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Original Research Paper

FORMULATION AND EVALUATION OF FLOATING MICROSPHERE OF AMLODIPINE BESYLATE BY USING ETHYLCELLULOSE AND HPMC

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ABSTRACT

The purpose of this research work was to develop a novel gastro retentive floating microsphere of Amlodipine Besylate. Amlodipine besylate has maximum solubility in acidic pH and thus most suitable to prolong release of drug in stomach so an attempt has been made to sustain the drug release by incorporation oh hydrophilic swellable polymers such as HPMC and ethylcellulose and present it in the form of gastro retentive floating microspheres which after oral administration are designed to provide the desired controlled and complete release of drug for prolonged period of time in the treatment of hypertension. Floating microsphere of Amlodipine Besylate were formulate using various material HPMC, ethylcellulose, ethanol, dichloromethane, SLS. The concentration of these agents was also optimized to get desired controlled release of drug. The floating microsphere were evaluated for physical characterization, size of microsphere, entrapment efficiency, swelling index, buoyancy studies and *in vitro* release studies. The result indicated that the optimized intragastric floating microsphere (F8) composed of 1g Amlodipine Besylate, 4g ethylcellulose, 0.3g HPMC exhibited 97% release in 8 hrs, while the buoyancy lag time was 20 sec and the intragastric floating microsphere remain buoyant for 20 hrs. *In vitro* drug release kinetics evaluated using the linear regression methods was using found to follow the Zero order kinetics. Optimized intragastric floating microsphere showed no significant change in physical appearance, drug content, total buoyancy time or *in vitro* dissolution pattern after storage at 40°C/75% relative humidity for 1 month.

Keywords: Amlodipine besylate, Floating microspheres, Gastro retentive, Intragastric floating, Floating drug delivery, Controlled release.

INTRODUCTION

The Floating drug delivery system (FDDS) is of special interest in improving the bioavailability of drugs that are poorly soluble or unstable at higher pH of the intestinal or colonic environment[1]. In order to obtain local and sustained drug delivery in the stomach and proximal parts of the small intestine, it is desired to have prolonged gastric retention of the drug. This helps to have improved bioavailability and therapeutic efficacy which may also results in the reduction in dosing frequency of the dosage form.[2-6] The diminished efficacy of the administered dose may be observed due to inter-subject variability and short time of gastric emptying which may results because of incomplete drug release from the drug delivery system above the absorption zone (stomach ,upper part of small intestine).[8,9] Moreover, it has been reported that drug delivery system is one of the commercial system which is attributed to obtain the higher bioavailability than that of the non floating system.[10] The FDDS system is widely useful for the drugs which effectively act in the stomach and have absorption window in stomach.[1,11] To formulate FDDS the drug moiety should have good solubility at acidic pH and absorption window in upper GIT. To

overcome the disadvantages of conventional dosage forms, such as the intersubject variability of GI transit time, due to their all or none effect of the multiple unit dosage form systems are developed. Multiple unit dosage form have proven the lower possibility of dose dumping as well as reduced inter and intra subject variability of the drug absorption.[12,14] FDDS are classified as effervescent and non-effervescent systems depending on the use of two formulation variables. non-effervescent systems are matrix types of systems prepared with the help of swellable polymers like methyl cellulose, ethyl cellulose , HPMC, polysaccharides (e.g., chitosan). When the system comes in contact with the acidic gastric contents, the polymeric system causes swelling of the dosage resulting a bulk density less than 1. It then remains buoyant and floats in the gastric fluid and responsible for prolonged gastric residence time. These systems have the advantage of distributing uniformly throughout the GIT resulting in longer lasting effects and reduced inter-subject variability and also risk of local irritation compared to single unit floating systems such as buoyant tablets or capsules.[18] Amlodipine besylate is long acting calcium channel blocker and used in the treatment of hypertension, and angina pectoris.[19] It is one of the most frequently prescribed antihypertensive drugs in the world. The drug is available as amlodipine besylate, for oral administration in the form of tablets and capsules. The drug has some adverse side effect such as peripheral edema, headache, nausea, dizziness, gastric irritation, fatigue, dyspepsia, when given orally. However, the greatest therapeutic effect of many drugs can be obtained with minimal side effects when the drug is released in the stomach, particularly when the release is prolonged in a continuous, controlled manner.[20] Amlodipine besylate has maximum solubility in acidic pH and thus most suitable to prolong the release of drug in the stomach. Hence, the present investigation aims at developing Non-effervescent floating microspheres of amlodipine besylate to increase the drug bioavailability after oral administration. Many studies have shown that Non-effervescent floating microspheres retain in stomach for long time and improve solubility, bioavailability, reduces drug waste and decrease side effect such as gastric irritation and nausea.[21,22] Thus, floating microspheres of amlodipine besylate can be used conveniently to achieve safe, highly effective therapy in the management of severe hypertension and angina pectoris while reducing undesirable adverse effects with improved patient compliance and acceptance.

In the present study, an attempt was made to develop GRDDS for CP using Ethyl cellulose and HPMC as a release retarded material by solvent evaporation technique. The prepared CP microspheres were evaluated for drug content, particle size, percentage yield, entrapment efficiency, particle size distribution, surface morphology, *in vitro* drug release and stabilities studies.

MATERIALS AND METHODS

Materials

Amlodipine Besylate(AB),Ethyl cellulose (EC 7cps) and Hydroxypropylmethyl cellulose (HPMC K100M) were provide by Noida Institute of engineering and technology. All solvents used were of analytical grades and were used as obtained.

Preparation of AB Microspheres

AB microspheres were prepared based on solvent evaporation technique. Different batches of AB microspheres, F1 to F8 were prepared by varying the concentration of ethyl cellulose polymer in the formulation from 1 to 4 g, respectively (Table 1). Weighed quantities of drug and polymers were dissolved in mixture of ethanol and dichloromethane (1:1 solvent ratio) at room temperature. This solution was poured into 100 mL distilled water containing 0.1% SLS. The resultant emulsion was stirred with a propeller type agitator at 900 rpm for 45 min to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried overnight at room temperature. Concentrations of the ethyl cellulose were optimized based on the % drug release, % entrapment efficiency.

Compatibility Studies

The pure drug and the mixtures of drug-ethyl cellulose and drug-HPMC K100M in the ratio of 1:1 were kept at room temperature for 30 days. Samples were subjected to FT-IR studies using KBr as a blank and the IR spectrum of pure drug and drug-excipient mixtures were compared to find any interaction between drug and excipients used for the formulation of microspheres.

Particle Size Analysis

The size was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.[15]

Determination of Drug Content

The drug content was determined by UVspectrophotometer at a wavelength of 360 nm. The calibration curve for AB was constructed by plotting absorbance against the drug concentrations in the range of 10-100 µg/mL. AB microspheres equivalent to 50 mg of AB was accurately weighed, extracted the drug into 0.1N HCl, adjusted the volume to 10 mL, vortex mixed, allowed to stand for 24 h and then filtered through 0.45 µ membrane filter. From this solution, further dilutions were made using ethanol to get a final concentration of 5 µg/mL of AB. The drug content of the AB microspheres was calculated using the above calibration curve.

Percentage Yield

The prepared microspheres were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of all non-volatile components. The percentage yield of microspheres was calculated as follows.[16]

% Yield = (Actual weight of product /Total weight of excipients and drug) x100

Floating Ability

Floating behavior of hollow microspheres was studied in a USP dissolution test apparatus by spreading the microspheres (50 mg) on a 0.1 M HCl containing 0.02% SLS as a surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 8 h, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.[16]

Swelling Index

Swelling is also a vital factor to ensure buoyancy and drug dissolution of microsphere. The floating microsphere composed of polymeric matrices build a gel layer around the microsphere core when they come in contact with water. This gel layer governs the drug release from the microsphere. Swelling ratio describe the amount of water that is contained in the hydrogel at equilibrium.

In Vitro Drug Release Studies

The release rate of AB from microspheres was determined using USP dissolution testing apparatus I (Basket type). The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5°C and 100 rpm.[17] Microspheres equivalent to 200 mg of CP were used for the test. A 1 mL sample solution was withdrawn from the dissolution apparatus for 1 h, and there after every 1 h upto 8 h. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatmann filter paper and solutions after appropriate dilution were analyzed at 360 nm by UV Spectrophotometer (Shimadzu). Cumulative percentage drug release was calculated.

Stability Studies

The accelerated stability studies were carried out according to ICH guidelines optimized formulation F8 was packed in strip of aluminum foil and this packed formulation was stored in stability chamber maintained at 40°C and 75% RH (Zone III conditions as per ICH Q_1 guidelines) for 1 month. The microsphere were evaluated before and after 1 month for change in appearance and *In vitro* release.

RESULTS AND DISCUSSION

The drug excipient compatibility studies reveal that there were no physical changes observed in drug and polymer mixtures. The IR spectrums of the drug, drug-ethyl cellulose mixture, drug-

HPMC K100M mixture and microsphere formulation F8 were compared to find any change in frequency of functional group in microspheres with respective functional group of the drug. The spectral observations indicated that the principal IR absorption peaks observed in the spectra of drug were close to those in the spectra of the microspheres containing drug. IR spectrums indicate that there is no strong interaction between the drug and the polymers.(Fig.1). The microsphere of different formulation were evaluate for Bulk density and tapped density results are shown in table no. 2. The bulk density and tapped density for all the formulation varies from 0.606 to 0.666 and 0.714 to 0.769 g/cc respectively. The values lie between the acceptable range and not a large difference exists between the bulk density and tapped density. This result helps in calculating %compressibility of microsphere.(Table 1). The %compressibility of microsphere was determined using carr′s compressibility index. carr′s index lies within the range 9.52 to 18.09. In all the formulations F8 show excellent % compressibility. F4,F6,F7 show good %compressibility. F1,F2,F3,F5 show fair %compressibility. All the results are shown in table no. 1. The percentage yield of microsphere is varied from 47 to 90%, where it was found that %yield increased with increase in concentration of ethyl cellulose.(Table 2). The mean particle size of the microsphere was fond to be increased with increasing ethyl cellulose concentration and was in the range 186µm to 480µm shown in table no.2. The viscosity of the medium increases at higher ethyl cellulose concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of large particle.

The drug entrapment efficiency of microsphere varied from 27 to 95%. Results demonstrated that increase in concentration of ethyl cellulose increase the entrapment of the drug.(Table 2). The floating ability of microsphere is varied from 72 to 96% shown in table no. 5. Percentage of floating ability was found to be increased with increase in concentration of ethyl cellulose. (Table 2) Swelling study was performed on all the batches for 8 hrs and the results of swelling index are given in tablet no 6. From the result it was concluded that swelling index increase with time because the polymer gradually absorbs water due to its hydrophilicity. The outer most layer of the polymer hydrates, swells and a gel barrier is formed at the outer most surface. As the gelatinous layer progressively dissolved or is dispersed, the hydration, swelling and release process is repeated towards new exposed surface, thus maintaining the integrity of dosage forms. In the present study, the higher swelling index was found for formulation F8 (Table 3).

On immersion in 0.1N HCl, pH 1.2 solution at 37±0.5^{o}C. All floating microsphere float immediately and remain buoyant up to 20 hrs. The *in vitro* buoyancy of microsphere was induced by swelling without compromising the matrix integrity with the possible shortest buoyancy lag time and buoyancy duration of up to 20 hrs.

It was observed that the microsphere protected within the gel formed by hydration of polymers, thus decreasing the density of the microspheres below 1 and microsphere becomes buoyant. The microsphere swelled radially and axially during *in vitro* buoyancy studies. The shortest buoyancy lag time was observed in F8 was 20 sec with more total buoyancy time 20 hrs as shown in table no.3.

The accelerated stability studies were carried out according to ICH guidelines optimized formulation F8 was packed in strip of aluminum foil and this packed formulation was stored in stability chamber maintained at 40^{o}C and 75% RH (Zone III conditions as per ICH Q_1 guidelines) for 1 month. The microsphere were evaluated before and after 1 month for change in appearance and *In vitro* release.

After a period of one month, the sample were observed for any change on appearance. It was observed that microsphere that microsphere was devoid of any change in color or appearance of any kind of spot on it. It was also noted that microsphere was free of any kind of microbial or fungal growth or bad odour. The drug content of formulation was found to be 94% which shows there was small decrease in drug content but

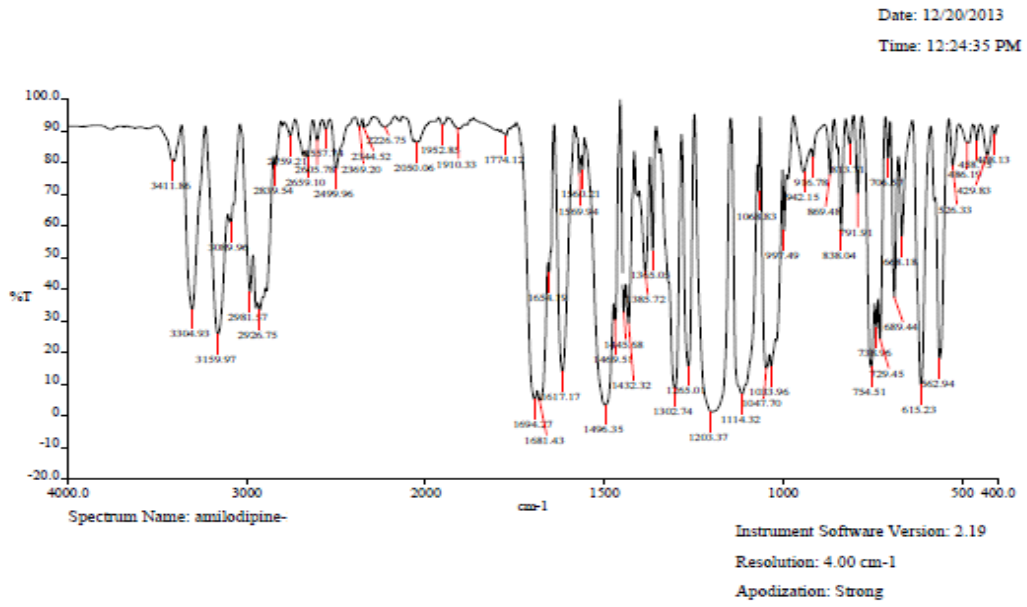
difference is insignificant. *In vitro* dissolution data of optimized formulation F8 during stability studies at 40°C and 75% RH for 1 month is tabulated in table 4.

CONCLUSION

Gastroretentive floating drug delivery system offers simple and practical approaches to achieve increased gasteic residence and to modify drug release profile essential for controlled, site specific and localized drug action. IR identification results of drugs indicate the purity of drug. IR spectra of pure drug and with the excipients are identical and do not show any incompatibility, thus the excipients are compatible with the drug. Lower values of angle of repose below 30 indicate good flow properties of microsphere. All prepared microsphere were found to be in circular shape with no cracks. The drug polymer ratio was found to influence the release of drug and floating characteristics of microsphere. Formulation F8 showed satisfactory results with short buoyancy lag time, long total buoyancy time and controlled drug release up to 8 hrs. The drug release data were explored for the type of release mechanism followed. The best fit with highest determination R^2 coefficient was shown by Zero Order model. Drug content, physical appearance and comparable release profile of floating microsphere F8 after 1 month indicates stability of the formulation.

Table1: Formulation of Amlodipine Besylate Microsphere

Ingredients	Formulation Code							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Amlodipine besylate (g)	1	1	1	1	1	1	1	1
Ethyle Cellulose (g)	0.5	1	1.5	2	2.5	3	3.5	4
HPMC (g)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Ethanol (ml)	25	25	25	25	25	25	25	25
Dichloromethane (ml)	25	25	25	25	25	25	25	25
(1%w/v)SLS (ml)	100	100	100	100	100	10	10	100



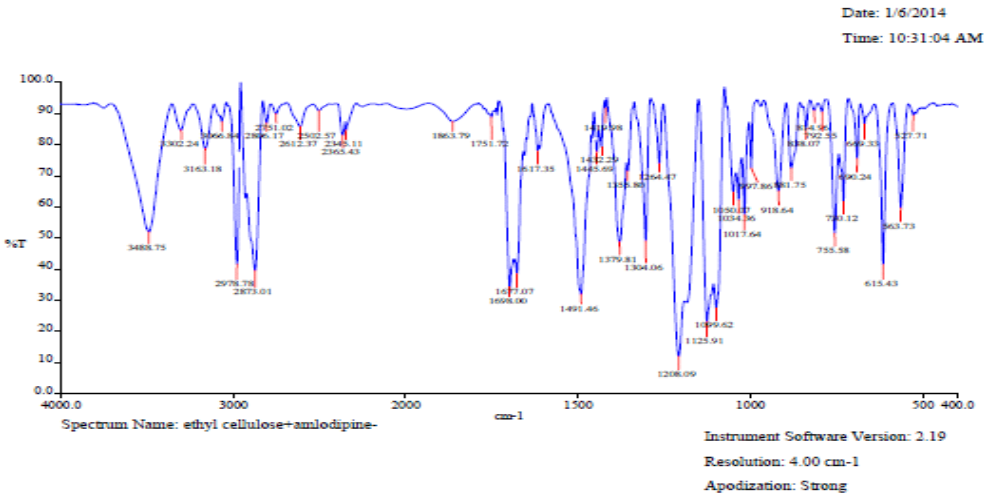


Figure1: IR Spectra of pure AB, AB+Etylecellulose, AB+HPMC

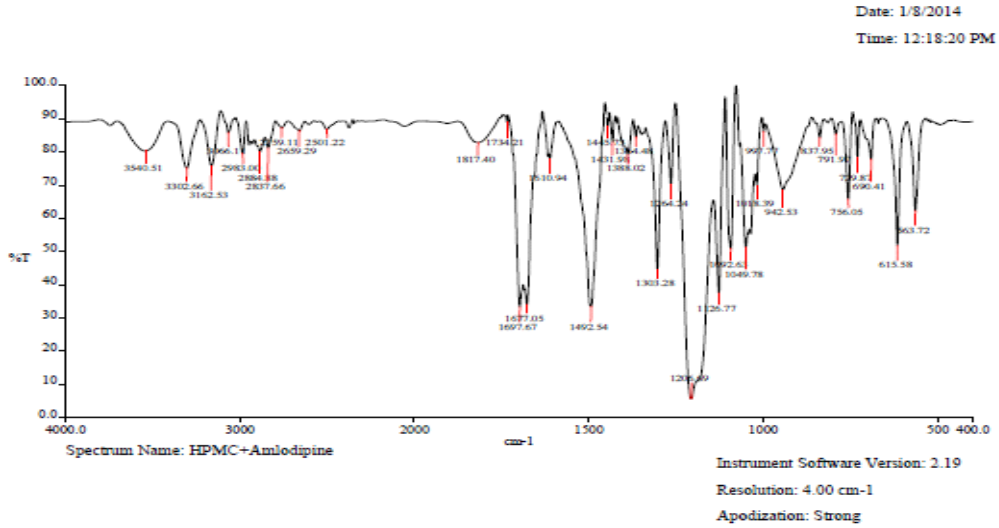


Figure 2: Comparison of *in vitro* Drug release profile of optimized formulation F8 at initial day and after 1 month during stability studies

Table 1: Bulk Density, Tapped density, Angle of Repose, Carr's index, Housner's ratio

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's index (%)	Housner's Ratio
F1	0.620±0.073	0.757±0.062	39.69±0.664	18.09±0.064	1.25±0.061
F2	0.606±0.024	0.740±0.056	38.86±0.754	18.18±0.036	1.24±0.064
F3	0.609±0.043	0.735±0.046	38.65±0.612	17.14±0.014	1.20±0.023
F4	0.625±0.036	0.714±0.065	34.99±0.534	12.46±0.025	1.17±0.046
F5	0.641±0.035	0.769±0.074	32.00±0.633	16.64±0.064	1.15±0.018
F6	0.666±0.065	0.769±0.078	29.68±0.732	10.30±0.012	1.11±0.019
F7	0.625±0.068	0.724±0.058	28.81±0.550	13.67±0.051	1.10±0.014
F8	0.646±0.076	0.714±0.026	27.92±0.80	9.52±0.026	1.10±0.003

Table 2: Particle Size, %Yield of Microsphere, Entrapment Efficiency, Floating Ability

Formulation	Mean Particle Size (µm)	% Yield	Entrapment Efficiency (%)	Floating Ability (%)
F1	186	47	27	72
F2	198	56	30	78
F3	256	67	45	81
F4	279	72	50	85
F5	326	79	57	89
F6	372	79	70	92
F7	416	78	81	95
F8	480	90	95	96

Table 3: Swelling index, Floating lag time and total floating time of floating microsphere

Formulation	Swelling index (%)	Floating lag time(s)	Total Floating Time (Hrs)
F1	82	30	9
F2	92	33	10
F3	158	35	12
F4	161	29	13
F5	175	25	16
F6	178	22	17
F7	182	20	19
F8	195	20	20

Table 4: Initial %CDR and after 1 month %CDR

Time	Initial % CDR	After 1 Month % CDR
1	12	11
2	30	27
3	43	39
4	58	57
5	69	65
6	79	78
7	89	85
8	97	94

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