FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING MICROSPHERES OF FELODIPINE

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ABSTRACT

The purpose of the research work was to prepare and evaluate the floating Microspheres of Felodipine as a model drug in prolongation of Gastric retention time for oral delivery. Felodipine is a cardiovascular drug, where it requires frequent dosing to maintain the therapeutic effect. The Floating microspheres of Felodipine were prepared by solvent evaporation method using PEG 4000, Sodium Alginate and HPMC K 100 as a rate controlling polymers. The floating microspheres were evaluated for micromeritic properties, particle size, % yield, invitro buoyancy, incorporation efficiency and drug release. The size of average diameter of prepared microspheres were recognized and characterized by scanning electron microscopic method. The prepared microspheres were found to be spherical and free flowing and remain buoyant for more than 12 hours due to the hollow cavity present in the microspheres. The drug loaded microspheres (F3) showed encapsulation efficiencies up to 93.72 % and also good micromeritic properties for their suitability as oral dosage forms. The microspheres having lower densities exhibited good buoyancy effect and hence, these could be retained in the gastric environment or more than 12 hours. Thus the present formulations would be capable of reducing the frequency of administration and the dose – dependent side effects associated with the repeated administration of conventional Felodipine Tablets.

KEYWORDS: Felodipine, Sodium Alginate, PEG 4000, Solvent Evaporation Method, Gastro retentive floating microspheres.
INTRODUCTION
Oral drug delivery system is the most preferable system because of ease in administration, patient compliance and flexibility.\(^1\) An effective drug therapy not only depends on the inherent therapeutic activity of the drug molecule but also the efficiency of its delivery at the site of action. Drug absorption at the desired rate means, first, to reach the effective plasma level within an acceptable short time period, second, to avoid an overshoot in the case of rapidly absorbed drugs, and third, to maintain effective plasma levels over the desired time period.\(^2\)

To develop a drug delivery system for oral administration, it is necessary to optimize not only the release rate of an active ingredient from the system but also the residence time of the system in the gastrointestinal tract\(^3\) Drugs that are easily absorbed from the Gastro intestinal tract and have short life are eliminated quickly from the blood circulation and require frequent dosing. To avoid these problems, the oral controlled release formulations have been developed in attempt to release the drug, slowly into the GIT and maintain the constant drug concentration in the serum for longer period of time. Such oral controlled drug delivery device may be complicated by limited GRT, a physiological limitation. Gastro retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs.\(^4\)

Floating microspheres, despite tremendous advancement in drug delivery, oral route remains the perfect route for the administration of therapeutic agent, low cost of Therapy and ease of administration leads to higher levels of patient compliance \(^5\). Felodipine is cardiovascular drug. It is used in various antianginal, antihypertension, and Hepatic Dysfunction. Normal dosage regimen varies from 10-20 mg administered twice in a day. In severe cases, long-term therapy may also be required. Biological half-life of drug is from 11-16 hrs. As it requires frequent dosing to maintain the therapeutic effect, it was chosen as a model drug for the present study. These particles consist of core material, which is the drug, and a coating material. The coat material can be of various types ranging from natural polymers, such as Sodium Alginate and synthetics such as PEG 4000 and HPMC K 100. Microspheres are sometimes referred to as micro particles. (1,000micrometers = 1 millimeter = 0.04 inches.)
MATERIALS USED
Felodipine (Micro labs, Pvt, Ltd Bengaluru ,India.), PEG 4000,sodium alginate &, HPMC K 100 were procured from (Lobachemi, Pvt Ltd.Mumbai , India ) ,Ethanol, Tween 80 from (S.D fine chemicals Pvt Ltd, Mumbai, India ), n-hexane (Qualigens fine chemicals Pvt Ltd. India), Dichloro methane (Merck Pvt Ltd, Mumbai, India ).

Preformulation studies
FT-IR STUDIES
The FT-IR analysis was conducted for the analysis of drug polymer interaction and stability of the drug during microencapsulation process [6]. The FT-IR spectrum of pure Felodipine, sodium alginate, HPMC K 100, and PEG 4000.was studied. The physical mixtures of the floating microspheres formulation also were recorded.

Preparation of Floating Microspheres
The floating microspheres were prepared by solvent evaporation method. The formulation of the floating microsphere was performed by taking the drug and the polymer in the ratio of 1:3 and 1:5.

SOLVENT EVAPORATION METHOD
The solvent evaporation method for Felodipine microsphere was as follows:
Sodium alginate, HPMC K100, PEG 400 solution in the ratio of 1:3 were prepared by taking the weighed amount of sodium alginate and added into 100 ml of distilled water in 250ml beaker. The remaining HPMC K100 and PEG 400 also were prepared individually. Similarly sodium alginate solution, HPMC K100, PEG 400 in the ratio of 1:5 were prepared by taking the weighed amount of sodium alginate and added into 100 ml distilled water in 250 ml beaker. The remaining HPMC K100 and PEG 4000 were also prepared individually. The organic phase was prepared by taking 0.5 ml groundnut oil and added into the 100 mg of Felodipine in 100 ml beaker [7].

CaCl₂ solution was prepared by weighing 40 gms of CaCl₂ and was added to 200 ml distilled water in 250 ml beaker. The sodium alginate, HPMC K100, PEG 4000, solutions were added into oily phase (organic phase) individually and ultimately primary solutions were prepared. With the help of micro syringe above prepared primary emulsions were added in the 20% CaCl₂ solution. Before the addition of primary emulsion into 20% CaCl₂ solution magnetic stirrer was kept with a constant speed of 200 rpm and at constant room
temperature (37.5±1 °C). N-hexane was added to avoid the collapse of drops of primary emulsions during the addition in 20% CaCl₂, since n-hexane plays an important role in microsphere formation.

**Characterization of microspheres**

The following parameters are determined for floating microspheres of Felodipine.

**Tapped Density**

The floating microspheres were tapped gently as surface till the powder occupies maximum volume and noted the volume as tapped volume [8, 9]. The mechanical tapping of cylinder was carried out manually 500 times. The tapped density was calculated in g/cm² by the following formula.

\[
\text{Tapped Density} = \frac{\text{Weight of the Microspheres}}{\text{Tapped Volume}}
\]

**Angle of Repose**

The frictional forces in floating microspheres can be measured by the angle of repose θ[8, 9]. This is the maximum angle possible between the surface of a pile of microspheres and the horizontal plane. A funnel is fixed at a particular height ‘h’ on a burette stand. A white paper is placed bellow the funnel. The sample is passed slowly through the funnel until it forms a pile further addition of drug stopped as soon as the drug pile touches the tube of the funnel. Circle of the pile of drug is drawn. Without disturbing the pile, radius of the pile was noted. Angle of repose is calculated from the following formula:

\[
\tan \theta = \frac{h}{r}
\]

θ=angle of repose degrees, \( h \)=height of pile, \( r \)=radius of the pile in cm.

**Carr’s compressibility index**

The percentage compressibility index was calculated according to following formula.

\[
\% \text{compressibility index} = [1 - \frac{V}{V_0}] \times 100
\]

where \( V \) and \( V_0 \) are the volume of the sample after and before the standard tapping respectively. Each determination was made in triplicate [8, 9].

**Drug entrapment**

The various formulations of the floating microspheres were subjected for drug content. 100mg of floating microspheres from all batches were accurately weighed[10]. The
Microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 1.2 pH acidic buffer. The resulting solution is then filtered through whatmann filter paper no 44. After filtration, from the solution 10ml was taken out and diluted up to 100ml with pH1.2. From the above solution 10ml was taken out and diluted up to 100ml with pH1.2 and the absorbance was measured at 362nm against pH1.2 as blank. The percentage drug entrapment was calculated as follows.

\[
\text{Percentage Drug Entrapment} = \frac{\text{Calculated Drug Concentration}}{\text{Theoretical Drug Concentration}} \times 100
\]

**Particle size analysis**

Particle size analysis plays an important role in determining the release characteristic and floating property \[^{8,9}\]. The size of floating microspheres were measured by using an optical microscope, and the mean practical size was calculated by measuring nearly 200 particles with the help of calculated ocular micrometer.

**Percentage yield**

The prepared microspheres weighed from different formulations the measured weight was divided by the total amount of all non-volatile components which were used for the preparation of microspheres \[^{11}\].

\[
\text{Percentage Yield} = \frac{\text{actual weight of product}}{\text{total weight of drug and polymer}} \times 100
\]

**Buoyancy percentage**

100 mg of floating microspheres were placed in pH1.2 (900ml) containing 0.02% of tween80 and the mixture was stirred with paddle at 100 rpm \[^{7}\]. The layer of buoyant microsphere were pipetted and separated by filtration at 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hrs. The collected microspheres were dried in a desiccators over night. The percentage of microspheres was calculated by the following equation:

\[
\text{Percentage Floating Microspheres} = \frac{\text{weight of Floating microsphere}}{\text{Initial weight of Floating microsphere}} \times 100
\]
Scanning electron microscopy

Dry microspheres were placed on an electron microscope brass stub encoated with gold in an ion sputter. Then picture of microsphere were taken by random scanning of stub. The SEM analysis of the microspheres was carried out by using JEOL, JSM-670F japan (Sastra University, Tanjavur). the microspheres were viewed at an accelerating voltage of 3.0.

In-vitro Drug release studies

The drug release rate from floating microspheres was carried out using the USP type –II dissolution basket assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were taken. The dissolution media of 900 ml of stimulated gastric fluid (pH1.2) was maintained at 37±0.5 °C and stirred at 100 rpm. Aliquots of samples (1ml) sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were suitably diluted with pH 1.2 and analyzed spectrophotometrically at 362 nm to determine the concentration of drug present in the dissolution medium.

Stability studies

The stability study was carried out for the all formulations by exposing it to different temperatures 5-8 °C, 27 °C and 40 °C for 3 months. The samples were analyzed for drug content at the regular intervals.

RESULTS AND DISCUSSION

The Floating microspheres of Felodipine were prepared by solvent evaporation method using Sodium alginate, HPMC K 100 and PEG 4000. The prepared Floating microspheres were evaluated for different physicochemical tests.

FT-IR Studies

The drug and polymer interaction was studied by taking FT-IR spectra of drug and polymers were carried out by using KBR pellet technique. The spectrum was observed for the drug and the polymers individually and when the drug mixed with the different polymers and the range of the mixture was compared with the drug to find whether there is any drug polymer interaction. The results showed that there was no drug polymer interaction when IR spectra of pure drug Felodipine in the presence of PEG 4000, sodium
alginate and HPMC K 100, thus revealing compatibility of the selected drug in different polymers.

**Evaluation of microspheres**

The tapped density was determined by tapping method the tapped density value of different microspheres range from 0.303 – 0.402 g/cc as shown in the Table 1. Angle of repose of microspheres was determined by fixed funnel method. Angle repose of microspheres was in range of 24°36’ - 33°58’ as shown in Table 1. All formulation showed excellent flowability as represented in term of angle of repose. Compressibility index was determined by same tapping method and its range was found to be 9.37-19.81% (Table 1). The compressibility index less than 20% was suggested for all formulations showed excellent flow property. The flow properties of the microspheres have been expressed in terms of Carr’s index. The Carr’s index for all formulation was good and in the passable range, which indicates good flow property and suggested that the microspheres could be easily handled during the processing.

**Drug entrapment**

The drug entrapment efficacies of different formulations were in range of 55.8 -64.4%w/w as shown in the Table 1. Drug entrapment efficacy slightly decreased with increase in HPMC K100. This is due to the permeation characteristic of HPMC K100 that could facilitate diffusion as a part of entrapped drug to surrounding medium during preparation of floating microspheres. It was observed that the microspheres of all the formulations, that the core coat ratio of 1:5 gave highest encapsulation of the drug when compared to the ratio of 1:3. The drug loading of Felodipine microspheres decreased with increase in the concentration of polymer and drug entrapment efficiency of Felodipine floating microspheres increased with the increase in the concentration of the polymer.

**Particle size analysis**

The particle size was determined by optical microscopy method. It plays an important role in floating ability and drug release. If the size of microspheres is less than 500µm release rate of drug will be high and floating ability will be reduced, microspheres ranging between 500µm - 1000µm, the floating ability will be more and release rate will be in sustained manner.
The mean particle size of microspheres was in range 675-897 µm and the results were tabulated in the Table 1. The particle size distribution was almost uniform and narrow in all the formulations. It was observed that microspheres with core coat ratio of 1:3 were of less in size, when compared to the particle size of 1:5. This may be due to the viscosity of the polymers used.

**Percentage yield**

The percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of developed formulations of Felodipine floating microspheres F1-F6 were found to be in the range of 53.7 - 78.3%.

**Floating behavior of microspheres**

Microspheres was dispersed in pH 1.2 containing Tween 80 (0.02% w/w) to simulate gastric fluid. Tween 80 (0.02% v/v) was used to impart wetting effect of the natural surfactants such as phospholipids in the GIT. The F3-F4 Formulations shows best floating ability (96.39 - 70.23%) in 12 hours. Comparatively the remaining formulations showed less floating ability with the floating ability of all formulations within the range of (45.08 - 96.39 %). as showed in Table2. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. It was found that the Felodipine microspheres of the formulation F3 showed desirable buoyancy with adequate release characteristics. Fig 1

**Scanning Electronic Microscopy**

Shape and surface characteristics of microspheres were examined by Scanning Electron Microscopy. Surface morphology of F3 formulation was examined at an different magnification of 40X and 200X, which illustrate the smooth surface of floating microspheres and small hollow cavity present in microspheres which is responsible for floating property [15]. SEM revealed pores on the microsphere as well as hollow microsphere interior. The surface morphology internal structure of microspheres was determined by SEM as shown in figure 24. From this figure it was observed that so many pores are formed due to the drug release. Some pores may be small on big in size due ot the blasting of the drug.
Dissolution studies

The *in-vitro* release studies of the floating microspheres were studied for all the formulations. The drug release data obtained for the formulations from F1 – F6 were tabulated in the Table 3. The cumulative percentage drug released from floating microspheres decreased with increase in concentration of polymers PEG 4000, Sodium alginate and HPMC K 100 respectively. Among the definite Felodipine floating microspheres formulations, the formulation F3 was selected as the ideal formulation based on its micrometrics properties, spherical in shape, floating behavior, drug loading, drug entrapment efficiency and percentage of drug release over a prolonged period over 12hrs (Fig 2) for further studies like stability study.

Stability studies

The stability study was carried out for the F3 formulation by exposing it to different temperatures 5 -8ºC, 27ºC and 40ºC for 3 months. The sample was analyzed for drug content at regular intervals. It was found that no remarkable change in the drug content in F3 formulation. This indicates that F3 was stable for following temperature. The drug release profile indicated that there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence it can be concluded from the results that the developed felodipine floating microspheres were stable and retained their pharmaceutical property over a period of 3 months.

Table 1: Formulation of Floating Microsphere

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug</th>
<th>PEG 4000</th>
<th>Sodium alginate</th>
<th>HPMC K 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100 mg</td>
<td>300 mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F2</td>
<td>100 mg</td>
<td>500 mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F3</td>
<td>100 mg</td>
<td>-</td>
<td>300 mg</td>
<td>-</td>
</tr>
<tr>
<td>F4</td>
<td>100 mg</td>
<td>-</td>
<td>500 mg</td>
<td>-</td>
</tr>
<tr>
<td>F5</td>
<td>100 mg</td>
<td>-</td>
<td>-</td>
<td>300 mg</td>
</tr>
<tr>
<td>F6</td>
<td>100 mg</td>
<td>-</td>
<td>-</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

Table 2: Physical Characterisation of Microspheres

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation</th>
<th>Tapped density g/cc</th>
<th>Angle of repose</th>
<th>Compressibility index %</th>
<th>Drug entrapment</th>
<th>Mean particle size (µm)</th>
<th>Percentag e yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>0.321</td>
<td>29°31'</td>
<td>17.59</td>
<td>55.6</td>
<td>723</td>
<td>64.2</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>0.303</td>
<td>27°59'</td>
<td>19.81</td>
<td>58.6</td>
<td>796</td>
<td>61.8</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>0.402</td>
<td>28°47'</td>
<td>9.37</td>
<td>61.2</td>
<td>862</td>
<td>78.3</td>
</tr>
<tr>
<td>4.</td>
<td>F4</td>
<td>0.383</td>
<td>26°51'</td>
<td>12.46</td>
<td>64.6</td>
<td>897</td>
<td>72.8</td>
</tr>
<tr>
<td>5.</td>
<td>F5</td>
<td>0.364</td>
<td>30°38'</td>
<td>14.23</td>
<td>59.2</td>
<td>675</td>
<td>59.2</td>
</tr>
<tr>
<td>6.</td>
<td>F6</td>
<td>0.326</td>
<td>29°54’</td>
<td>16.78</td>
<td>56.7</td>
<td>689</td>
<td>53.7</td>
</tr>
</tbody>
</table>
Table 3: Floating Behavior of Microspheres

<table>
<thead>
<tr>
<th>Time (Hrs.)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84.61</td>
<td>81.35</td>
<td>96.39</td>
<td>93.13</td>
<td>89.23</td>
<td>87.16</td>
</tr>
<tr>
<td>2</td>
<td>78.05</td>
<td>75.74</td>
<td>94.11</td>
<td>91.09</td>
<td>86.73</td>
<td>83.19</td>
</tr>
<tr>
<td>4</td>
<td>71.82</td>
<td>68.94</td>
<td>91.76</td>
<td>88.71</td>
<td>79.84</td>
<td>75.02</td>
</tr>
<tr>
<td>6</td>
<td>66.79</td>
<td>61.96</td>
<td>84.19</td>
<td>80.91</td>
<td>74.20</td>
<td>71.33</td>
</tr>
<tr>
<td>8</td>
<td>62.93</td>
<td>57.71</td>
<td>81.34</td>
<td>78.47</td>
<td>68.51</td>
<td>61.68</td>
</tr>
<tr>
<td>10</td>
<td>53.68</td>
<td>51.87</td>
<td>79.73</td>
<td>76.68</td>
<td>63.17</td>
<td>58.75</td>
</tr>
<tr>
<td>12</td>
<td>51.76</td>
<td>45.08</td>
<td>73.62</td>
<td>70.23</td>
<td>59.06</td>
<td>55.92</td>
</tr>
</tbody>
</table>

Table 4: *In vitro* Drug Release Studies of the Gastro Retentive Floating Microspheres

<table>
<thead>
<tr>
<th>Time (Hrs.)</th>
<th>Percentage drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>3.62</td>
</tr>
<tr>
<td>2</td>
<td>15.43</td>
</tr>
<tr>
<td>3</td>
<td>25.72</td>
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<tr>
<td>4</td>
<td>33.06</td>
</tr>
<tr>
<td>5</td>
<td>38.98</td>
</tr>
<tr>
<td>6</td>
<td>45.02</td>
</tr>
<tr>
<td>7</td>
<td>52.10</td>
</tr>
<tr>
<td>8</td>
<td>60.51</td>
</tr>
<tr>
<td>10</td>
<td>69.92</td>
</tr>
<tr>
<td>12</td>
<td>76.10</td>
</tr>
</tbody>
</table>

Table 5: Stability studies of the Formulation (F3) Gastro Retentive Floating Microspheres

<table>
<thead>
<tr>
<th>S. No</th>
<th>Days</th>
<th>% Drug retained 5-8°C</th>
<th>%Drug retained 27°C</th>
<th>%Drug retained 42°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>100±0.00</td>
<td>100±0.00</td>
<td>100±0.00</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>94.6±0.015</td>
<td>94.9±0.003</td>
<td>94.7±0.041</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>94.4±0.013</td>
<td>94.7±0.027</td>
<td>94.3±0.036</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>94.2±0.15</td>
<td>94.3±0.012</td>
<td>94.1±0.02</td>
</tr>
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</table>
Fig 1: Floating Behaviour of microspheres of Felodipine

Fig 2: Graph showing the In vitro Drug release studies of the Gastro Retentive Floating Microspheres.

CONCLUSION
Gastro retentive floating microspheres of Felodipine were prepared by the solvent evaporation technique. Felodipine is a slightly water soluble drug which has good absorption in gastric pH. Felodipine suffers from poor oral bioavailability (22–66%) since it is less soluble in water and shows poor absorption in lower GIT. Hence, such a drug requires a novel gastro retentive drug delivery system which can provide an extended period of time in stomach and improve oral bioavailability. Hollow microspheres are the suitable drug delivery system for the drugs that have poor absorption from lower GIT. Hollow microspheres were formed via an o/w type emulsion by rapid diffusion of volatile solvents. Gastro retentive floating microspheres were studied for characterization,
compatibility study, particle size and shape, in vitro drug release, entrapment efficiency, and buoyancy time. The formulation using Drug:Sodium Alginate, in the ratio1:3 showed a constant rate of release. Thus, prepared Gastro retentive floating microspheres of Felodipine may prove to be potential candidate for a multiple-unit drug delivery device adaptable for any intra gastric condition.

REFERENCES


