Formulation and Characterization of Floating Tablets of Diltiazem Hydrochloride

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Abstract

The purpose of the present study was to develop an optimized floating drug delivery system of Diltiazem hydrochloride. Diltiazem floating tablets were formulated with different concentrations of two grades of HPMC polymers (HPMC K4M and HPMC K100M) by using wet granulation technique and evaluated for the different evaluation parameters such as thickness, diameter, drug content uniformity, friability, floating lag time, *in-vitro* buoyancy, *in-vitro* drug release studies and stability studies were performed. All the evaluation parameters results were significant. *In-vitro* drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both Higuchi and Korsemeyer and Peppa’s equation. The drug release mechanism was found fickian type in most of the formulations. The prepared formulation shows better and significant results for all the evaluated parameters. The formulation A4 containing (HPMC K4 M) shows maximum percentage of drug release (99.87 %) and prolonged release for time period of about 12 h, thereby improves the bioavailability and patient compliance.

**Keywords:** Floating drug delivery system, Diltiazem HCl, Buoyancy period, Higuchi plots, Accelerated stability studies.
Introduction

Various approaches have been worked out to improve the retention of an oral dosage form in the stomach e.g. floating system, swelling and expanding system, bioadhesive system, modified shape system, high-density system and other delayed gastric emptying devices\(^1\). Floating drug delivery systems (FDDS) or hydrodynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach without affecting the gastric emptying rate for a prolonged period. These systems are useful for drugs acting locally in the gastrointestinal tract, drugs which are poorly soluble and unstable in intestinal fluid. While the system is floating on gastric contents, the drug is slowly released at a desired rate from the floating system and after the complete release; the residual system is expelled from the stomach. This leads to an increase in the gastric residence time and better control over fluctuations in plasma drug concentrations\(^2\).

Gastric retention drug delivery systems can be retained in the stomach for a long time. Such retention systems are important for drugs that are degraded in intestine or for drugs like antacids or certain antibiotics and enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine its retention in gastric region may increase the solubility before they are emptied, resulting in increased bioavailability. Such systems are more advantageous in improving GI absorption of drugs with narrow absorption windows as well as for controlling release of the drugs having site-specific absorption limitation. Retention of drug delivery systems in the stomach prolong overall GI transit time, thereby resulting in improved bioavailability for some drugs\(^3\).

The rate of gastric emptying depends mainly on viscosity, volume and caloric content of meals. Nutritive density of meal helps to determine the rate of gastric emptying, increase in acidity and caloric values slows down the gastric emptying rate. Biological factors such as
age, body mass index, gender, posture and diseased states influence gastric emptying. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. Gastric emptying of dosage form is different in fasted and fed condition. Volume of liquids affects the gastric emptying i.e. larger the volumes faster the emptying. Fluids taken at body temperature leave the stomach more quickly than either colder or warmer fluids. The gastric residence time may increase by the ingestion of a meal prior to administration of liquids. Park et al have reported the residence time for both liquid and solid foods in each segment of the GIT.

Diltiazem hydrochloride is one of the new generation calcium channel blocker with peripheral and coronary vasodilator properties, which is used in the management of classical, Vasospastic angina pectoris and also in the treatment of essential hypertension. The plasma half life of the Diltiazem HCl is 3 - 4 hrs. The success of a therapy depends on selection of the appropriate delivery system as much as it depends on the drug itself. Sustained released dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Diltiazem is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration, but undergoes extensive first pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations. Diltiazem is around 50% bound to plasma protein. It is extensively metabolized in the liver, one of the metabolites desacetyldiltiazem has been reported to have 25 to 50% of the activity of the parent compound. The plasma half-life is 3-4 hours. Approximately 60% of the dose is excreted in the bile and 35-40% in the urine, 2-4% as unchanged diltiazem.

**Materials and Methods:**

Diltiazem HCl was obtained as a gift sample from the Cipla Ltd. Goa, India. Hydroxy Propyl Methyl cellulose (HPMC K4M and HPMCK100M) was obtained from the Zydus-Cadila
HealthCare Ltd. Ahmedabad, India. Sodiumcarboxy methyl cellulose was obtained as a gift sample from the BPRL, Bangalore, India. Another excepients and chemicals were purchased from the DrugsIndia, Hyderabad. All the ingredients used were analytical grade only.

**Preformulation Studies**

Identification of the pure drug and polymer were performed usinginfrared spectroscopy. IR spectroscopy (using Perkin Elmer) by KBr pelletmethod was carried out on drug and polymer. They are compressed under 10 tones pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000 to 400 cm-1 in a spectrophotometer and peaks obtained were identified.

**Drug Excipient Compatibility Studies**

About 90 mg of diltiazem hydrochloride with various excipients in 1:1 ratio in glass vials were taken and kept at various accelerated condition (300°C/65%RH, 400°C/75%RH and 600°C/80%RH) in stability chamber (Osworld Stability Chamber, India) for one month in open and closed condition. The sample were withdrawn on 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 14th, 21st and 30th day and physical characteristics like colour change, if any was recorded. Finally the mixtures with no colour change were selected for formulation.

**Formulation of Floating Tablets**

The composition of different formulations DiltiazemHCl tablets is shown in Table-01. The floating tablets of DiltiazemHCl were prepared using low density polymers like HPMC K4M and HPMC K100M (individual and combination) by using the wet granulation technique. Accurately weighed quantities of hydroxyl propyl methyl cellulose, lactose, sodium bicarbonate and the active ingredient were mixed homogeneously. Alcoholic solution of HPMC (1%W/V) was used as a granulating agent. The granules were dried in a conventional hot air oven. The dried granules were sieved through the sieve No: 40/60. The prepared granules were evaluated for the different flow properties parameters. The prepared floating
granules were mixed with the Magnesiumstearate as a lubricant and the granules were compressed into tablets using Pilot Press TM 9 station Model No IPM Rotary tablet punching machine.  

**Flow Properties of Floating Granules**

**Angle of repose**

The frictional forces in loose granules can be measured by the angle of repose ($q$). The angle of repose of the prepared granules was evaluated by using the fixed funnel method. Specified quantity of the granules were taken and poured into the funnel, so automatically form the heap. So this formed heap diameter and height were measured. Then calculate the angle of repose by using below mentioned formula:

$$q = Tan^{-1} \left( \frac{h}{r} \right)$$

**Determination of Bulk density and tap density**

Apparent bulk density ($rb$) was determined by pouring the granules into a graduated cylinder. The bulk volume ($Vb$) and weight of the powder ($M$) was determined. The bulk density was calculated using the formula:

$$rb = \frac{M}{Vb}$$

The measuring cylinder containing a known mass of granules was tapped for a fixed time. The minimum volume ($Vt$) occupied in the cylinder and the weight ($M$) of the granules was measured. The tapped density ($rt$) was calculated using the following formula

$$rt = \frac{M}{Vt}$$

**Compressibility Index**

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index ($I$), which is calculated as

$$I = (rt - ro/rt) \times 100$$
The value below 15% indicates a powder which usually give rise to good flow characteristics whereas above 25% indicate poor flow ability.

**Hausner ratio** is an indirect index of ease of powder flow. It is calculated by the following formula

\[
\text{Hausner ratio} = \frac{rt}{rd}
\]

Where, \(rt\) = tapped density and \(rd\) = bulk density

**In Vitro Buoyancy Study**

The time, tablets took to emerge on the water surface (floating lag time) and the time, tablets constantly float on the water surface (duration of floating) were evaluated. The buoyancy of the tablets was studied in USP 24 type II dissolution apparatus at 37±0.5°C with paddle rotation at 100 rpm in 900 ml of simulated gastric fluid at pH 1.2. The measurements were carried out for each formulation of tablets. The time of duration of floatation was observed visually.

**Evaluation of Floating Tablets**

**Thickness and Diameter**

The thickness and diameter of the tablets was carried out using vernier caliper. Five tablets were selected from each batch and results were expressed in millimeter.

**Weight variation test**

Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. Specifications. As per IP not more than two of individual weights should deviate from average weight by more than 5% and none deviate more than twice that percentage.
Hardness test

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsanto hardness tester was used for the measurement of hardness of the prepared floating tablets. Five tablets were selected from each batch and results were expressed in Kg/cm².

Friability test

It was done in Roche friabilator apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Preweighed samples of 20 tablets were placed in the friabilator, which was operated for 100 revolutions. The tablets were reweighed. Conventional compressed tablets, loss less than 0.5 to 1.0% of their weight are generally considered acceptable.

\[
\text{Friability} = \frac{\text{Weight loss}}{\text{Weight of tablets before operations}} \times 100
\]

Drug content uniformity

Ten tablets were weighed, taken in a mortar and crushed to powder form. The powder weighed equivalent to 100 mg of diltiazem HCL was taken in a 100 ml volumetric flask and dissolve with 0.1 N HCl. It was then heated at 600°C for 30 minutes. The solution was filtered using membrane filter (0.45 nm) and then its absorbance was measured at 238 nm. The amount of drug was calculated using standard graph.

Study of release profile

The release of Diltiazem hydrochloride from floating tablets was determined by using Dissolution Tester USP XXII. The dissolution test was performed using 900 ml 0.1 N HCl.
solution at 37 ± 0.5°C and the paddles were rotated at 50 rpm. At every 1 hour interval, samples were withdrawn from the dissolution medium and it was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to suitable concentrations with 0.1 N HCl solutions. The absorbances of the solutions were measured at 238 nm for diltiazem hydrochloride with a Shimadzu UV-Visible double beam spectrophotometer (Shimadzu, Japan). Cumulative percentagedrug release was calculated using an equation obtained from standard curve.

**Kinetic Modeling of Drug Release**

The dissolution profile of all the batches was fitted to zero order, first order, Higuchi, Korsmeyer and Peppas, equations to ascertain the kinetic modeling of drug release.

**Stability Studies**

Stability studies were carried out for optimized formulations. The tablets were packed in aluminum foil placed in airtight container and kept at 40°C in refrigerator, 40°C/75% RH in stability chamber (Oswald, Mumbai) and 60°C in incubator for 1 month. At the interval of 15 days, the tablets were withdrawn and evaluated for physical properties, *In-vitro* drug release.12

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**Table-1: Composition of the ingredients in the different batches of the Diltiazem HCl floating tablets**
S No | Ingredients | Quantity of ingredient for particular Batch |
--- | --- | ---
1 | Diltiazem Hydrochloride | 90 90 90 90 90 90 90 90 |
2 | HPMC K 100M | 75 120 150 - - - 60 60 |
3 | HPMC K 4M | - - 75 125 150 70 100 |
4 | Sodium Bicarbonate | 20 20 20 20 20 20 20 20 |
6 | Lactose | 87 42 - - 12 87 42 12 32 12 |
7 | Magnesium Stearate | 3 3 3 3 3 3 3 3 |

Table-2: Physical Characteristics of Granules

<table>
<thead>
<tr>
<th>S Batch No</th>
<th>Angle of Repose (°)</th>
<th>Bulk density (g/ml)</th>
<th>Tap density (g/ml)</th>
<th>Carr’s Hausner index</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A1</td>
<td>21.3±0.03</td>
<td>0.56±0.01</td>
<td>0.65 ± 0.01</td>
<td>13.8 ±0.03</td>
</tr>
<tr>
<td>2</td>
<td>A2</td>
<td>24.4±0.02</td>
<td>0.57±0.03</td>
<td>0.67±0.04</td>
<td>14.9±0.02</td>
</tr>
<tr>
<td>3</td>
<td>A3</td>
<td>25.3±0.04</td>
<td>0.64±0.02</td>
<td>0.74±0.031</td>
<td>13.5±0.01</td>
</tr>
<tr>
<td>4</td>
<td>A4</td>
<td>21.3±0.03</td>
<td>0.60±0.02</td>
<td>0.67±0.120</td>
<td>10.5±0.210</td>
</tr>
<tr>
<td>5</td>
<td>A5</td>
<td>23.1±0.90</td>
<td>0.62±0.030</td>
<td>0.69±0.022</td>
<td>10.1±0.003</td>
</tr>
<tr>
<td>6</td>
<td>A6</td>
<td>22.5±0.910</td>
<td>0.64±0.281</td>
<td>0.74±0.208</td>
<td>13.5±0.02</td>
</tr>
<tr>
<td>7</td>
<td>A7</td>
<td>26.2±0.04</td>
<td>0.53±0.027</td>
<td>0.62±0.003</td>
<td>14.5±0.2311.16</td>
</tr>
<tr>
<td>8</td>
<td>A8</td>
<td>20.7±0.05</td>
<td>0.49±0.040</td>
<td>0.56±0.02</td>
<td>12.5±0.004</td>
</tr>
</tbody>
</table>

Table-3: Physicochemical evaluation of Prepared tablet formulations
<table>
<thead>
<tr>
<th>S.No</th>
<th>Batch code</th>
<th>Buoyancy lag time (sec)</th>
<th>Duration of Buoyancy (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A 1</td>
<td>&gt;60</td>
<td>&gt;12</td>
</tr>
<tr>
<td>2</td>
<td>A 2</td>
<td>&gt;40</td>
<td>&gt;12</td>
</tr>
<tr>
<td>3</td>
<td>A 3</td>
<td>70</td>
<td>&gt;12</td>
</tr>
<tr>
<td>4</td>
<td>A 4</td>
<td>80</td>
<td>&gt;12</td>
</tr>
<tr>
<td>5</td>
<td>A 5</td>
<td>60</td>
<td>&gt;12</td>
</tr>
<tr>
<td>6</td>
<td>A 6</td>
<td>90</td>
<td>&gt;12</td>
</tr>
<tr>
<td>7</td>
<td>A 7</td>
<td>120</td>
<td>&gt;12</td>
</tr>
<tr>
<td>8</td>
<td>A 8</td>
<td>120</td>
<td>&gt;12</td>
</tr>
</tbody>
</table>

**Table-4: Floating properties of tablets formulations**

<table>
<thead>
<tr>
<th>No. Code</th>
<th>mm</th>
<th>mm Variation (%) (Kg/cm²) Uniformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>±S.D</td>
<td>±S.D (mg) (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>A 1</td>
<td>4.98 ±0.01 7.98 ±0.02 300.1 ±0.02 0.9 ±0.024 4.10 ±0.01 99.48 ± 0.02</td>
</tr>
<tr>
<td>2</td>
<td>A 2</td>
<td>4.97 ± 0.05 7.97 ± 0.01 299.7±0.03 0.8 ±0.01 4.22 ± 0.02 98.88 ± 0.04</td>
</tr>
<tr>
<td>3</td>
<td>A 3</td>
<td>4.98 ± 0.03 7.98 ±0.02 299.8±0.03 0.8 ±0.03 4.41 ± 0.03 99.89 ± 0.03</td>
</tr>
<tr>
<td>4</td>
<td>A 4</td>
<td>4.14 ± 0.01 8.01 ±0.02 299.9 ±0.01 0.8 ±0.03 4.41 ± 0.03 99.89 ± 0.03</td>
</tr>
<tr>
<td>5</td>
<td>A 5</td>
<td>5.01 ±0.04 7.99 ± 0.01 299.7 ± 0.18 0.7 ±0.03 5.02 ± 0.02 99.69 ± 0.14</td>
</tr>
<tr>
<td>6</td>
<td>A 6</td>
<td>5.01 ±0.04 7.99 ± 0.01 299.7 ± 0.18 0.7 ±0.03 5.02 ± 0.02 99.69 ± 0.14</td>
</tr>
<tr>
<td>7</td>
<td>A 7</td>
<td>4.99 ± 0.03 8.02 ±0.02 299.8 ±0.19 0.7 ±0.03 4.36 ± 0.03 97.95 ± 0.17</td>
</tr>
<tr>
<td>8</td>
<td>A 8</td>
<td>4.97 ± 0.03 7.97 ±0.03 299.8 ±0.02 0.8 ± 0.03 4.41 ± 0.01 98.88 ± 0.03</td>
</tr>
</tbody>
</table>

**Table-5: Drug release kinetics of prepared formulations of DiltiazemHCl**
<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Regression for zero order plot</th>
<th>Regression for first order plot</th>
<th>Regression for Higuchi’s plot</th>
<th>Slope for Peppa’s plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>0.983</td>
<td>0.963</td>
<td>0.994</td>
<td>0.981</td>
</tr>
<tr>
<td>A2</td>
<td>0.992</td>
<td>0.948</td>
<td>0.988</td>
<td>0.994</td>
</tr>
<tr>
<td>A3</td>
<td>0.995</td>
<td>0.939</td>
<td>0.977</td>
<td>0.985</td>
</tr>
<tr>
<td>A4</td>
<td>0.996</td>
<td>0.663</td>
<td>0.981</td>
<td>0.997</td>
</tr>
<tr>
<td>A5</td>
<td>0.997</td>
<td>0.637</td>
<td>0.973</td>
<td>0.995</td>
</tr>
<tr>
<td>A6</td>
<td>0.990</td>
<td>0.677</td>
<td>0.971</td>
<td>0.992</td>
</tr>
<tr>
<td>A7</td>
<td>0.990</td>
<td>0.970</td>
<td>0.991</td>
<td>0.998</td>
</tr>
<tr>
<td>A8</td>
<td>0.986</td>
<td>0.986</td>
<td>0.990</td>
<td>0.996</td>
</tr>
</tbody>
</table>

FIG-1 COMPARITIVE IN VITRO RELEASE PROFILE OF FORMULATIONS A1 TO A 4
Results and Discussion
The present study was planned to prepare and characterize floating tablets of DiltiazemHCl using different polymers by wet granulation technique. Different grades of HPMC (K4M and K100M) and SCMC were used as swellable polymers. HPMC was chosen because it is widely used as a low-density hydrocolloid system upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH. SCMC was used in combination with HPMC to retard the drug release; because of its low solubility at pH 1.2 to 3. No drug polymer incompatibility was noted in their FTIR spectral studies.

The granules prepared for compression of floating tablet were evaluated for their flow properties (Table-02). Angle of repose was in the range of 20.7 ± 0.05 to 26.20 ± 0.04. Bulk density ranged between 0.49 ± 0.04 to 0.64 ± 0.28gm/cm³. Tapped density ranged between 0.56 ± 0.02 to 0.74 ± 0.208. Carr’s Index was found to be 10.10 ± 0.003 to 14.9 ± 0.02 and Hausner ratio ranged from 1.1 ± 0.03 to 1.17 ± 0.21. These values indicate that the prepared granules exhibited good flow properties.

On immersion in 0.1 N HCl, pH 1.2 solution at 37 ± 0.5 °C all floating effervescent tablets floats immediately and remain buoyant up to 24 h without disintegration. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (HPMC K 100 M), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during in vitro buoyancy studies.

The thickness and diameter of the tablets were found in the range of 4.14 ± 0.01 to 5.01 ± 0.04 and from 7.97 ± 0.01 to 8.02 ± 0.02 respectively. The weight of the tablet varies between 299.7 ± 0.18 mg to 300.3 ± 0.02 with low standard deviation which indicating the uniformity of weight. The variation in weight was within the range of ± 5% complying with
pharmacopoeial specifications. The hardness for different formulation was found to be between $4.10 \pm 0.01$ to $5.02 \pm 0.02$ kg/cm$^2$ indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content uniformity varied between $97.95 \pm 0.17$ to $99.89 \pm 0.03$. The results show that all the parameters are within limits and are shown in Table-03. All the batches of tablets were found to exhibit short floating lagtimes and float for longer duration of time due to the presence of sodium bicarbonate and HPMC which is shown in Table-04 and in Fig-04.

The data obtained from in vitro dissolution studies were fitted indifferent models viz. zero order, Higuchi and KorsemeyerPeppa’s equation (shown in Table-05). The zero order plots were found to be fairly linear as indicated by their high regression values ($r^2 = 0.983$ to 0.997). To confirm the exact mechanism of drug release from these tablets, the data were fitted to Higuchi and KorsemeyerPeppa’s equation. The formulation A 4 with HPMCK 4 M (25%) shows maximum release of 99.87% at a time period of 12 hours in a controlled manner. The in-vitro release plot has shown drug release followed by zero order kinetics, which was evinced from the regression value. From the regression and slope value of Higuchi’s (0.981) and Peppa’s ($n = 0.997$) plot respectively, the drug release was confirmed to followed by diffusion mediated non-Fickian transport mechanism. The in-vitro drug release results for all the prepared formulations were shown in Fig-01 and 02.

In order to justify the suitability of the in-vitro kinetic pattern, to maintain constant plasma concentration of the drug molecules, the formulation must be clinically evaluated. Since the clinical studies are difficult to perform, in our study the formulation A 4 (25% HPMCK4M) was compared with a marketed available formulation. The comparative In-vitro release studies for prepared formulation A 4 and marketed SR tablet is shown in Fig-03.
The optimized A 4 formulation was subjected to stability studies for 1 month. At the interval of 15 days the tablets were withdrawn and evaluated for hardness, thickness, weight variation, friability. All the parameters have not shown much variation when compared to the initial data. The in-vitro dissolution was carried out for specified time intervals. Based on the results, we observed that, drug release profiles were not affected by exposing to temperature and the specified humidity conditions.

**Conclusion**

The approach of the present study was to develop floating tablets of Diltiazem HCl and henceforth evaluate the release profiles of these formulations. The results generated in this study, Formulation A4 containing 25% HPMCK4M was found to release a maximum of 99.87% at the 12th hour. The drug release from A4 was found to follow zero order kinetics. It was also found linear in Higuchi’s plot, which confirms that diffusion is one of the mechanisms of drug release. Comparison of A4 and commercial S.R. formulation of DiltiazemHCl revealed the fact that developed formulation (A4) showed comparable release characteristics, thus it may have fair clinical efficacy. Hence, the formulation A 4 has met the objectives of the present study.

**Acknowledgment**

The authors are thankful to Cipla ltd, Goa for providing the gift sample of Diltiazem HCl. The authors are also thankful to Zydus-Cadila HealthCare Ltd, Ahmedabad, India, for providing the polymers as a gift samples such as HydroxyPropyl Methyl cellulose (HPMC K4M and HPMC K 100M) was obtained from. And also thankful to management of Bhupal Nobels’ Girls College of Pharmacy, Udaipur (Rajasthan) for providing the all facilities to carried out this research work.
References


