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FORMULATION AND EVALUATION OF AMLODIPINE FLOATING MICRO BEADS

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ABSTRACT

The present research explains the preparation and evaluation of Amlodipine floating micro beads by iontotropic external gelation technique. Pre formulation studies like FT-IR and Differential Scanning Calorimetry (DSC) confirmed that no chemical interaction took place during encapsulation process. Surface Morphology of the prepared floating micro beads were characterized by scanning electron microscopy. Six formulations (FMB-1 to FMB-6) were prepared and evaluated for various physic chemical properties. Pre compressional parameters like Angle of repose, Hausner's Ratio, Carr's Index, Bulk density, tapped density etc were performed and the result shows excellent flow property. Post compressional parameters like the Percentage drug content, Entrapment efficiency, Percentage Yield, Swelling studies and In vitro dissolution studies were evaluated. The swelling Index of Amlodipine containing sodium alginate beads was found to be high in FMB-6 with 86.5%. Entrapment efficiency was in range of 15 to 88%. In-vitro studies revealed that 95% of drug released within 1Hour 45 min from FMB-6, which was found to be best among all the formulations.

CONTENTS

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INTRODUCTION

Bead is defined as a spherical particle having a size ranges from 2mm, including a core substance. It may deliver the active pharmaceutical ingredient in various stages to the particular organ/site to obtain the maximum therapeutic activity [1]. The Micro beads used in targeted drug delivery systems were introduced by Dr. Paul Ehrlich. When such systems was introduced into the body cavity or site of action it may provide maximum therapeutic response with decreasing toxic effects. [2] Micro beads are mainly effective in targeting a effective cytotoxic drugs to the cancer, because they have ability to deliver a specific concentrated of a dose of drug to the specific tumor site. Floating micro beads made with suspension has been used to deliver the drugs into eye for miotic activity and also used as diagnostic agents. [3,4]

Amlodipine may inhibit the calcium ion influx across the cell membrane, having a greater effect on the vascular smooth muscle cells. Amlodipine may act directly on the vascular smooth muscle to causes the reduction in blood pressure [5].

Hence in the present research Amlodipine floating micro beads were formulated using carbopol, sodium alginate in various ratios and evaluated for various physic-chemical properties.

MATERIALS AND METHODS

Amlodipine is the gift sample obtained from Aurobindo Pharma Ltd. Hyderabad, Sodium alginate (Arihant Trading Company, Mumbai.), Carbopol (Signet, Mumbai), Calcium chloride (S.D. Fine Chemical Ltd, Mumbai). All other reagents used were of analytical grade.

Methodology:
Pre formulation testing is the first step in rational development of dosage forms of a drug substance. Hence, pre formulation studies were performed for the obtained sample of drug for identification and compatibility studies.
The following pre formulation studies were performed for amlodipine and polymers.

1. Determination of melting point of Amlodipine
2. Drug - polymer compatibility studies

Determination of melting point:
Melting point was determined by taking small amount of Amlodipine in a capillary tube closed at one end [6]. The capillary tube-containing drug is placed inside melting point apparatus and the temperature at which the drug melts was recorded . This was performed thrice and average value was calculated.

Drug –Polymer Compatability studies:
FT-IR:
The drug-Polymer Interaction were studied by FTIR spectrometer, shimadzu 8400S 2% w/w of the sample with respect to a potassium Bromide (KBr) was mixed with drug KBr. The mixture was mixed into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned for 10 times at a resolution of $2cm^{-1}$ using Happ-Genzel apodization. The characteristic peaks were recorded.[7]

Differential Scanning Calorimetry (DSC):
DSC was carried out by the action of Argon purging with 10ml/min, where it is hermetically sealed with aluminum pans, from this sample 40µl is used with10^0C rise for every min. The onset peak and end set peaks are recorded for individual pure drug, polymer and in combination of drug and polymers. [8]

Preparation of Amlodipine Floating Micro beads:
Amlodipine floating micro beads were prepared by using Ionotropic gelation technique. Weigh the required quantity of amlodipine for each formulation along with polymers such as sodium alginate and carbopol in alcoholic solution[9]. Homogenously mix the above solution for proper dissolving of drug. With the help of hypodermic syringe the above solution is added drop wise into the beaker containing 1% $CaCl_2$ (calcium chloride solution). Finally, the formed beads were dried in a tray dryer at 40^oC for 30 minutes. The time of drying was optimized by weighing the beads repeatedly until, constant weight is obtained. Dried beads of 200 mg equivalent to 10mg of amlodipine were filled into the hard gelatin capsules. Details of formulation are given in table no-1.

EVALUATION OF BEADS
Pre-compression parameters:
Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. An amount of powder blend was introduced in a 100 ml measuring cylinder. Then the weight of Beads and the volume occupied was determined. [10] The cylinder was allowed to fall onto a hard surface from a height of 5 cm at 10 sec intervals. The tapping was continued till no volume change was noted. LBD and TBD were calculated by following formulas

LBD = Weight of the powder/Volume of packing
TBD = Weight of the powder/ Tapped volume

Carr's Compressibility Index:
An important measure that can be obtained from bulk density determinations is the percent compressibility, grading of the powders for their flow properties according to Carr's index [10]. % Carr's Index can be calculated by using the following formula

Carr's Index (%) = (TBD-LBD)/TBD x 100

Hausner's ratio:
Hausner's ratio can be calculated by using following formula.

Hausner's ratio = Tapped density/Bulk density
Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of repose:
The angle of repose of the beads was determined by using funnel method. The accurately weighed beads was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The diameter of the powder cone was measured and angle of repose was calculated by using the equation.

$$\tan \theta = h/r$$

Where, h and r are the height of pile and radius of the base of pile.

Surface Morphology:
SEM (Scanning Electron Microscopy):
Shape and surface of the beads were characterized. The beads were mounted directly on to the sample tube and coated with silver film (200 nm) under reduced pressure.[11]

Determination of drug encapsulation efficiency:
50 mg of Floating micro beads from each formulation were weighed and crushed in a mortar and pestle and the crushed beads was dissolved in 100 ml of phosphate buffer at pH 7.4. This solution was mechanically agitated on shaker at 200 rpm for 2 hours [12]. The resultant dispersions were filtered and analyzed at 360 nm using UV spectrophotometer. The encapsulation efficiency was determined by the following formula.
Encapsulation efficiency = (AQ/TQ) X 100
Where:AQ is the actual drug content of beads and TQ is the theoretical quantity of drug present in beads.

Swelling study:
The swelling behaviour of the calcium alginate beads was studied in 0.1N Hcl (pH 1.2) and phosphate buffer pH 7.4. Previously weighed (W_1) beads were immersed in respective media [13]. The weight (W_2) of the beads was determined for 8 h: Every 30 min for the first 2 h and then every hour after that. The swelling index (SI) of each batch was calculated using the following equation.

$$\% SI = (W_2 - W_1)/W_1 \times 100.$$

Percentage yield:
The Percentage yield of all formulations were calculated using theoretical yield and practical yield.

Buoyancy test:
The obtained beads were studied for buoyancy and floating time using USP Apparatus II (paddle type)[15]. One hundred beads of each batch were placed in 900 ml of 0.1 N HCl (pH 1.2) containing 0.02% w/v Tween 80 and agitated at 50 rpm, temperature was maintained at 37ºC.

Table No: 1 Ingredients used in the formulation

SI.No	Formulation Code	Amlodipine (mg)	Carbopol (gms)	Sodium alginate (gms)	Ethanol (ml)
1	FMB 1	100	0.5	1.5	10
2	FMB 2	100	1.5	0.5	10
3	FMB 3	100	1.0	1.0	10
4	FMB 4	100	0.5	1	10
5	FMB 5	100	0.5	0.5	10
6	FMB 6	100	1.0	0.5	10

***In vitro* dissolution studies:**

In vitro dissolution studies were performed for all the formulations using USP apparatus II (paddle type). An accurately weighed floating alginate beads were taken into 900 ml 0.1N Hcl buffer [16]. The temperature was maintained at 37ºC and stirred at a speed of 50 rpm. At 15 minutes time intervals, a 10-ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37ºC. The collected samples were filtered and analyzed at 360 nm using UV- visible spectrophotometer by taking 0.1N Hcl as blank.

RESULTS AND DISCUSSION

Determination of melting point:

The melting point of Amlodipine was found to be in the range of 102^{o}C to 104^{o}C which indicates the purity of the drug sample.

Drug-Polymer Compatibility studies

Fourier transform infra red spectroscopy:

The FT-IR study revealed that the scanning range was 400-4000cm^{-1}, resolution was 4cm^{-1}. Spectra of the Amlodipine, and the drug with sodium alginate were obtained and compared for the compatibility. The FT-IR spectrum of the pure Amlodipine, combination of amlodipine and polymers is shown in Figure. 1 to 4. Result revealed that there is no interaction between drug and polymers.

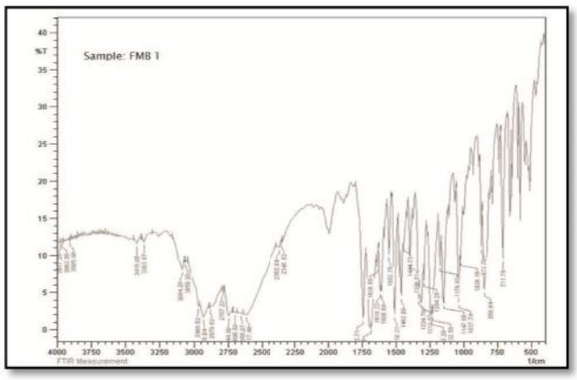

Figure: 1 FTIR Spectra of Amlodipine

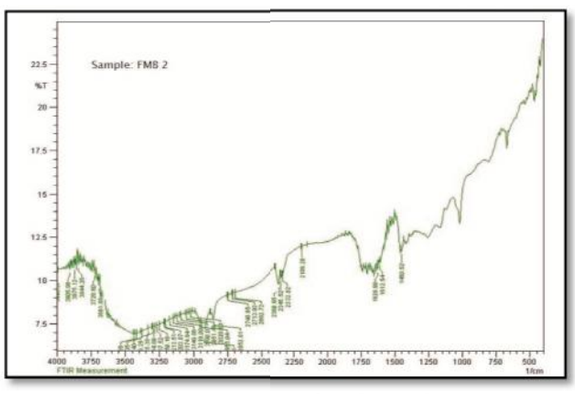

Figure: 2 FTIR Spectra of Sodium alginate

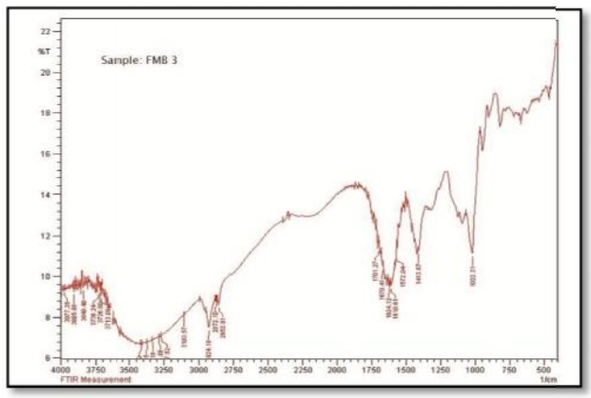

Figure: 3 FTIR Spectra of Carbopol

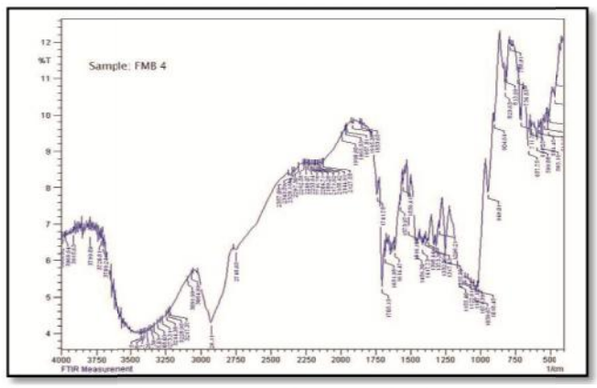

Figure: 4 FTIR Spectra of Mixture

DSC (Differential Scanning Calorimetry):

The Pure drug Amlodipine shown as an Exothermic peak 149.5^{o}C to 165.6^{o}C & Endothermic peak 158.3^{o}C. Exothermic peak for sodium alginate showed 146.5^{o}C to 166.9^{o}C. Carbopol shows the exothermic peak at 151.8 ^{o}C to 164.7^{o}C & endothermic peak 102.8^{o}C to 156.8^{o}C. Endothermic peak for physical mixture shows 104.8^{o}C to 258.2^{o}C & 151.7^{o}C to 167.2^{o}C. Pectin shows the endothermic peak at 224.30^{o}C. From the data obtained it was found that there is no Glass transition, Crystallization etc and there is no incompatibility in the formulation. Results are shown in Fig. 5 to 8.

Pre-compression parameters:

Results for bulk density, tapped density, angle of repose, hausner's ratio and compressibility index for all the formulations is shown in table no. 2. From the results it was found that all the formulations (FMB-1 to FMB-6) showed good flow properties.

Shape and surface morphology:

SEM analysis revealed that the prepared microbeads were found to be spherical in shape and the texture was found to be smooth. Results were shown in fig no-9.

Drug entrapment efficiency (%EE): Percentage entrapment efficiency of FMB 1, FMB 2, FMB 3, FMB 4, FMB 5, FMB 6 was found to be 15 ± 0.10,

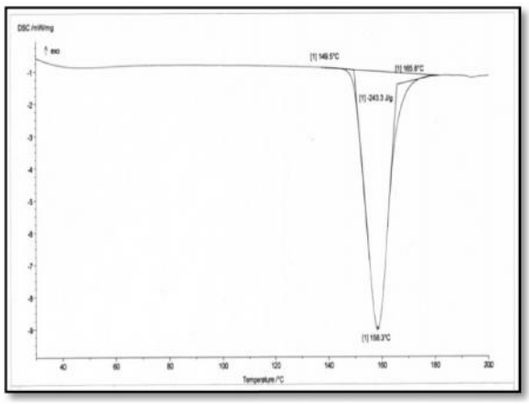

Figure: 5 DSC Spectra of Amlodipine

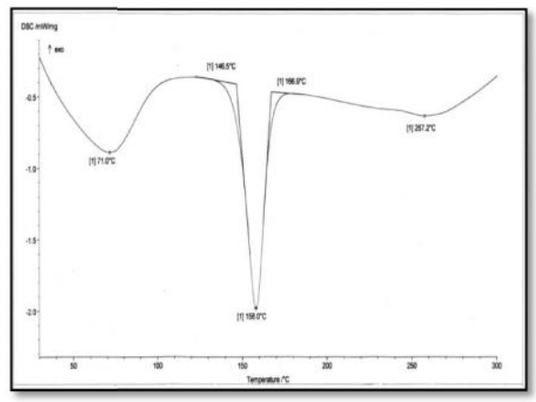

Figure: 6 DSC Spectra of Sodium alginate

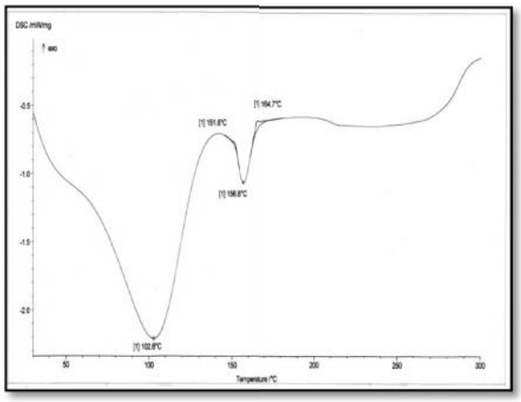

Figure: 7 DSC Spectra of Carbopol

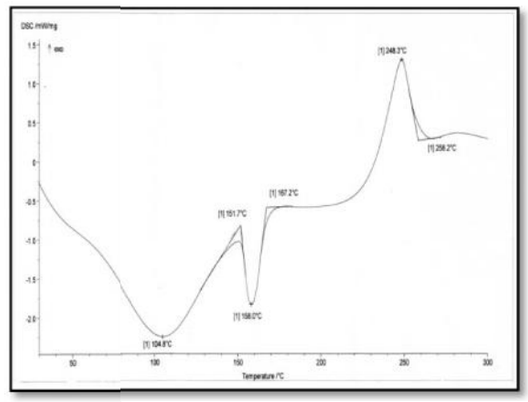

Figure: 8 DSC Spectra of Mixture

Table No: 2 Pre-formulation studies of amlodipine floating micro beads

S. No	Formulation code	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped density (g/cc)	Hausner's ratio	Carr's index (%)
1	FMB1	26	0.534	0.643	1.20	16.9
2	FMB2	25	0.538	0.652	1.21	17.4
3	FMB3	27	0.532	0.634	1.19	16.0
4	FMB4	28	0.563	0.633	1.12	11.0
5	FMB5	27	0.523	0.598	1.14	12.5
6	FMB6	29	0.578	0.656	1.13	11.8

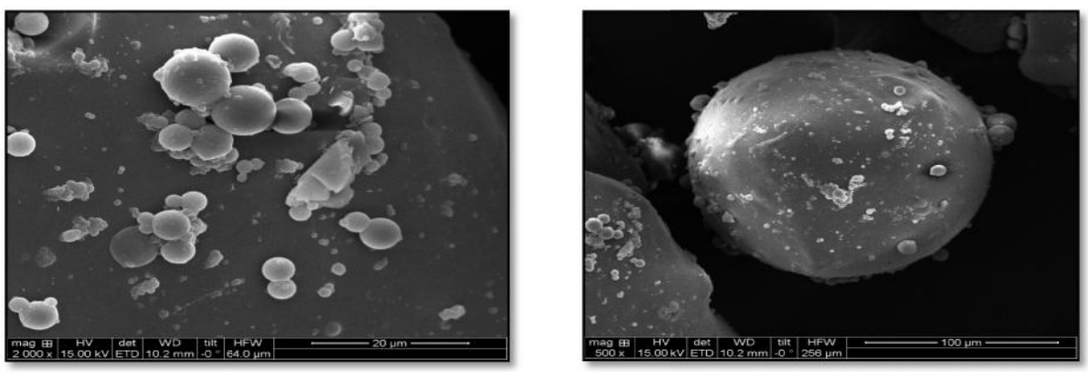

Figure: 9 SEM Picture of Amlodipine Floating Micro Beads FMB 6

28 ± 0.15, 40 ± 1.68, 50 ± 1.51, 64 ± 1.70, 88 ± 1.10 respectively. High drug incorporation is seen in FMB-6 which may be attributed to the fact that rapid quenching of drug occurred in polymer phase due to presence of carbopol, Sodium alginate and the drug. Results are shown in Table No. 3.

Swelling Index:

The swelling Index of amlodipine floating beads was found to be satisfactorily high i.e 50.4, 83.4, 46.7, 53.6, 62.1 & 86.5 for FMB 1- 6 respectively and the results are shown in table-16.

Percentage yield was found to be average and the beads floated in less than 15 sec. Results were given in table no-3.

***In vitro* Dissolution studies:**

The *In vitro* release of the drug from floating micro beads was studied in 0.1N Hcl, pH 1.2 with 900 ml buffer volume. USP basket type dissolution rate test

Table No: 3 Post formulation evaluation of amlodipine floating micro beads

SI.No	Formulation Code	Entrapment efficiency	Swelling Index	Percentage Yield	Buoyancy Testing
1	FMB 1	15 ± 0.10	50.4	84.1 ± 0.23	11 Sec
2	FMB 2	28 ± 0.15	83.4	80.7 ± 0.30	9 Sec
3	FMB 3	40 ± 1.68	46.7	62.7 ± 1.42	12 Sec
4	FMB 4	50 ± 1.51	53.6	73.2 ± 1.22	15 Sec
5	FMB 5	64 ± 1.70	62.1	55.4 ±1.67	10 Sec
6	FMB 6	88 ± 1.10	86.5	79.3 ± 1.28	6 Sec

Table No. 4 *In vitro* dissolution studies of floating micro beads FMB1 to FMB6

S.No	Time	Percent drug release					
		FMB1 (%)	FMB2 (%)	FMB3 (%)	FMB4 (%)	FMB5 (%)	FMB6 (%)
1	15min	45	50	70	60	48	64
2	30min	50.4	52	61	68	60	72
3	45min	57.6	60	65	72	65	80
4	60min	63	58	59	76	79	82
5	1 Hour 15min	72	62	74	80	83	86
6	1 Hour 30min	77.3	70	80	84	89	90
7	1 Hour 45min	86	84	88	90	90	95

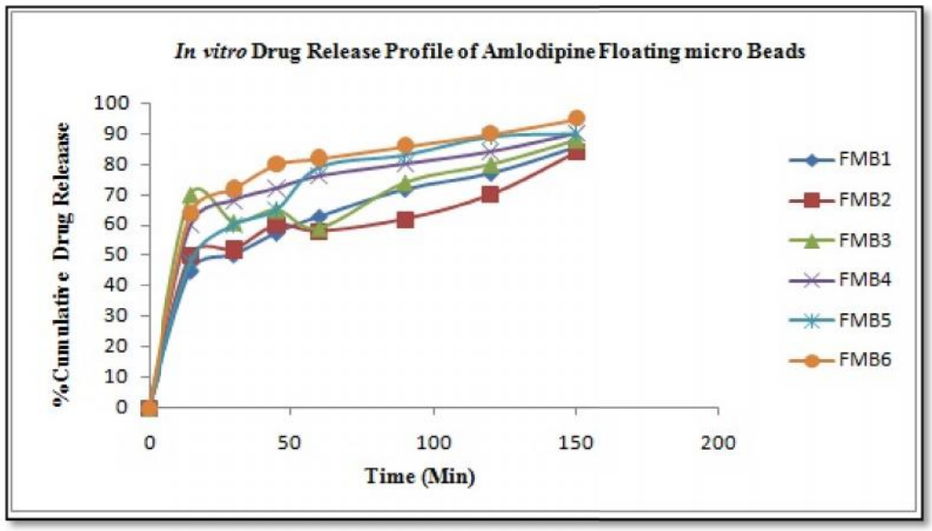

Figure No: 10 In Vitro Drug Release Profile of amlodipine Floating Micro Beads

apparatus is used to calculate the drug release from beads at 50 RPM. The samples were withdrawn at different time intervals and analyzed using UV-spectrophotometer at with wavelength 360 nm. Percentage cumulative drug release was calculated. The values and graphs are represented in table. 4 and fig no.10.

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CONCLUSION

Amlodipine floating micro beads was developed using ionotropic gelation technique. Six formulations were prepared and the best formulation was found to be FMB-6 (Carbopol:Sodium alginate (1:0.5)) based on drug encapsulation efficacy (88%) and in-vitro drug release (95%). Drug release limited for only 1 hour 45 minutes, hence further research should be done in order to prolong the in-vitro drug release by using other effective polymers.

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