</td>
<td>5.1±1.0</td>
<td>0.76</td>
</tr>
<tr>
<td>F8</td>
<td>199.61±0.23</td>
<td>4.2±0.05</td>
<td>0.59±0.076</td>
<td>101.00±0.5</td>
<td>19.05±0.28</td>
<td>5.7±0.6</td>
<td>0.78</td>
</tr>
<tr>
<td>F9</td>
<td>198.86±0.64</td>
<td>4.2±0.2</td>
<td>0.69±0.09</td>
<td>100.1±0.28</td>
<td>18.0±0.57</td>
<td>6.4±0.6</td>
<td>0.82</td>
</tr>
<tr>
<td>F10</td>
<td>200.2±0.40</td>
<td>4.1±0.15</td>
<td>0.76±0.1</td>
<td>100.5±0.50</td>
<td>12.9±0.2</td>
<td>20.6±1.0</td>
<td>0.64</td>
</tr>
<tr>
<td>F11</td>
<td>200.1±0.50</td>
<td>4.0±0.5</td>
<td>0.75±0.06</td>
<td>100.6±0.50</td>
<td>13.0±0.5</td>
<td>21.1±0.5</td>
<td>0.65</td>
</tr>
<tr>
<td>F12</td>
<td>200.2±0.90</td>
<td>4.2±0.25</td>
<td>0.68±0.07</td>
<td>99.9±1.00</td>
<td>12.95±0.3</td>
<td>20.9±1.2</td>
<td>0.65</td>
</tr>
<tr>
<td>F13</td>
<td>199.9±0.90</td>
<td>4.1±0.5</td>
<td>0.73±0.15</td>
<td>101.6±1.10</td>
<td>13.1±0.5</td>
<td>20.35±1.3</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Table 3: Overall dissolution parameters (n = 6) as per central composite design

<table>
<thead>
<tr>
<th>Batch</th>
<th>N</th>
<th>K</th>
<th>k₁</th>
<th>k₂</th>
<th>Q₁₂ (%)</th>
<th>T₅₀ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.4642</td>
<td>0.2597</td>
<td>1.2837</td>
<td>0.0064</td>
<td>88.8</td>
<td>4.09</td>
</tr>
<tr>
<td>F2</td>
<td>0.4673</td>
<td>0.2535</td>
<td>1.2769</td>
<td>0.0072</td>
<td>87.35</td>
<td>4.19</td>
</tr>
<tr>
<td>F3</td>
<td>0.4697</td>
<td>0.2514</td>
<td>1.2729</td>
<td>0.0077</td>
<td>86.72</td>
<td>4.23</td>
</tr>
<tr>
<td>F4</td>
<td>0.4703</td>
<td>0.2492</td>
<td>1.2693</td>
<td>0.0080</td>
<td>86.48</td>
<td>4.31</td>
</tr>
<tr>
<td>F5</td>
<td>0.4701</td>
<td>0.2461</td>
<td>1.2652</td>
<td>0.0081</td>
<td>85.84</td>
<td>4.41</td>
</tr>
<tr>
<td>F6</td>
<td>0.4761</td>
<td>0.2417</td>
<td>1.2578</td>
<td>0.0093</td>
<td>85.6</td>
<td>4.48</td>
</tr>
<tr>
<td>F7</td>
<td>0.4841</td>
<td>0.2364</td>
<td>1.2509</td>
<td>0.0116</td>
<td>84.97</td>
<td>4.61</td>
</tr>
<tr>
<td>F8</td>
<td>0.4783</td>
<td>0.2376</td>
<td>1.2574</td>
<td>0.0079</td>
<td>84.33</td>
<td>4.69</td>
</tr>
<tr>
<td>F9</td>
<td>0.4724</td>
<td>0.2343</td>
<td>1.2528</td>
<td>0.0084</td>
<td>83.69</td>
<td>4.82</td>
</tr>
<tr>
<td>F10</td>
<td>0.4799</td>
<td>0.2449</td>
<td>1.2651</td>
<td>0.0086</td>
<td>84.42</td>
<td>4.45</td>
</tr>
<tr>
<td>F11</td>
<td>0.4776</td>
<td>0.2426</td>
<td>1.2617</td>
<td>0.0094</td>
<td>85.84</td>
<td>4.48</td>
</tr>
<tr>
<td>F12</td>
<td>0.4757</td>
<td>0.2440</td>
<td>1.2605</td>
<td>0.0091</td>
<td>85.62</td>
<td>4.45</td>
</tr>
<tr>
<td>F13</td>
<td>0.4739</td>
<td>0.2436</td>
<td>1.2612</td>
<td>0.0087</td>
<td>85.6</td>
<td>4.45</td>
</tr>
</tbody>
</table>

Tablet floating behaviour

TFT for all formulation ranged from 9.28 - 20.65 h while FLT of all formulations was within the range 5.2 - 34.2 s (Table 2).

Drug release

Table 3 shows the various the dissolution parameters for the matrix formulations.

The drug release data shows that the values of release rate exponent (n), ranged between 0.4642 and 0.4841 drug released from all the formulations up to 12 h ranged between 83.69 and 88.8 % and it is clear from the results that the release tended to decrease with increase in
the content of either HPMC K4M or CP934P (Table 3).

**DISCUSSION**

Tablets (gel-forming matrices) possessing sufficient structure to form a gel layer and they achieve an overall specific gravity lower than that of gastric fluid. TFT of the tablets increased with increase in HPMC K4M content, owing ostensibly to swelling (i.e., hydration) of the hydrocolloid particles on the tablet surface, resulting ultimately in an increase in the bulk volume. The air formed because of bicarbonate and hydrochloric acid entrapped in the swollen polymer matrix and it results in a density less than unity which ultimately results in imparting buoyancy to the tablets [30]. TFT decreases with an increase in CP934P content because of its higher density (1.76 g/cc) when compared to that of HPMC (1.28 g/cc).

Values of “n” indicate non-Fickian release behaviour for all formulations. The result also shows that with increase in the amount of either polymer the values of k declines. Comparatively much higher magnitude of k1 vis-à-vis k2 clearly shows that the drug release was predominantly Fickian diffusion, with a very little contribution of polymer relaxation. As viscosity of the gel layer around the tablet increased with an increase in the hydrogel concentration, it decreases the release of drug [31,32]. The gel formed during the penetration of dissolution medium into the matrix consisted of closely packed swollen particles, with more polymer amount, more thick gel formed inhibits dissolution medium penetration more strongly, and resulting in a reduction in the drug release values in 12 h indicating slower drug release. Therefore the values of T50 enhanced markedly from 4.09 h, observed at low levels of both the variables, to as high as 4.82 h, observed at high level of both the variables, which shows considerable release retarding potential of the polymer. T50 shows that at high concentration of polymers the drug release slows besides having initial burst effect.

Various mathematical relationships were generated using MLRA for the studied response variables. High values of \( R^2 \) of the MLRA coefficients for all three responses, ranging between 0.9946 and 0.9999, vouch high prognostic ability of the RSM polynomials.

\[
T_{50}=4.44+0.25A+0.085B+0.018A^2B+0.015A^2-0.03B^2+0.003A^3B+0.027A^2B^2 \tag{5}
\]

\[
F_{LT}=17.41-9.80A+3.40B-2.05A^2B-4.02A^2+1.28B^2-0.65A^3B-1.00A^2B^2 \tag{6}
\]

where A and B are independent variables representing the amounts of HPMC K4M and CP934P in the formulation.

Figure 1 portray the 3-dimensional response surface plots for the studied response properties, viz., \( T_{50} \), FLT, and TFT along with the corresponding 2-dimensional contour plots. \( T_{50} \) shows a linear trend in the values of \( T_{50} \) markedly increasing with the increment of HPMC K4M levels while With CP934P, the values of \( T_{50} \) tend to increase almost linearly but to a slower extent where at the higher level of CP934P this linear increase in \( T_{50} \) vanishes. The same is evident from the corresponding contour plot, showing somewhat inclining linear contour lines, while combination of both shows almost synergistic effect on \( T_{50} \) by them. FLT shows a nearly linear ascending pattern for the values of FLT, as the content of HPMC K4M polymer is decreased, the effect being reverse and less prominent with CP934P decrease than with HPMC K4M.

TFT portrays a linear relationship of TFT with increasing amounts of HPMC K4M and CP934P. At low HPMC K4M levels, the value of TFT is less and it increases linearly with an increase in HPMC K4M. On the other hand, the value of TFT at low levels of CP934P is more and with increasing amount of CP934P it decreases; the same is shown by the contour plot for TFT.

The increase in \( T_{50} \) with HPMC K4M was due to its higher hydrophilic ability. Furthermore, the gel layer formed was more viscous resulting to a greater retard in drug release when compared with CP934P.

It was observed that FLT for all tablets was below 35 s regardless of the content of various polymers used, it indicates there is a significant effect of the concentration of polymers (Table 1). Evolution and entrapment of carbon dioxide inside the hydrated polymeric matrices, resulted from the interaction between the gas generating agent (NaHCO3) and dissolution medium (0.1 mol L−1HCl, pH 1.2). This was responsible for the lowering of the density of matrices enabling the tablets to float. From the results of multiple regression analysis, it was found that the dependent variables, \( T_{50} \), FLT and TFT are strongly dependent on the independent variables (Figure 1, Table 4). The correlation coefficients indicate a good fit in the T50%, FLT and TFT linear plots. Polynomial equations (Eq. 5-7) can be used to draw a conclusion after considering...
Figure 1: Response surface and contour plots for various variables and the T50%, FLT and TFT linear plots between observed and predicted values for various variables

The magnitude of the coefficient and the mathematical sign it carries (positive or negative). As the amount of CP934P increased, T50 decreased; this may be due again to high affinity of HPMC K4M and CP934P toward water, which promotes water penetration into tablet matrices, leading to decreased density. As the amount of HPMC K4M increased, TFT increased; this is because of increased gel strength of matrices, which prevents escape of evolved carbon dioxide from matrices, leading to decreased density. As the amount of HPMC K4M and CP934P increased, T50 decreased; this may be due again to high affinity of HPMC K4M and CP934P toward water, which promotes water penetration into tablet matrices, leading to solubilisation of glipizide.

Selection of optimum formulation and DoE validation

For selecting optimum formulation, the responses observed (experimental) were compared with the expected ones (predicted),
Table 4: Checkpoint composition and their results

<table>
<thead>
<tr>
<th>Validation batch</th>
<th>A (mg)</th>
<th>B (mg)</th>
<th>Response variable</th>
<th>Prediction value</th>
<th>Experimental values</th>
<th>Percentage error</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCP1</td>
<td>45.16</td>
<td>8.52</td>
<td>$T_{50}$</td>
<td>4.49</td>
<td>4.46</td>
<td>0.668151</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TFT (h)</td>
<td>13.65</td>
<td>13.45</td>
<td>1.465201</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FLT (s)</td>
<td>14.39</td>
<td>14.3</td>
<td>0.625434</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$T_{50}$</td>
<td>4.51</td>
<td>4.49</td>
<td>0.443459</td>
</tr>
<tr>
<td>VCP2</td>
<td>44.8</td>
<td>9.6</td>
<td>TFT (h)</td>
<td>13.06</td>
<td>13.11</td>
<td>-0.38285</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FLT (s)</td>
<td>14.39</td>
<td>14.3</td>
<td>0.625434</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$T_{50}$</td>
<td>4.56</td>
<td>4.53</td>
<td>0.657895</td>
</tr>
<tr>
<td>VCP3</td>
<td>46.96</td>
<td>9.12</td>
<td>TFT (h)</td>
<td>14.57</td>
<td>14.61</td>
<td>-0.27454</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FLT (s)</td>
<td>15.93</td>
<td>15.98</td>
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</tr>
<tr>
<td></td>
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<td>$T_{50}$</td>
<td>4.51</td>
<td>4.5</td>
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</tr>
<tr>
<td>VCP4</td>
<td>47.32</td>
<td>8.4</td>
<td>TFT (h)</td>
<td>15.04</td>
<td>15.06</td>
<td>-0.13298</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>FLT (s)</td>
<td>11.36</td>
<td>11.41</td>
<td>-0.44014</td>
</tr>
</tbody>
</table>

and a very small percentage error which varied between -0.27 and 1.47 % was found. Linear correlation plots drawn between the predicted and observed responses of validation check points (VCP) and it demonstrated high values of $R^2$ (0.932 to 0.999) (Figure 1, Table 1), indicating excellent goodness of fit ($p < 0.05$). The optimum formulation was selected by trading off various response variables and adopting the following maximizing criteria: $T_{50}>4$ h; TFT>12 h and FLT<15 s. Upon comprehensive evaluation of grid searches, the formulation (HPMC: 47.32 mg and CP934P: 8.4 mg) fulfilled the optimal criteria of best regulation of the release rate $T_{50}=4.5$ h; TFT=15.06 h and FLT=11.41 s, this formulation was taken as optimized formulation.

CONCLUSION

The task of attaining and balancing the required floatation and drug release profile was achieved in the present study using appropriate DoE i.e. CCD with blends of polymers like carborbers and methylcellulloses because of the diverse nature of these polymers. Carborbers, have higher density than the cellulosuses They are also considered unsuitable to impart buoyancy but useful for controlling drug release while lighter hydrophilic methylcellulloses impart floatation and also influence drug release. Hence, the present work can be considered a platform technology in the manufacture of gastroretentive floating formulations of glipizide.

REFERENCES

13. Das NG, Das SK. Controlled-Release of Oral Dosage Forms-Formulation, Fill and Finish (Supplement to Pharmaceutical Technology); 2003. 10-16
ABSTRACT:
Oral bioavailability of some drugs can be limited by the residence time of pharmaceutical formulation in the upper gastrointestinal tract. Gastric emptying plays an important role in the dynamics of drug absorption and can lead to variable and unpredictable bioavailability. And it becomes more critical for drugs which are exclusively absorbed in the upper small intestine or in a limited segment of the intestine “regional absorption”. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used. Approaches for achieving prolonged residence times of the devices in the upper part of the gastrointestinal tract include the use of bio-adhesive, size increasing, and floating drug delivery systems.

KEYWORDS: Gastroretentive, Floating, Regional Absorption, Effervescent

INTRODUCTION:
Oral route of administration is the predominant and most preferable route for drug delivery. Importantly, it allows unassisted administration by the patient without the need for trained personnel (as this is the case with most parenterally administered dosage forms).

As the scientists acquire a better understanding of the physicochemical and biological parameters pertinent to oral drug delivery system performance these are becoming increasingly sophisticated. Despite tremendous advancements in drug delivery, time-controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects); and a reduction of the administration frequency, leading to improved patient compliance.

While, ‘standard’ controlled-release dosage forms offer only limited advantage for drugs that have an absorption window in the upper small intestine e.g. levodopa [Erni W., 1987], furosemide [Ozdemir N., 2000] and riboflavin [Hoffman A., 2004]. In order to increase the bioavailability of this type of drug, the residence time of the controlled-release dosage forms in the upper gastrointestinal tract needs to be prolonged.

Physiology of intestinal tract:
The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the GI tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents (Figure 1). Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH1–3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes: inter-digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The inter-digestive motility pattern is
commonly called as the 'migrating motor complex' (‘MMC’) and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the inter-digestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/ gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the 'housekeeper wave' as the powerful contractions, this phase tend to empty the stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the inter-digestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern and/or by the presence of food. The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal. Generally, a meal of ~450kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to ≤1mm and propel the food through the pylorus. However, it has been shown that ingestible solids ≤7mm can empty from the fed stomach in humans.

**Requirement for gastric retention:**
From the discussion of the physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

**Factors affecting gastric retention:**
Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. (Wilson CG., 1989) The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn’t get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state. The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron’s disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. (Singh BN., 2000) The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.

Based upon physiology and factor effecting gastric emptying various approaches have been followed to encourage gastric retention of an oral dosage form (Figure 2) and the main approaches to prolonging the gastric residence time of pharmaceutical dosage forms include bioadhesive delivery systems, which adhere to mucosal surfaces(Lee JW., 2000; Ch’ng H.S.,1985; Jimenez N R., 1993); devices that rapidly increase in size once they are in the stomach to retard the passage through the pylorus(Klausner E, 2003); and density-controlled delivery systems, which float on gastric fluids (Hwang SJ., 1998; Singh BN., 2000; Machida. Y., 1989; Bardonnet PL., 2006; Streubel A., 2006)
Bioadhesive drug delivery systems:
Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the gastroretention time by increasing the intimacy and duration of contact between the dosage form and the biological membrane. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases; also it helps as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses (Gupta P.K., 1992). The adherence of the delivery system to the gastric wall increases residence time of dosage form at a particular site and improve bioavailability, this binding of polymers to the mucin–epithelial surface can be subdivided into three broad categories: hydration-mediated adhesion, bonding-mediated adhesion, and receptor-mediated adhesion (Park K., 1984).

Hydration-mediated adhesion:
Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

Bonding-mediated adhesion:
The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical–mechanical bonding and chemical bonding. Physical–mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive Vander Waals interactions and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups (Chien Y.W., 1992).

Receptor-mediated adhesion:
Certain polymer binds to specific receptor sites on the surface of cells, and there for enhances the gastric retention of dosage forms. Certain plant lectins like tomato lectins interact specifically with the sugar groups present in mucus or on the glycoalyx. An unresolved issue related to bio/mucoadhesive systems is the attachment site of the system in the gut wall. The systems can attach both to the mucus layer and the epithelial surface of the stomach. In the former case, it is important to realize that the mucus layer in the stomach turns over continuously, and the mucus can be found not only on the surface of the lumen but also within the lumen (called the soluble mucus) (Lehr C.M., 2002). So, it is difficult to understand how mucoadhesive systems identify the designated attachment site.

Bioadhesive polymers are classified on the basis of their charge. A few examples of bioadhesive polymers are listed in Table 1.

<table>
<thead>
<tr>
<th>Cationic</th>
<th>Anionic</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly-L-lysine</td>
<td>CMC</td>
<td>Bovine serum albumin</td>
</tr>
<tr>
<td>Polysine</td>
<td>Dextran sodium</td>
<td>Polyethylene pyrrolidone</td>
</tr>
<tr>
<td>Polyvinyl methyl imidazole</td>
<td>Poly acrylic acid</td>
<td>Dextran</td>
</tr>
<tr>
<td>Poly-L-aspartic acid</td>
<td>Polyvinyl sulfate</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>Heparin</td>
<td>Poly glutamic acid</td>
<td>Chondroitin sulfate</td>
</tr>
</tbody>
</table>

Akiyama et al., (1999), proposed the use of mucoadhesive microspheres consisting of a drug and Carbopol 934P (polyacrylic acid, polymerized in benzene and highly cross-linked with allyl sucrose), dispersed within a waxy matrix of polyglycerol esters of fatty acids. These systems adhered to the stomach mucosa in rats and Mongolian gerbils and thus prolonging the drug’s gastrointestinal residence time after oral administration. The adherence can be attributed to the hydration and swelling of Carbopol in the microspheres upon contact with water. Importantly, parts of the macromolecules remain within the microspheres, whereas the rest is ‘anchored’ within the mucus layer.

The major challenge for bioadhesive drug delivery systems is the high turnover rate of the gastric mucus and the resulting limited retention times. Furthermore, specific targeting of the gastric mucus with bioadhesive polymers is difficult. Bioadhesive polymers (e.g. polycarbophil, Carbopol and chitosan) will stick to various other surfaces that they come into contact with (Khosla R., 1987; Sakkinen M., 2004). In addition, some time possible oesophageal binding of dosage form presents a challenge regarding safety aspects.

Floating drug delivery systems:
Another promising approach for retention is floating drug delivery systems these float immediately upon contact with gastric fluids for increasing the bioavailability of drugs with absorption windows in the upper small intestine. However,
immediate floating can only be achieved if the density of the device is low at the very beginning. Devices with an initially high density (which decreases with time) first settle down in the stomach and, thus, undergo the risk of premature emptying. Inherent low density can also be provided eg. Entrapment of air (e.g. hollow chambers [Krogel I., 1999]) or by the (additional) incorporation of low density materials (e.g. fatty substances or oils [Sriamornsak P., 2005], or foam powder [Streubel A., 2003 and 2002]).

Davis (1968) first described floating systems, these are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at a desired rate (Mitra S.B., 1984), which results in increased gastro-retention and reduction of fluctuation in plasma drug concentration (Fell J.T., 2000). Floating systems are classified as effervescent and non-effervescent systems.

**Effervescent Floating Dosage Forms:**
Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO₂ produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts (Sakr F.M., 1999). This CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a predetermined amount of time to permit the spontaneous ejection of the inflatable system from the stomach (Chawala et al., 2003).

Ichikawa et al (Ichikawa M., 1991) developed a new multiple type of floating dosage system comprised of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO₂ was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0g/mL. The system was having good floating ability independent of pH and viscosity while the drug (para-amino benzoic acid) released in a sustained manner.

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>DOSAGE FORMS</th>
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<td>AZITHROMYCIN</td>
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<td>US PATENT 5783212</td>
</tr>
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<td>US PATENT APPLN. 2006013876</td>
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<td>WO PCT APPLN 0110405</td>
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<td>SR FLOATING CAPSULE FORM</td>
<td>US PATENTAPPLN 2006121106</td>
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<td>HBS OF BILAYER CAPSULE</td>
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Table 3 – Various Patents under Floating Drug Delivery System (Dehgan et al, 2009)

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</tr>
</tbody>
</table>

None-effervescent systems:
Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like poly carbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid and forming into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers, polysaccharides and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the dosage form (Chawala et al., 2003).

The following approaches are being investigated in intragastric floating systems (Bardonnet et al., 2006).

Thanoo et al (Thanoo BC., 1993) developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated bio-fluids. Drug-loaded microspheres were able to float on gastric and intestinal fluids.

Whitehead et al (Whitehead L., 2000) prepared floating alginate beads incorporating amoxycillin. The beads were produced by drop-wise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved.

The major drawback of low-density, floating drug delivery systems is their performance dependency upon the filling state of the stomach. However, this approach can successfully prolong the gastric retention time of drugs [Talukder R., 2004]

Floating delivery systems are being investigated by a number of investigators and various patents had taken on them showing the potential of the delivery system for further development (Table 3).

High-density systems:
The systems, which have a density of ~3 g/cm³, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements (Devereux J.E., 1990). Such systems can be retained in the lower part of the stomach above a threshold density of 2.4–2.8 g/cm³, (Clarke G.M., 1995). Diluents such as barium sulphate (density = 4.9), zinc oxide and iron powder must be used to manufacture such high-density formulations.

The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm³.

Swelling and expending systems:
It is a promising approach for achieving gastro-retention. Here after being swallowed, the dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a
longer duration. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric cavity for several hours even in the fed state. These dosage forms must not swell or expand in the oesophagus or in the intestine if it is emptied prematurely from the stomach. The Gastroretentive dosage form will also need to display controlled release properties. The system should have sufficient rigidity to remain intact in the stomach and to withstand the mechanical forces in stomach. However it should decrease in size after it has performed its function and then transit through the intestine in the normal way. Various systems usually achieve increased size by expansion or swelling or through unfolding.

Expansion or swelling process either involve generation of gas in form of carbon dioxide, or use the properties of compressed porous material like hydrogels. The swelling system composed with super-porous hydrogel have been investigated as Gastroretentive systems by Chen et al. (2000)

Klausner E. A., (2003) an Israeli worker developed an unfolding system comprising an inner polymeric and/or drug matrix layer with two shielding outer layer with a coat of microcrystalline cellulose to prevent adhesion.

The fasted stomach presents a challenge in terms of limited time available for increase in size and for retention to be achieved, while the lightly fed stomach provide sufficient residence time for a suitable size increase.

LIMITATIONS:
OCGRDDS have ultimate potential for improving bioavailability of drugs that exhibit an absorption window, but with certain limitations. One of the major disadvantages in the case of bioadhesive systems, which form electrostatic and hydrogen bonds with the mucus, the acidic environment and the thick mucus prevent bond formation at the mucus–polymer interface. The high turnover rate of mucus may further increase the problem. In case of floating systems high levels of fluids in the stomach is required for the delivery system to float and work efficiently. These systems also require the presence of food to delay their gastric emptying. In addition, there are limitations to the applicability of floating systems for drugs that have solubility or stability problems in the highly acidic gastric environment or that are irritants to the gastric mucosa. For swellable systems, the major limiting factor is that the system must maintain a size larger than the aperture of the resting pylorus for the required time period. Above all, any dosage form designed to stay in the stomach during the fasted state must be capable of resisting the housekeeper waves.

CONCLUSIONS:
A controlled drug delivery system with increased residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine or unstable in other parts of intestine (Table 2).

Adequate control of the gastric residence time combined with time-controlled drug release patterns can significantly increase the bioavailability of the drug and, thus, the efficiency of the treatment. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing these techniques.

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Formulation and Optimization of Gastric Bioadhesive Tablets of Diltiazem Hydrochloride using Central Composite Design

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Abstract

Purpose: To develop bioadhesive tablets of diltiazem hydrochloride with a unique combination of bioadhesion and drug release.

Method: Tablets were prepared by physical blending of diltiazem hydrochloride with two polymers, viz., carbopol and hydroxylpropyl methyl cellulose in different ratio along with other excipients. A 3² central composite design was employed to optimize the formulations on the basis of phynochemical properties, bioadhesive strength (measured as force of detachment from gastric mucosa) and in vitro drug release. HPMC K 4M and Carbopol 934P were taken as the independent variables. Contour plots were drawn and optimum formulations were selected by feasibility and grid searches.

Results: The tablets showed excellent bioadhesive strength which varied from 7.6 to 21 g. Both polymers had effect on the bioadhesive strength of the tablets and maximum bioadhesion was observed at the highest level of both the polymers. The drug release from the formulation varied from 79.74 to 94.54 % in 12 h. The diffusion exponent (n) of Korsmeyer-Peppas model ranged from 0.491 to 0.658 which indicates the mechanism of drug release was anomalous transport; the diffusion exponent (n) increased with increase in the amount of either polymer in the bioadhesive tablet.

Conclusion: Floating bioadhesive tablets of diltiazem hydrochloride with good bioadhesion and controlled release characteristics is feasible.

Keywords: Drug delivery, Gastroretentive, Bioadhesive, Diltiazem, Central composite design.

INTRODUCTION

Diltiazem hydrochloride (DTZ) is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina. It has an elimination half-life of 3.5 h and an absorption zone from the upper intestinal tract. Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone. DTZ requires multiple daily drug dosage in order to maintain adequate plasma concentrations [1]. A suitable drug delivery system can improve controlled delivery of a drug exhibiting an absorption window by continuously releasing the drug for a prolonged period before it reaches the absorption site, thus ensuring its optimal bioavailability [2,3].

Various approaches including floating systems, bioadhesive systems, swelling and expanding
systems and high density systems have been successfully employed to improve the gastric residence time of a delivery system [4,5]. Though highly efficient for gastroretention, floating systems suffer from a major disadvantage that they are effective only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded [6]. This serious limitation can be overcome by making the system eventually adhere to the mucous lining of the stomach wall.

Mucoadhesion has been an extensively adapted approach for achieving site-specific drug delivery through the amalgamation of mucoadhesive polymers within pharmaceutical formulations along with the active pharmaceutical ingredient (API). Mucoadhesive materials are hydrophilic macromolecules containing numerous hydrogen bond forming groups. The mechanism by which mucoadhesion takes place has been said to be in two stages: the contact (wetting) stage followed by the consolidation stage (establishment of adhesive interactions) [7].

The objective of the current study was to develop bioadhesive tablets of diltiazem hydrochloride and optimize their bioadhesive and drug release characteristics using the benefits of central composite design methodology [8].

EXPERIMENTAL

Materials

Diltiazem hydrochloride, Carbopol 934P and HPMC K4M were obtained as gifts from Modi Mudi Pharmaceuticals, Meerut and all other chemicals used were of analytical grade.

Preparation of Bioadhesive Tablets

Different bioadhesive tablet formulations of diltiazem hydrochloride were formulated using varying amount of two polymers (carbopol and HPMC) and Microcrystalline cellulose as diluent, which does not interfere with the floating property of the tablets due to its low bulk density [9] along with fixed quantity of talc and magnesium stearate as glidant and lubricant respectively. All ingredients, except magnesium stearate, were passed through 200 µ aperture sieve and then mixed for 20 min. Finally, Magnesium stearate was added into powder blend as a lubricant and mixed for an additional 3 min before compaction process. Then, 360 mg tablets containing 90 mg diltiazem hydrochloride were prepared by a lab press [8]. The tablet formulations are shown in Table 1.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem Hydrochloride</td>
<td>90 mg</td>
</tr>
<tr>
<td>Carbopol 934P</td>
<td>60-100 mg</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>90-150 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1%</td>
</tr>
<tr>
<td>Talc</td>
<td>3%</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>q.s. to 360 mg</td>
</tr>
</tbody>
</table>

Experimental design

A central composite design (CCD) for two factors at three levels each (α = 1) was selected to optimize the varied response variables. The two factors, viz., polymer X₁ (CP) and polymer X₂ (HPMC) of each polymer bland, were varied as required by the experimental design and the factor level were suitably coded (Table 2). The extent of drug release in 12 h (Q₁₂), time to release 60 % (t₆₀%) and bioadhesive strength (BS) were taken as responsive variables [10].

<table>
<thead>
<tr>
<th>Formulation no.</th>
<th>Trial no.</th>
<th>X₁</th>
<th>X₂</th>
<th>Coded factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F3</td>
<td>3</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>F4</td>
<td>4</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>F5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F6</td>
<td>6</td>
<td>0</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>F7</td>
<td>7</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>F8</td>
<td>8</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F9</td>
<td>9</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
</tbody>
</table>

Translation of coded levels in actual units

<table>
<thead>
<tr>
<th>Coded level</th>
<th>X₁: Carbopol 934P (mg)</th>
<th>X₂: HPMC (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>0</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>+1</td>
<td>100</td>
<td>150</td>
</tr>
</tbody>
</table>

Physical characterization of diltiazem tablets

The formulated tablets were subjected to the following physical characterization studies. The drug content of each batch of the formulated tablets was determined in triplicate by UV–visible method at 237nm. The weight variation was determined based on 20 tablets using electronic balance. Mean tablet hardness was determined on six tablets from each batch using Monsanto tablet hardness tester. Friability was determined (n = 10) using Roche friabilator for 5 min at 25
Measurement of bioadhesive strength of tablets

Gastric mucosa of goat was used as the model membrane for ex vivo measurement of bioadhesive strength. The mucosal membrane was excised by removing the underlying connective tissues. The mucosa was tied on the slide and the slide was fixed in the petri plate filled with distilled water and the petri plate was placed inside the left arm of the physical balance. The tablet was fixed on the left pan of the physical balance. The left arm was lowered until a tablet contact with the membrane was made. A contact force of 10 g was placed on the left arm for 5 min. After 5 min, the weight was removed from the left pan and the assembly was kept undisturbed. Weight was slowly added on the right hand side pan until the tablet just got detached from the membrane surface. The peak detachment force was recorded as a measure of bioadhesive strength [11].

Swelling index

Tablets were weighed (W₁) individually and placed in a USP XXII paddle method (apparatus 2) (model DS 8000, Lab India) containing 900 ml 0.1N HCl, stirred at 50 rpm and maintained at 37 ± 0.5 °C. At regular intervals, the tablets were removed from the dissolution apparatus, excess water removed carefully using filter paper and reweighed (W₂). Swelling index (S) of each tablet was calculated by using following formula [12]:

\[ S = (W_2 - W_1)/W_1 \]  

In vitro drug release studies

Dissolution studies were carried out on all the tablet formulations in triplicate, employing USP XXII paddle method (Apparatus 2) at 50 rpm and 37 ± 0.5 °C, using 900 ml simulated gastric fluid (SGF) pH 1.2 without pepsin as the dissolution medium. Five ml of sample was withdrawn periodically at suitable time intervals and replaced with an equivalent volume of fresh dissolution medium. The withdrawn samples were analyzed by UV Spectrophotometer (UV 1800 Shimadzu) at 237 nm. Drug release data obtained were analyzed using Zorel software [13] which has in-built provisions for applying the correction factor for volume and drug losses during sampling [14].

The drug release data were fitted to Korsemeyer-Peppas model (Eq 2) [15].

\[ \frac{M_t}{M_{\infty}} = k_1 t^n + k_2 t^{2n} \]  

where, \( M_t \) is amount of drug released at time ‘t’, \( M_{\infty} \) is amount of drug released at an infinite time, \( k_1 \) is the magnitudinal contribution of diffusion mechanism, \( k_2 \) is the magnitudinal contribution of polymer relaxation mechanism, and \( n \) is the Fickian diffusion coefficient.

Based on phenomenological analysis, the type of release (i.e., whether Fickian, non-Fickian (anomalous) or zero order) was predicted [11]. \( t_{60\%} \) value was calculated using Stineman interpolation option of the Graph 2.0 software (M/s Micromath Inc, St Louis, USA).

Optimization data analysis and validation of optimization model

The response variables which were considered for systematic optimization included \( t_{60\%} \), \( Q_{12} \) and BS. For the studied design, multiple linear regression analysis (MLRA) method was applied to fit full second-order polynomial equation with added interaction terms to correlate the studied responses with the examined variables using Design expert software version 8.0.5 (Stat-Ease, USA 45days trial version). The polynomial regression results were demonstrated for the studied responses. Finally, the prognosis of optimum formulation was conducted using a two-stage brute force technique using MS-Excel spreadsheet software. First, a feasible space was located and second, an exhaustive grid search was conducted to predict the possible solutions. Six formulations were selected as the confirmatory check-points to validate RSM. The observed and predicted responses were critically compared. Linear correlation plots were constructed for the chosen eight optimized formulations. The residual graphs between predicted and observed responses were also constructed separately, and the percent bias (= prediction error) was calculated with respect to the observed responses [11].

RESULTS

Physicochemical characteristics of the tablets

Physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all formulations were satisfactory, as shown in Tables 3. It was observed that all the tablets showed acceptable physicochemical properties.

Sharma et al
Table 3: Some physicochemical properties of the bioadhesive tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Mean hardness (kg)</th>
<th>Mean weight (mg)</th>
<th>Mean friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.5 ± 0.051</td>
<td>360.4 ± 1.26</td>
<td>0.65</td>
<td>98.53</td>
</tr>
<tr>
<td>F2</td>
<td>4.5 ± 0.054</td>
<td>361.5 ± 1.69</td>
<td>0.68</td>
<td>98.38</td>
</tr>
<tr>
<td>F3</td>
<td>4.6 ± 0.083</td>
<td>361.0 ± 1.07</td>
<td>0.64</td>
<td>98.46</td>
</tr>
<tr>
<td>F4</td>
<td>4.4 ± 0.054</td>
<td>359.5 ± 1.70</td>
<td>0.56</td>
<td>99.42</td>
</tr>
<tr>
<td>F5</td>
<td>4.6 ± 0.10</td>
<td>360.5 ± 0.99</td>
<td>0.58</td>
<td>99.78</td>
</tr>
<tr>
<td>F6</td>
<td>4.5 ± 0.12</td>
<td>360.0 ± 1.15</td>
<td>0.68</td>
<td>97.32</td>
</tr>
<tr>
<td>F7</td>
<td>4.6 ± 0.10</td>
<td>359.5 ± 1.13</td>
<td>0.69</td>
<td>100.52</td>
</tr>
<tr>
<td>F8</td>
<td>4.8 ± 0.081</td>
<td>360.8 ± 1.10</td>
<td>0.45</td>
<td>99.02</td>
</tr>
<tr>
<td>F9</td>
<td>4.7 ± 0.136</td>
<td>359.5 ± 1.35</td>
<td>0.46</td>
<td>101.56</td>
</tr>
</tbody>
</table>

Table 4: Dissolution parameter for different bioadhesive tablets formulations

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>N</th>
<th>K</th>
<th>k₁</th>
<th>k₂</th>
<th>Rel12 hrs (%)</th>
<th>t₆₀%</th>
<th>Drug rel rate (mg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.4911</td>
<td>0.2590</td>
<td>1.2895</td>
<td>0.0132</td>
<td>94.54</td>
<td>4.95</td>
<td>8.298</td>
</tr>
<tr>
<td>F2</td>
<td>0.5049</td>
<td>0.2539</td>
<td>1.2863</td>
<td>0.0147</td>
<td>91.04</td>
<td>4.66</td>
<td>8.047</td>
</tr>
<tr>
<td>F3</td>
<td>0.5153</td>
<td>0.2452</td>
<td>1.2715</td>
<td>0.0177</td>
<td>90.79</td>
<td>4.75</td>
<td>7.875</td>
</tr>
<tr>
<td>F4</td>
<td>0.5154</td>
<td>0.2397</td>
<td>1.2629</td>
<td>0.0178</td>
<td>87.60</td>
<td>5.19</td>
<td>7.64</td>
</tr>
<tr>
<td>F5</td>
<td>0.5409</td>
<td>0.2198</td>
<td>1.2310</td>
<td>0.0240</td>
<td>86.25</td>
<td>5.16</td>
<td>7.39</td>
</tr>
<tr>
<td>F6</td>
<td>0.5884</td>
<td>0.1876</td>
<td>1.1788</td>
<td>0.0351</td>
<td>84.86</td>
<td>5.81</td>
<td>6.88</td>
</tr>
<tr>
<td>F7</td>
<td>0.6189</td>
<td>0.1621</td>
<td>1.1346</td>
<td>0.0426</td>
<td>84.56</td>
<td>7.14</td>
<td>6.39</td>
</tr>
<tr>
<td>F8</td>
<td>0.6333</td>
<td>0.1519</td>
<td>1.1195</td>
<td>0.0445</td>
<td>82.39</td>
<td>7.66</td>
<td>6.17</td>
</tr>
<tr>
<td>F9</td>
<td>0.6585</td>
<td>0.1417</td>
<td>1.1041</td>
<td>0.0489</td>
<td>79.74</td>
<td>7.78</td>
<td>6.04</td>
</tr>
</tbody>
</table>

Bioadhesive strength of tablets

The bioadhesive strength of the tablets ranged between 7.6 to 21 g, and increased with increase in the concentration of the polymer in the tablet; However, this effect was more pronounced for Carbopol.

**Fig 1:** Bioadhesive strength of the formulations. *Note:* F1 – F9 are as defined in Table 1.

In vitro drug release

Table 4 enlists various dissolution parameters calculated for all the bioadhesive tablets. The value of diffusion exponent (n) showed an increasing trend with increase in the content of either polymer. The values of Fickian diffusion constant (k₁) varied between 1.104 and 1.289, while those of polymer relaxation constant (k₂) varied between 0.0132 and 0.0489. The values of Q₁₂h ranged between 79.74 and 94.54%. An almost linear descending trend was observed in Q₁₂h with an increase in CP 934P or HPMC fraction.

Response surface analysis

The coefficient of the polynomial equation (Eq 2) generated using MLRA for Q₁₂h, t₆₀%, and BS of the tablet, formed excellent fits to the data, with quite high value of r² ranging between 0.9898 and 0.999.

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2 \]  

(3)

Seven coefficients (β₁ to β₇) were calculated representing β₀ as intercept, and β₃ to β₇ various quadratic and interaction terms.

Figs 2 to 4 show the various three dimensional response surface plots for the studied response properties, viz, t₆₀%, Q₁₂, and BS. Fig 2 showed a linear increasing trends in the value of t₆₀% with increase in the amount of either polymer but the
influence of CP was more significant than HPMC, indicating that the former has better release controlling properties than the latter. Hence, the higher levels of CP have to be complemented with lower levels of HPMC and vice-versa to maintain the value of $t_{60\%}$ at a constant level.

Fig 2: Response surface plot showing the influence of CP and HPMC on the value of $t_{60\%}$ of bioadhesive tablets of diltiazem hydrochloride.

Fig 3 shows a decline in the value of $Q_{12}$ with an increase in the concentration of each polymer. Nonlinear descending lines elucidate that the variation in $Q_{12}$ is a function of polymer levels, the effect of HPMC being less significant.

Fig 3: Response surface plot showing the influence of CP and HPMC on the value of $Q_{12}$ of bioadhesive tablets.

Fig 4: Response surface plot showing the influence of CP and HPMC on the value of bioadhesive strength of bioadhesive tablets of diltiazem hydrochloride.

Fig. 4 shows nearly linear ascending pattern for the values of bioadhesive strength as the content of either polymer increased in the formulation and the effect of CP is more prominent than HPMC. The maximum bioadhesive strength was observed at the highest levels of both the polymers. The results are in consonance with literature reports stating high contribution of carbomers in attainment of bioadhesive strength in hydrophilic matrices [10].

Selection of optimized formulation

The optimum formulation was selected by trading off various response variables and adopting the following maximizing criteria: $t_{60\%} > 5.0$ h, $Q_{12} > 88\%$, BS > 12. Upon comprehensive evaluation of grid searches, the formulation (CP 84 mg, HPMC 90 mg) fulfilled the optimal criteria of best regulation of the release rate and bioadhesive characteristics with $t_{60\%}$ of 5.33 h, $Q_{12}$ of 90.95 % and bioadhesive strength of 12.79 g. Thus, besides controlling drug release, the formulation has definite gastroretentive potential to retain the drug in the gastric environment and upper part of intestine.

Validation of response surface methodology results

Linear correlation plots drawn between predicted and observed responses, also demonstrated the high value of $r$, in the range of 0.991 - 0.987 indicating excellent fit. Upon comparison of the observed responses with those of anticipated ones, the prediction error varied between -4.4 and 3.64.

DISCUSSION

The present investigation describes the development of an optimized gastric bioadhesive tablet formulation of diltiazem hydrochloride. A combination of ionic polymer (such as CP) and nonionic polymer (such as HPMC) were chosen because they are known to provide a formulation with controlled drug release and/or desired mucoadhesive properties [17].

Bioadhesive strength increased with increase in the content of either polymer, an observation that has previously been made [16]. Hydrogels are known to swell readily on contact with the hydrated mucous membrane [17]. Water sorption reduces glass transition temperature below ambient conditions, and hydrogels become progressively rubbery due to uncoiling of polymer chains and subsequent increased mobility of the polymer chains. The glass-rubber transition provides hydrogel
plasticization, resulting in a large adhesive surface for maximum contact with mucin and flexibility to the polymer chain for interpenetration with mucin. Increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting in augmentation of bioadhesive strength. Although the maximum value of bioadhesive strength was attained at higher levels of both polymers and the effect carbopol on the bioadhesion was distinctly more pronounced than that of HPMC. The swelling of the formulation increased as the amount of either polymer increase in the tablet but the effect of HPMC on the swelling was more pronounced than that of carbopol due to the hydrophilic nature of the former.

The bioadhesive tablets showed values of $n$ ranging between 0.4911 and 0.6585, indicating the non-Fickian release behaviour of all formulations. The values of $n$ showed increasing trend with increase in HPMC content, even at higher levels of Carbopol. On the other hand, the kinetic constant, $k$, showed a decline with increase in the content of either polymer. Relatively much higher magnitude of Fickian diffusion constant, $k_1$, vis-à-vis the polymer relaxation constant, $k_2$ clearly showed that drug release was predominantly determined by Fickian diffusion, with a negligible contribution of polymer relaxation. This is in agreement with earlier findings that a mixture of HPMC and Carbopol resulted in the reduction of polymer viscosity due to reduced hydration [11,18].

This reduction of viscosity could facilitate drug diffusion through polymer hydrogel. The overall rate of drug release tended to decrease with increase in the concentration of either HPMC or carbopol. Similarly, the values of $Q_{12h}$ decreased with increase in polymer content. However, the values of $t_{100%}$ increased from 4.95 to 7.78 h for both polymers.

In Central Composite Design (CCD), all the factors are studied for all plausible combinations, as it is considered to be most efficient in estimating the influence of individual variables and their interactions, using minimum experimentation. Hence, CCD for two factors at three levels with $a = 1$ was chosen. The high values of $r^2$ exhibited by the polynomial relationships vouch high statistical validity ($p < 0.001$) of Equation 2 for fitting to the experimental data. The amounts of CP and HPMC had a positive influence on the values of coefficients of $t_{100%}$, the effect being more apparent with HPMC. On the other hand, the positive effect of CP is vividly far more pronounced than that of HPMC in regulating the values of BS.

**CONCLUSION**

Suitable balancing between the levels of the two polymers (CP and HPMC) is imperative to attaining maximum prolongation of drug release and adequate bioadhesive strength. The bioadhesive nature of the formulation may prolong gastrointestinal (GI) residence time thus ensuring maximum absorption. The optimized formulation showed good controlled release and bioadhesive characteristics indicating the success of experimental approach employeed.

**REFERENCES**


