Ionotropic Gelation Technique For Microencapsulation Of Antihypertensive Drug

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Ionotropic Gelation Technique For Microencapsulation Of Antihypertensive Drug

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Abstract

Micropellets of verapamil hydrochloride were formulated by ionotropic gelation technique using sodium alginate, hydroxy propyl methyl cellulose and hydroxy propyl cellulose. Prepared micropellets were evaluated for flow behaviour, drug entrapment efficiency, *in-vitro* dissolution and stability studies, including scanning electron microscopy and optical microscopy. Of the nine formulations prepared and evaluated formulations F3, F6 and F9 were found to show satisfactory results. The release of the drug from the micropellets was found to be following Non-Fickian diffusion. Drug diffusion coefficient and correlation coefficient were also assessed using various mathematical models. From the study it was concluded that, prolonged release Verapamil hydrochloride micropellets can be achieved with success using ionotropic gelation technique.

Introduction

Verapamil hydrochloride is calcium channel blocker used in the treatment of hypertension, angina pectoris, certain cardiac arrhythmia and obstructive cardiomyopathies. It has a short half life of 4 h. It also causes gastric irritation on sudden release. It is usually administered as conventional tablets containing 40-120 mg, 3 times a day. Due to its ready solubility in water and shorter half-life, the drug is an ideal candidate for prolonged release formulation. Drug requires enough dosing by oral route due to its inherent short half-life, prolonged release formulation administration will lead to reduction of dosing frequency and in contrary improves patient compliance. It deserves merit to which there is increase in bioavailability inspite of drug undergoing substantial first pass metabolism. The aim of the present study is to develop a suitable microparticulate system of verapamil hydrochloride for prolonged release delivery system. In the proposed method of ionotropic gelation technique, strong spherical beads with a narrow particle size distribution and low friability could be prepared with high yield and a drug content approaching 98 percent.

Methods

Preparation of micropellets:
The micropellets of Verapamil hydrochloride were prepared by using ionotropic gelation technique. In this method weighed quantity of Verapamil hydrochloride was added to 50 ml sodium alginate solution and thoroughly mixed at 500 rpm. Resultant solution was extruded dropwise with the help of syringe and needle into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained micropellets were washed with water and dried at 70°C for 6 h in an oven.

Three sets of micropellets were prepared. In the first set micropellets of Verapamil hydrochloride were prepared using only sodium alginate in different concentrations. In the second set, micropellets of the drug were prepared in a combination of coating polymers like hydroxy propyl methyl cellulose and sodium alginate. In the third set, micropellets of the drug were prepared using a combination of polymers like hydroxy propyl cellulose and sodium alginate. The detailed composition of various formulations prepared is as mentioned in Table 1.

Drug entrapment efficiency:
Accurately weighed 100 mg micropellets was suspended in 100 ml of simulated intestinal fluid of pH 7.2±0.1 and kept for 24 hrs. Next day it was stirred for 5 min, and subjected for filtration. After suitable dilution, Verapamil hydrochloride content in the filtrate was analyzed spectrophotometrically at 278nm using Shimadzu 1201 UV-Visible Spectrophotometer.

Flow property:
Angle of repose method was employed to assess the flowability. Micropellets were allowed to fall freely through a funnel fixed at 1 cm above the horizontal flat surface until the apex of conical pile just touched the tip of the funnel. The angle of repose (q) was determined by the formula, q= tan-1 (H/R); H=cone height of micropellets; R=radius of the circular base formed by the micropellets on the ground.

*In-vitro release studies:*
Dissolution studies were carried out in triplicate for all the formulations, employing USP XXIII apparatus (basket method) at 50 rpm and 37±0.50 C using acid buffer (pH 1.2) and phosphate buffer (pH 7.2) as the
dissolution medium. An aliquot of the sample was periodically withdrawn at suitable time intervals and the volume replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 278 nm.

Scanning electron microscopy (SEM) analysis:
The micropellets were observed under SEM at 2-15 kV by mounting sample on the aluminum stubs having double adhesive tape and subsequent evaporation of gold palladium alloy in the ion sputter unit. The microphotographs of suitable magnifications were obtained for surface photography.

Particle size analysis:
Samples of micropellets were analyzed for particle size by optical microscopy. The Olympus Model (SZX-12) having resolution of 30X was used for this purpose. The instrument was calibrated where in 1 unit of eye piece micrometer was equal to 1/30 mm (33.33 mm). All the three dimensions (l x b x h) of the micropellets were measured.

Accelerated stability studies:
Stability studies were performed according to WHO guideline. The formulations were stored in oven at 37±10 C and 60±10 C for a period of six weeks. The samples were analyzed for drug content every week by spectrophotometer at 278 nm.

Kinetics of drug release:
In order to understand the mechanism and kinetics of drug release, the results of the in-vitro dissolution study of the micropellets was fitted with various kinetic equations like zero order (% release Vs time, t), first order (log % remained Vs t) and Korsmeyer and peppas (mt/m¥ Vs tn). ‘r’ values were calculated for the linear curves obtained by regression analysis of the above plots.

Results and Discussion

The micropellets were prepared by the ionotropic gelation of sodium alginate and calcium chloride. Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for micropellets of verapamil hydrochloride core material. From the preliminary studies it is observed that with the increase in stirring speed of the calcium chloride (Counter ion solution), the pellet size is decreased. Also it was found that with the increase in harvesting time, the pellets formed in calcium chloride solution in turn decrease the drug entrapment efficiency.

Acceptable range for angle of repose is 200 to 400. All the formulations showed an angle of repose within a range as shown in Table 1. Formulation F3, F6 and F9 showed angle of repose of 270 40',240 20' and 250 40' respectively, which indicates a good flow property. The drug entrapment efficiency of all the formulations were in the range between 76.6% to 97.8% as shown in Table-1. Drug entrapment efficiency of micropellets increases with increase in percentage of sodium alginate, hydroxy propyl methyl cellulose, hydroxy propyl cellulose. But the amount of calcium chloride has no significant effect on the drug entrapment efficiency.

Verapamil hydrochloride release from the micropellets was studied in acid buffer (pH 1.2) and phosphate buffer (pH 7.2) for a period of 8 hrs. The release pattern of micropellets was slow and spread over extended periods of time. The values of co-efficient of correlation (r) was calculated and were found to be linear for first order release as compared to zero order. Cumulative % drug released was subjected to curve fitting data using PRISM software. The data was best fitted to Korsmeyer and Peppa’s model and good regression co-efficient was observed (Table 2). The values of diffusion co-efficient ranged between n=0.4286 to 0.8165. This indicates that the release of the drug occurs by diffusion following non-fickian transport mechanism. The entrapment efficiency and cumulative percent drug released studies indicated, among the nine formulations F3, F6 and F9 gave a good pattern of release and were represent among of three used polymers selected for the further studies (Fig. 1).

Scanning electron microscopy (SEM) of formulation F3 indicated that the micropellets gave rough and sandy appearance (fig-2). SEM (fig-3) of formulation F6 indicated that the micropellets are spherical in shape and exhibited bridging. SEM (fig-4) of formulation F9 showed surface was rough and polymer deposits were seen. The scanning electron microphotograph of F6 indicated bridging of micropellets which accounts for the dense nature, the surface of the micropellets was quite smooth, the porosity of the coating material was very low and the particle size was bigger, which in turn account for slow release of the drug.

Particle size of the micropellets was determined by optical microscopy. The mean particle size for F3, F6 and F9 was found to be 0.366mm, 0.655 mm and 0.511mm respectively. The fig-5 of F6 formulation indicates the formation of the thick coat around the drug particles, which is supported by an increase in the particle size of the micropellets. Stability studies conducted at 37±10 C and 60±10 C showed that polymer used were compatible with the drug and the formulations were stable.
Conclusion

The micro pellets indicated good entrapment efficiency and release of the drug from the micro pellets was found to be following non-fickian diffusion mechanism. Thus prolonged release preparation intended for twice a day dosage was developed for verapamil hydrochloride as a calcium channel blocker. This accounts for the prolonged release of Verapamil hydrochloride.

References

Illustrations

Illustration 1

Composition and Physical Characteristics of the Micropelletes

Table 1 Composition and Physical Characteristics of the Micropelletes

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Sodium Alginate % (w/v)</th>
<th>Calcium Chloride % (w/v)</th>
<th>HPMC % (w/v)</th>
<th>HPC % (w/v)</th>
<th>Drug Entrapment Efficiency</th>
<th>Angle of Repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>76.5</td>
<td>350 30'</td>
</tr>
<tr>
<td>F2</td>
<td>3</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>78.7</td>
<td>330 10'</td>
</tr>
<tr>
<td>F3</td>
<td>4</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td><strong>85.1</strong></td>
<td>270 40'</td>
</tr>
<tr>
<td>F4</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>85.5</td>
<td>320 20'</td>
</tr>
<tr>
<td>F5</td>
<td>3</td>
<td>5</td>
<td>1.5</td>
<td>-</td>
<td>93.6</td>
<td>280 20'</td>
</tr>
<tr>
<td>F6</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>-</td>
<td><strong>97.8</strong></td>
<td>240 10'</td>
</tr>
<tr>
<td>F7</td>
<td>2</td>
<td>4</td>
<td>-</td>
<td>2</td>
<td>80.0</td>
<td>300 30'</td>
</tr>
<tr>
<td>F8</td>
<td>3</td>
<td>5</td>
<td>-</td>
<td>3</td>
<td>87.2</td>
<td>280 10'</td>
</tr>
<tr>
<td>F9</td>
<td>4</td>
<td>6</td>
<td>-</td>
<td>4</td>
<td><strong>93.5</strong></td>
<td>250 40'</td>
</tr>
</tbody>
</table>

HPMC: Hydroxy propyl methyl cellulose, HPC: Hydroxy propyl cellulose.
Illustration 2

In Vitro Release Kinetic Data of Micro Pellets

Table-2 In Vitro Release Kinetic Data of Micro Pellets

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Cum % Drug Released</th>
<th>Correlation Coefficient (r)</th>
<th>Korsmeyer and Peppa’s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First order</td>
<td>Zero order</td>
</tr>
<tr>
<td>F1</td>
<td>96.86</td>
<td>0.9803</td>
<td>0.9773</td>
</tr>
<tr>
<td>F2</td>
<td>95.39</td>
<td>0.9824</td>
<td>0.9789</td>
</tr>
<tr>
<td>F3</td>
<td>84.83</td>
<td>0.9509</td>
<td>0.9245</td>
</tr>
<tr>
<td>F4</td>
<td>86.39</td>
<td>0.9433</td>
<td>0.9192</td>
</tr>
<tr>
<td>F5</td>
<td>74.13</td>
<td>0.9849</td>
<td>0.9737</td>
</tr>
<tr>
<td>F6</td>
<td>66.75</td>
<td>0.9662</td>
<td>0.9488</td>
</tr>
<tr>
<td>F7</td>
<td>89.23</td>
<td>0.9936</td>
<td>0.9679</td>
</tr>
<tr>
<td>F8</td>
<td>80.21</td>
<td>0.9917</td>
<td>0.9743</td>
</tr>
<tr>
<td>F9</td>
<td>72.62</td>
<td>0.9898</td>
<td>0.9705</td>
</tr>
</tbody>
</table>

F1 to F9 represent various formulations prepared using various polymer such as sodium alginate, HPMC & HPC, n=diffusion exponent related to mechanism of drug release, according to equation - $m t / m^\infty = k t^n$. 

Illustration 2

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<td>F9</td>
<td>72.62</td>
<td>0.9898</td>
<td>0.9705</td>
</tr>
</tbody>
</table>
Illustration 3

Cumulative % drug released v/s time for formulations F3, F6 and F9

Fig. 1: Cumulative % drug released V/s. Time for formulations F3, F6 & F9.
Illustration 4

SEM of Formulation F3 at 3000X

Figure No.2 SEM of Formulation F3 at 3000X
Illustration 5

SEM of Formulation F6 at 3000X

FIGURE NO.3 SEM of Formulation F6 at 3000 X
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