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Formulation and Evaluation of Amlodipine Besylate Floating Tablets

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ABSTRACT

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. The objective of this work is to develop GFDDS of amlodipine, employing swellable polymer hydroxypropylmethylcellulose (HPMC) of different viscosity grades (K100M and K4M) and sodium bicarbonate as gas generating agent, and to evaluate the effect of polymer concentration on amlodipine release from the prepared GFDDS. Seven formulations of floating tablets of amlodipine besylate using the polymer of different grades namely Hydroxy Propyl Methyl Cellulose K100M (HPMC K 100 M), and Hydroxy Propyl Methyl Cellulose K4 M (HPMC K 4M) in different concentrations were prepared separately by direct compression method. The developed formulations were evaluated for pre compression and post compression properties. When comparing all the formulations, F3 with polymer HPMC K 100M showed a better controlled drug release of 67.6% at the end of 12 hours when compared to all other formulations. It was observed that Amlodipine Besylate floating tablets prepared by using hydrophilic controlled release polymer HPMC K100M can able to float for maximum duration of time and released the drug at a slow and controlled manner. The percentage of drug release rate depends on the percentage of polymer used.

Keywords: Amlodipine Besylate, HPMC K100M, Gastroretentive dosage forms.

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INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process [1].

(GRT) of drugs. Minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

Gastroretentive floating drug delivery systems (GFDDS) can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs which are less soluble in some fluid medium. The gastric emptying time has been reported to be from 2 to 6 hours in humans in the fed state. [1]

Amlodipine is long acting calcium channel blocker and used in the treatment of hypertension, and chronic stable angina. In hypertension or angina, initially 5 mg. once daily and adjusted to maximum dose 10 mg once daily dose of Amlodipine is given orally. Amlodipine has maximum solubility in acidic pH [2].

In present work, floating tablets of different formulations were developed with an objective of achieving 24 hrs floating and drug release time and floating tablet was compared with marketed formulation of Amlodipine besylate for drug released time.

The objective of this work is to develop GFDDS of amlodipine, employing swellable polymer hydroxypropylmethylcellulose (HPMC) of different viscosity grades (K100M and K4M) and sodium bicarbonate as gas generating agent, and to evaluate the effect of polymer concentration on amlodipine release from the prepared GFDDS.

MATERIALS AND METHODS

Materials

Amylodipine Besylate**,** Hydroxy Propyl Methyl Cellulose K100M, K4M was obtained as gift sample form Sun Pharmaceuticals, Chennai, Polyvinyl Pyrrolidine, Talc, Magnesium stearate, Lactose received from Loba Chemie Pvt. Ltd, Mumbai.

Experimental

Preparation of Standard Curve

UV sphectrophotometric method was developed for the quantitative estimation of Amlodipine Besylate. 50 mg of amlodipine besylate is dissolved in sufficient quantity of methanol and makes upto 50 ml with methanol. From this 5 ml was pipetted out and make upto 50 ml with methanol. From this 20 ml was taken and make up to 100 ml with pH 1.2 buffer. From this aliquots of 2, 4, 6, 8, 10, 12, 14 and 16 (equivalent to 2, 4, 6, 8, 10, 12, 14 and 16 µg/ml) were pipetted out to 100ml standard flask separately and make up to 100 ml with pH 1.2 buffer. The absorbance of the solution was determined in UV-Visible Spectrophotometer at 237 nm using buffer pH 1.2 as blank.

Preparation of Amlodipine Besylate Floating Tablets

Seven formulations of Amlodipine Besylate were prepared. For the first six formulations pure amlodipine Besylate, sodium bicarbonate, HPMC K 100M and HPMC K4M with different concentrations, Polyvinyl Pyrrolidone(PVP K30), sodium bicarbonate and lactose were mixed together in mortar and pestle to get uniform mixture. Then the powder mixture was passed through sieve no. 100. The powder blend was subjected to different preformulation studies namely Bulk density, Tapped Density and Angle of Repose. After that the powder blend was mixed with talc and magnesium stearate uniformly and then compressed in to tablets by direct compression method.

Pre compression properties

Angle of Repose [3]

Angle of Repose is defined as maximum angle possible between the surface of the pile of powder and horizontal plane. To assess the flow property of powder or granules, the angle of repose of the powder or granules was determined by fixed funnel method. The height of the funnel was adjusted so that the tip of the funnel just touches the apex of the heap of the powder or granules above a paper that was placed on a flat horizontal surface. Accurately weighed powder blend was allowed to flow through the funnel freely on to the surface of the paper to form a cone shaped file. The diameter of the powder cone (d) and the height (h) of the pile were noted. From the diameter, radius r was calculated. The angle of repose (**Error! Reference source not found.**) was calculated using the following formula:

tan**Error! Reference source not found.**= h/r or **Error! Reference source not found.**= $\tan^{-1}$ (h/r)

While there is some variation in the qualitative description of powder flow using the angle of repose, much of the pharmaceutical literature appears to be consistent with the classification by Carr in the table given below. With an angle of repose of 25-40 degrees that can be used for manufacture satisfactorily. When the angle of repose exceeds 50 degrees, the flow is rarely acceptable for manufacturing purposes.

Bulk Density and Tapped Density [4]

Bulk density is the ratio between a given mass of powder or granules and its bulk volume. Tapped density is the ratio between a given mass of powder or granules and the volume of powder or granules after tapping. An accurately weighed quantity of powder(W) is passed through 250ml measuring cylinder and its intial volume(v_o) is noted.then the cylinder is tapped on the wooden surface from height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume (until a constant Volume) was obtained (V_f). The bulk density and tapped density are calculated by using the following formula.

Bulk Density = w/vo

Tapped Density = w/v_f

Compressibility Index and Hausner Ratio [5,6]

The compressibility index and the closely related Hausner Ratio have become the simple, fast and popular methods of predicting powder flow characteristics in recent years. The compressibility index and Hausner ratio are determined by measuring both the bulk volume and tapped volume of a powder.

Post compression properties

Evaluation of Amlodipine Besylate Floating Tablets

To design tablets and later to monitor tablets production, quality, quantitative evaluation, assessments of tablets physical, chemical, and bioavailability properties must be made.

The above formulated tablets of Amlodipine Besylate were evaluated by the following studies

Hardness test or Crushing Strength [7]

Hardness test are made during tablet production, which is now more appropriately called crushing strength determinations and are used to determine the need for pressure adjustement on tablet machine.

The tablet was placed horizontally in contact with lower plunger of the Mosanto hardness tester and zero reading was adjusted. The tablet was then compressed by forcing the upper plunger until the tablets breaks. This force was noted.

Friability test [8]

Friability is the loss of weight of tablet in the container/package, due to the removal of fine particles from the surface. To determine the friability Roche friabilator is used. Ten tablets were weighed(w_1) and placed in the apparatus and allowed to turn with the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed(w_2) and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as percentage. Generally acceptable weight loss is not more than 1% of the weight of the tablet. Broken or smashed tablets should be avoided. The percent friability was determined using the following formula :

$$\text{Friability} = \frac{(w_1 - w_2)}{W_1} \times 100$$

Uniformity of weight or Weight variation test [9]

Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted. From the weight of all tablets average weight was calculated. The individual weight were compared with the average weight. Not more than two of the tablets must differ from the average weight by the percentages stated in table below. The percentage deviation was calculated by using the following formula :

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Estimation of drug content [10]

Each unit in a batch should have active substance content within a narrow range around the label claim, to ensure the consistency of dosage units. Dosage units are defined as dosage forms containing a single dose or a part of a dose of an active substance in each dosage unit. The term “uniformity of dosage unit” is defined as the degree of uniformity for substance among dosage units. The test for content uniformity is based on the assay of the active medicament is within the limit (±10%) in the formulation.

Two tablets were taken in a mortar and powdered by crushing. Powder equivalent to 10 mg of Amlodipine Besylate was weighed and dissolved in 100ml of pH 1.2 buffer. From this 1ml was pipette out and make upto 10 ml with pH 1.2 buffer. Then the absorbance was measured using UV-visible Spectrophotometer at 237 nm. This was noted as absorbance of sample. Similarily absorbance of standard also determined by taking 10 mg of pure amlodipine besylate by adopting the same procedure. Drug content can be determined by using the formula:

$$\frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 100$$

Thickness of tablets [11]

The tablets should have uniform thickness. Thickness was measured by using vernier calipers. To get required thickness before compression these values are checked and adjusted.

Buoyancy determination [12]

Buoyancy Lag Time (BLT)

The time interval between the introduction of Amlodipine besylate floating tablets into the dissolution medium and its flotation to the top of dissolution medium was termed as BLT.

BLT may be explained as a result of time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for the entrapment of CO_2 generating in situ. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the matrix.

Duration of Buoyancy (DB)

The duration upto which the dosage form floats over the dissolution medium was termed as DB.

Duration of buoyancy of tablet depends on the amount of sodium bicarbonate involved in CO_2 formation, for a floating system. In order to initiate rapid generation of CO_2 and allowed to release CO_2 to promote floating, the ideal matrix of coating material should be highly permeable.

Method: The buoyancy lag time and duration of buoyancy were carried using USP 24 type II dissolution apparatus in 900 ml of 0.1N HCl at 37 ±1 ^{o}C

Swelling index [12]

The swelling index studies were carried out in petri dishes using simulated gastric fluid (pH 1.2).The randomly selected tablets from each formulation were weighed individually (W_0) and placed separately in 50 ml of simulated gastric fluid (pH 1.2) in petri dish. After 8 hours swollen tablet was removed from the medium the excess water was blotted with filter paper and immediately weighed (w_1). The swelling index (SI), (expressed as a percentage) and was calculated from the following equation:

$$SI = \frac{W_1 - W_o}{W_0} \times 100$$

IR spectral Analysis [13]

IR spectral analysis for drug, polymer and excipients was carried out. The peaks and patterns produced by the pure drug were compared with the peaks and patterns of the polymer and excipients. The results are presented in Tables 8-11 and figures 2-5.

Dissolution rate studies

***In-vitro* drug release [14]**

In-vitro release study of F1 to F7 formulations and a marketed sample of Amlodipine besylate were carried out in the dissolution test apparatus (USP Type 2). The tests were carried out in 900 ml of dissolution medium in 1.2 pH buffer for 12 hrs at 50 rpm at 37± 0.5^{o}C. 5 ml of aliquot were withdrawn at different time intervals (1-12 hrs) and diluted to 10 ml with pH 1.2 buffer and the percentage drug release was calculated by using UV spectrophotometer at 237 nm. 5 ml of sample was replaced after each withdrawal to maintain the same volume of dissolution medium.

Stability studies [15]

The optimized formulation (F3) was subjected to stability studies in stability chamber (Remi Pvt.Ltd Chennai) for 3months as per the International Conference of Harmonization (ICH) guidelines. Stability Study was aimed at determining the result of aging under various storage conditions on the formulated floating tablet. It was carried out to evaluate the stability of the drug, Amlodipine Besylate in floating drug delivery system. The tablets were stored at 4^{o} ± 2^{o}C in refrigerator, 27^{o} ± 2^{o}C in room temperature and 40^{o}± 2^{o}C at 75% ± 5% RH in stability chamber for 45 days. The samples were taken periodically at the intervals of 15th, 30th, and 45th days and evaluated for drug content and in vitro release studies.

RESULTS AND DISCUSSION

The present study was to formulate Amlodipine Besylate floating tablets in seven different batches F1 to F7 using polymer Hydroxy propyl methyl cellulose of two different grades (HPMC K100M and HPMC K4M) in different concentrations and one formulation without polymer. All the formulations were prepared by direct compression method. Before compression the powder blend was subjected to various evaluation studies such as Bulk density, Tapped density, Angle of repose, Compressibility index and Hausner ratio. After compression, evaluation tests of tablet such as hardness, weight variation, friability, buoyancy determination, swelling index and content uniformity, IR spectral analysis, in vitro-drug release studies and stability studies were carried out. All results are presented in appropriate tables and figures.

Evaluation of Amlodipine Besylate Powder blend

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Angle of Repose [3]

The angle of repose of all the formulations was within 35^0. The result showed that the angle of repose was $32^0 07' - 34^0 55'$. It proved that the flow properties of all formulations are good.

Bulk density [4]

By using measuring cylinder the bulk density of all formulations was measured. The bulk density was found in the range of 0.507-0.624. It is within the acceptable limits.

Tapped density [4]

Tapped density of all formulations also measured by measuring cylinder and values were determined. The tapped density was found in the range of 0.572 - 0.706 gm/cm^3. It showed that tapped density is within the acceptable limit.

Compressibility Index [5]

The granules show good flow character, if the compressibility index is between 11 - 15. Here all the formulations exist in the range between 11.0 -13.16. It indicates that the granules show good flow character.

Hausner Ratio [6]

The result showed that Hausner ratio of all the formulations was between 1.12-1.14. If the Hausner ratio lies between 1.12-1.18, it shows good flow behavior of the granules or powder. The results indicate good flow property of the powder blend. The results were tabulated in table no.1.

Evaluation of Amlodipine Besylate Floating Tablets

The formulated Amlodipine Besylate Floating tablets were evaluated and the results are shown in table no.-2.

Hardness [7]

By using Monsanto hardness tester, the hardness of the tablets was tested and the results are tabulated in the Table-7. The hardness of the tablets of all formulations was within the range of 6.0-6.2 Kg/cm^2. So all the formulations passes the hardness test.

Thickness [11]

Thickness of the tablet is measured by using Vernier callipers. The result showed that the tablets of all formulation showed uniform thickness.

Friability [8]

The results are shown in table-7. A maximum weight loss was not more than 1% of the weight of the tablet being tested during the friability test. The friability of all the formulated tablets was within 1%. So all the formulated tablets passed the test.

Estimation of drug content [10]

Equivalent to 10mg of Amlodipine Besylate from each formulations were dissolved in pH 1.2 buffers and make upto 100 ml with pH 1.2 buffers. From this solution 1ml was taken and make up to 10 ml with pH 1.2 buffer. The resulting solution is estimated spectrophotometrically at 237nm. This was noted as absorbance of sample. The absorbance of standard was also estimated in a similar manner by taking 10mg of pure drug.. Drug content was calculated by using the formula.

$$\text{Percentage of drug content} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 100$$

Buoyancy Determination [12]

Buoyancy Lag Time (BLT): If Buoyancy Lag Time is less than 15 min, it shows good floatability. The Buoyancy Lag Time is in between 30-180sec for all formulations.

Duration of Buoyancy (DB): Duration of Buoyancy (DB) of all the first six formulations is more than 20 hours. Formulation without polymer has Duration of Flotation only upto 2 hours

Swelling Index [12]

Swelling Index was within the range of 51- 69% for the formulations F1-F6. For F7, tablets did not swell well and swelling index was 32%.

Infrared Spectral Studies

The IR spectrascopic studies of pure Amlodipine Besylate and higher proportion of the polymers HPMC K100M and HPMC K4M were carried out to study the interaction between the drug and polymers used. The results are shown in figures 1,2, 3 and 4 and tables 3,4,5 and 6.

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TABLE NO 1: EVALUATION OF POWDER BLEND OF AMLODIPINE BESYLATE

S.NO	parameters	PHYSICAL CHARACTERISTICS OF AMLODIPINE BESYLATE POWDER BLEND *						
		F1	F2	F3	F4	F5	F6	F7
1	angle of repose (Error! Reference source not found.)	$32^0 64' \pm 0.05$	$33^0 02' \pm 0.03$	$32^0 24' \pm 0.02$	$33^o 10' \pm 0.02$	$32^0 07' \pm 0.02$	$32^0 64' \pm 0.03$	$34^0 55' \pm 0.03$
2	bulk density (gm/cc)	0.507 ±0.01	0.614 ±0.05	0.624±0.06	0.592±0.09	0.554±0.06	0.568±0.05	0.509±0.05
3	tapped density (gm/cc)	0.572 ±0.01	0.690 ±0.06	0.706 ±0.04	0.676 ±0.05	0.625 ±0.07	0.640 ±0.09	0.576 ±0.08
4	compressibility index (%)	11.3 ± 0.76	11.0 ± 0.54	11.6 ± 0.64	12.4 ± 0.33	11.36 ±0.54	11.25 ±0.72	13.16 ±0.76
5	hausner's ratio	1.12 ± 0.15	1.12 ± 0.28	1.13 ± 0.12	1.14 ± 0.87	1.12 ± 0.35	1.12 ± 0.54	1.13 ± 0.48

* All values are expressed as mean ± standard deviation, n=3

Table No 2: Evaluation of Floating Tablets of Amlodipine Besylate

S.No	PARAMETERS	PHYSICAL CHARACTERS OF AMLODIPINE BESYLATE FLOATING TABLETS*						
		F1	F2	F3	F4	F5	F6	F7
1	Hardness(kg/cm^2)	6.1±0.11	6.0 ± 0.20	6.1 ± 0.25	6.0 ± 0.34	6.0 ± 0.20	6.2 ± 0.42	6.1± 0.25
2	Thickness(mm)	3.5 ± 0.05	3.6 ± 0.03	0.92 ± 0.04	0.58 ± 0.02	0.55 ± 0.04	0.53 ± 0.03	0.96 ± 0.05
3	Uniformity of Weight (mg)	400±2.08	400 ±0.57	398± 1.00	399 ±2.05	400 ±0.57	397±0.57	399 ±2.00
4	Friability(%)	0.98 ± 0.06	0.96 ± 0.08	0.92 ± 0.05	0.98 ±0.04	0.95 ± 0.04	0.93 ± 0.05	0.96 ± 0.05
5	Drug Content (%)	99.98 ± 0.25	93.18 ±0.49	96.15 ±0.35	99.99 ±0.64	98.60 ±0.36	97.46 ± 1.2	93.01 ± 0.65
6	Buoyancy Lag Time (seconds)	30 ± 4.58	45 ± 2.68	56 ± 3.47	90 ± 5.10	120 ± 5.03	180 ± 1.65	126 ± 2.84
7	Duration of Buoyancy (hrs)	>20	>20	>20	>16	>16	>16	Upto2hrs
8	Swelling Index (%)	64 ± 0.23	66 ± 0.48	69 ± 0.65	51 ± 0.38	56 ± 0.45	59 ± 0.37	32 ± 0.44

*All values are expressed as mean ± standard deviation, n=3

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Weight Variation Test [9]

From the results of weight variation test, all the weights of formulated tablets were within 397- 400mg. So all the tablets passed the weight variation test.

Table No 3: IR SPECTRUM VALUE OF PURE AMLODIPINE BESYLATE

S.No.	Wave number (cm^{-1})	Functional groups present
01	3298.28	NH stretching of primary amino group
02	3157.47	0H stretching of SO_3H
03	2985.52	CH stretching of benzene ring
04	1685.79	C=O stretching of carbonyl group
05	1614.42	C=C stretching of carbonyl group
06	1201.65	C-S stretching of so_3H
07	1099.43	NH stretching of secondary amino group
08	1026.13	C-O stretching of carbonyl group
09	754.17	OH bending of SO_3H

Table No 4: IR SPECTRUM OF PURE HPMC K 100M

S.No	Wave number(cm^{-1})	Functional groups present
01	3456.44	OH stretching of ether
02	2926.01	CH stretching of aromatic ring
03	1651.07	C=O stretching of carbonyl group
04	1463.97	C=C stretching of carbonyl group
05	1120.64	C-O-C stretching of aromatic ring
06	1060.85	C-O stretching of aromatic compound
07	947.05	Overtone C-H deformation

Table No 5: IR SPECTRUM OF AMLODIPINE + HPMC K 100M (1:8)

S.No	Wave number (CM^{-1})	Functional groups present
01	3471.87	OH Stretching of ether
02	3302.13	NH stretching of primary amino group
03	2935.66	CH stretching of benzene ring
04	1685.79	C=O stretching of carbonyl group
05	1618.28	C=C stretching of carbonyl group
06	1203.58	C-S stretching of sulphonic acid
07	1099.43	NH stretching of secondary amino group
08	1028.06	C-O stretching of carbonyl group
09	754.17	OH bending of so_3H

Table No 6: IR SPECTRUM OF AMLODIPINE BESYLATE TABLET (F1)

S.No.	Wave number(cm^{-1})	Functional groups present
01	3527.80	OH stretching of so_3H
02	3379.29	NH stretching of primary amino group
03	2906.73	CH stretching of benzene ring
04	1670.35	C=O stretching of carbonyl group
05	1431.18	C=C stretching of carbonyl group

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06	1083.99	NH stretching of secondary amino group
07	1029.99	C-O stretching of carbonyl group
08	771.53	OH bending of so_{3H}

It showed that IR spectrum of pure Amlodipine Besylate and Amlodipine Besylate formulations containing higher proportion of polymers were similar fundamental peaks and pattern. The result proved that there were no interactions between the drug and polymers.

Figure No 1: IR SPECTRUM OF PURE AMLODIPINE BESYLATE

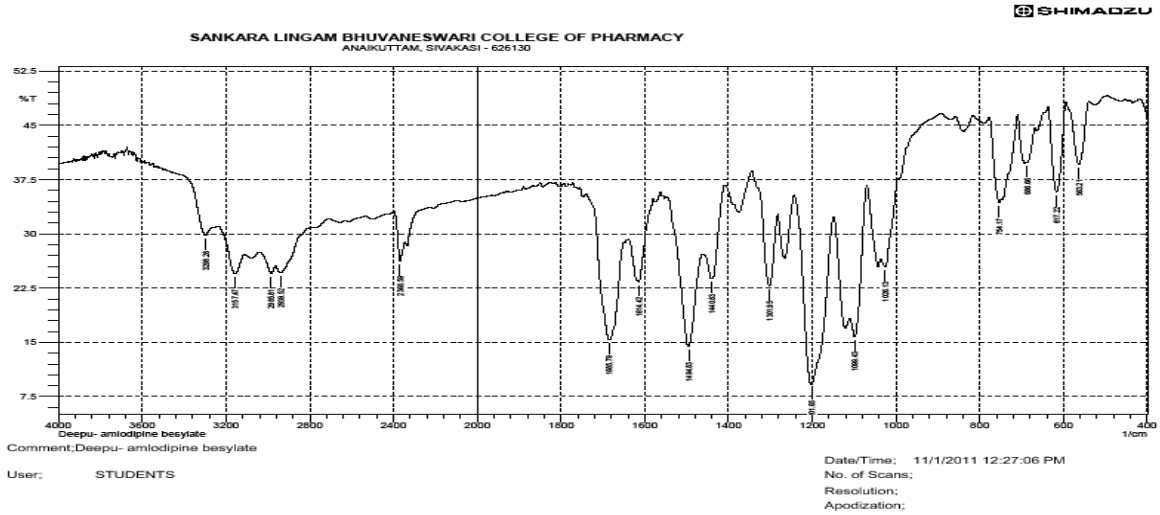

Figure no 2: IR SPECTRUM OF HPMC K100M

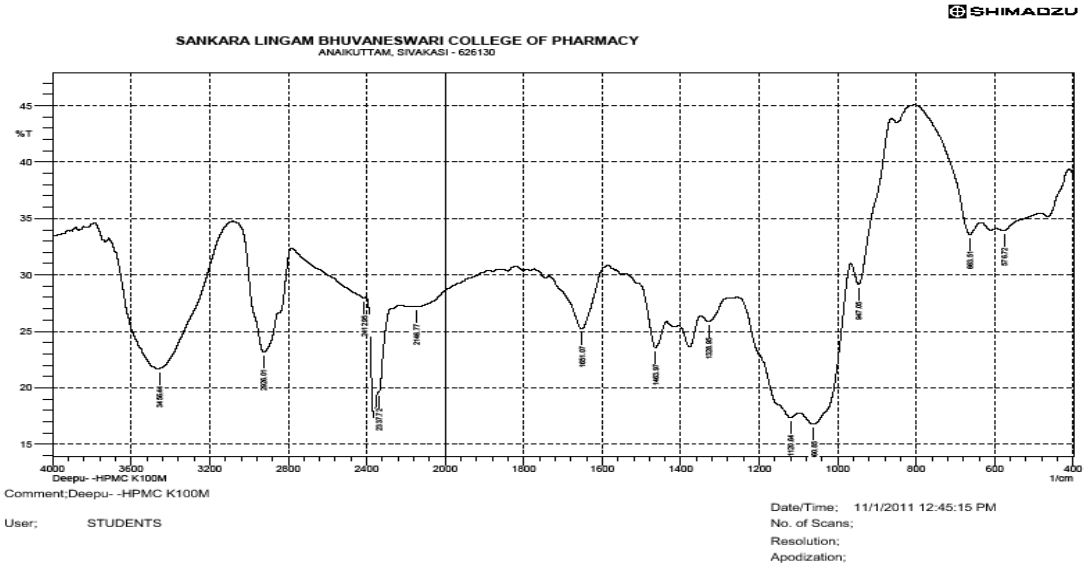

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Figure no: 3 IR SPECTRUM OF PURE AMLODIPINE BESYLATE + HPMC K100M (1:8)

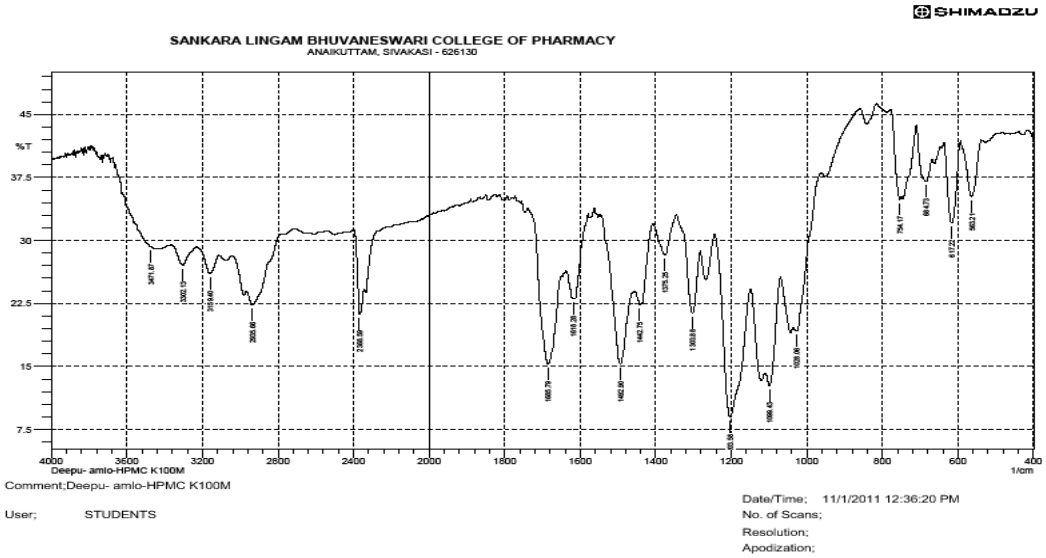
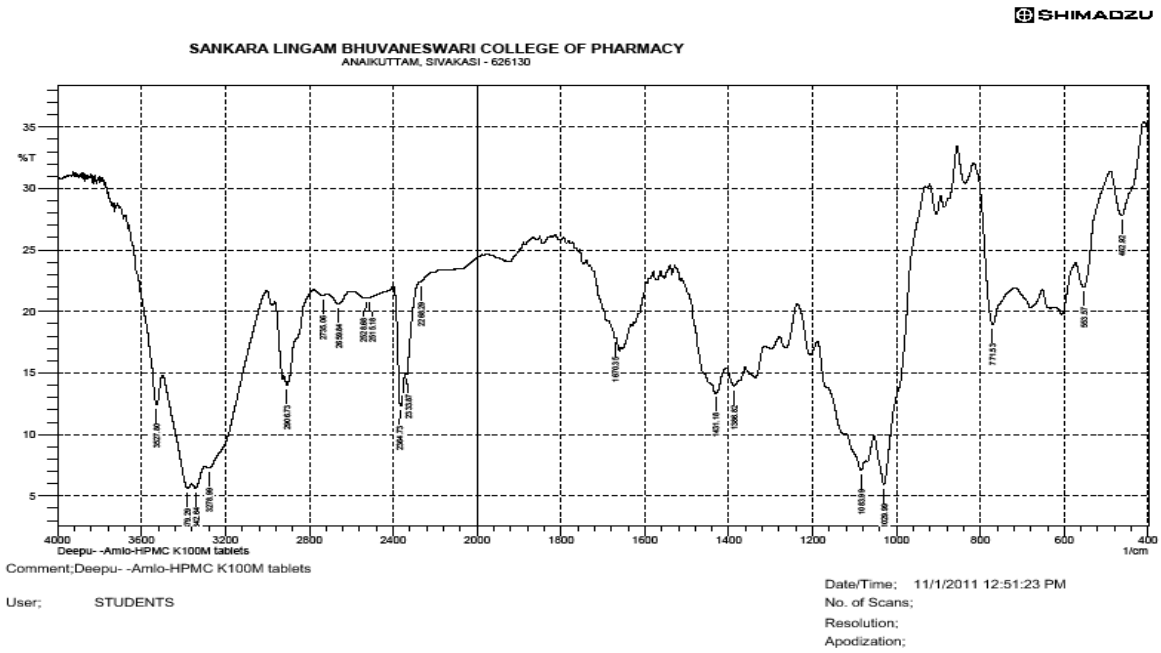


Figure no 4: IR SPECTRUM OF PURE AMLODIPINE BESYLATE + HPMC K100M TABLET



Dissolution Rate Studies

The dissolution rate studies were performed to evaluate the dissolution character of Amlodipine Besylate from floating tablets with polymer Hydroxy Propyl Methyl Cellulose (HPMC) of two different grades with three ratios. The drug release was compared with the marketed sample of Amlodipine Besylate and control (i.e drug without polymer). The results are presented in Table No.7 and 8 and in figure nos.5 and 6.

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Table No 7:DISSOLUTION STUDIES OF DRUG RELEASE FROM THE AMLODIPINE BESYLATE FORMULATIONS

Time (hrs)	CUMMULATIVE PERCENTAGE OF DRUG RELEASE FROM AMLODIPINE BESYLATE FLOATING TABLETS*						
	HPMC K 100M			HPMC K4M			Control
	F1	F2	F3	F4	F5	F6	F7
1	12.9±0.02	10.2±0.03	9.8±0.05	30.2±0.03	23.9±0.04	15.2±0.02	52.4±0.02
2	17.7±0.03	14.6±0.04	13.7±0.03	42.5±0.04	37.2±0.02	23.0±0.04	93.4±0.02
3	21.2±0.03	18.2±0.04	17.4±0.03	53.4±0.05	48.4±0.04	29.6±0.03	
4	27.2±0.02	23.2±0.03	21.2±0.05	65.6±0.02	59.6±0.03	41.7±0.04	
5	32.8±0.03	28.6±0.02	25.6±0.03	74.8±0.03	68.0±0.05	49.9±0.03	
6	46.2±0.02	40.2±0.04	36.8±0.05	81.5±0.04	74.6±0.02	58.6±0.03	
7	52.3±0.03	47.7±0.04	44.4±0.02	88.8±0.03	82.7±0.04	69.5±0.02	
8	57.8±0.04	53.8±0.02	49.6±0.03	94.7±0.02	89.1±0.05	82.0±0.05	
12	76.9±0.04	71.2±0.03	67.6±0.04	98.8±0.02	96.5±0.04	94.2±0.02	

*All values are expressed as mean ± standard deviation ,n=3

Table No 8: DISSOLUTION STUDIES OF AMLODIPINE BESYLATE MARKETED SAMPLE AND CONTROL (without polymer)

S.No	Time (mts)	Cumulative Percentage Drug Release*	
		Control (F7) (withoutpolymer)	Marketed sample
1	15	27.6±0.02	32.4±0.03
2	30	34.6±0.04	56.7±0.02
3	45	45.4±0.03	64.2±0.05
4	60	52.4±0.05	71.2±0.02
5	75	63.1±0.03	82.5±0.03
6	90	76.3±0.04	98.6±0.04
7	105	84.2±0.05	
8	120	93.4±0.03	

* All values are expressed as mean ± standard deviation, n=3

Figure No 5: Cummulative percentage of drug release from Amlodipine Besylate formulation

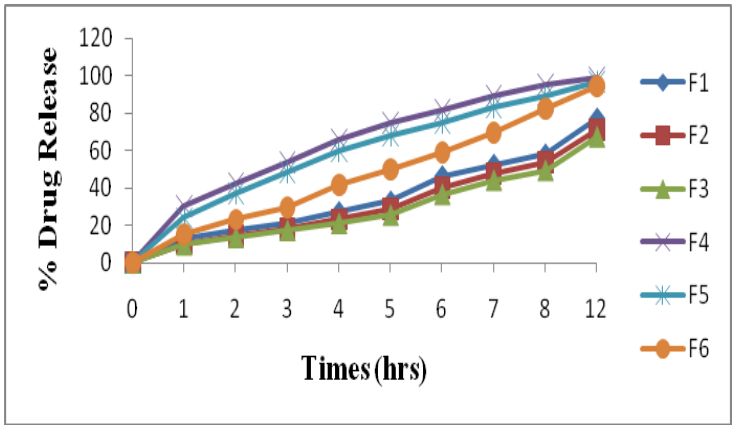

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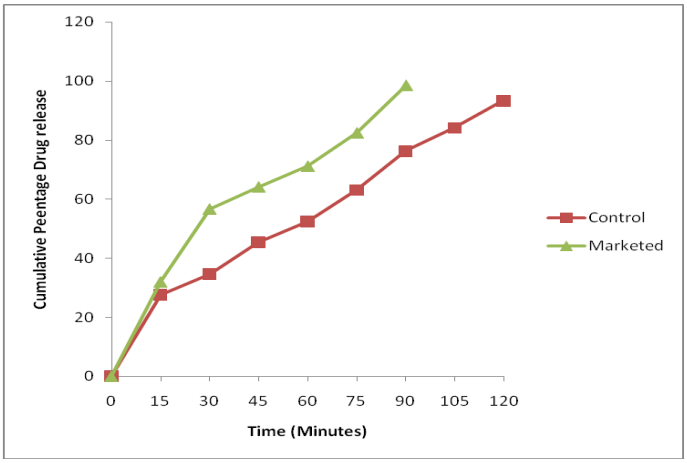
Figure No 6 : Cumulative Percentage Drug Release of Control (without polymer) And marketed sample



- The formulations F1, F2, F3, F4,F5 and ,F6 showed the percentage drug release of 76.9%,71.2%, 67.6%, using HPMC K100M and 98.8%, 96.5%, and 94.2% using HPMC K4M within 12 hours.
- Invitro dissolution studies of formulations F1 to F6 indicated that as the polymer concentration increases, there was a reduction in the drug release rate.
- Formulation containing higher HPMC viscosity grade (HPMC K100M) i.e F1 to F3 showed slower drug release (76.9%,71.2%,67.6%) when compared to the formulations with lower HPMC viscosity grades (HPMC K4M) i.e F4 to F6 (98.8%, 96.5% and 94.2%). This may be due to less water permeability of HPMC K100M than HPMC K4M. This result was in conformity with the reports of Manan et al [16].
- The percentage drug release of control F7 (drug without polymer) is found to be 93.4% in 120 minutes.
- The percentage drug release from the conventional Amlodipine Besylate tablet (Amlong) was found to be 98.6% in 90 minutes.
- Among all the formulations, formulation F3 containing drug-polymer ratio (1:8) prepared with HPMC K100M, showed promising result releasing 67.6% of drug in 12 hrs with a floating lag time of 56 seconds and duration of floating time is > 24 hrs.
- Floating property of the tablet is governed by the swelling (hydration) of the tablet, when it contacts with the gastric fluid which in turn results in increase in the bulk volume and pressure of internal voids in the centre of the tablet [17].
- As the concentration of HPMC increases, the swelling of the tablet increases, but the drug release decreases. It may be due to high concentration of HPMC forms a thick gel that retards the drug release [18].
- The results of dissolution studies revealed that the formulation F3 showed retarded drug release (67.6%) in controlled manner upto 12 hours
- The optimal formulation is F3 which exhibited optimal release pattern of drug (67.6%) upto 12hrs with afloating lag time of 56 sec and total floating time of 24 hrs

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was considered as the best optimized formulation among other formulations. Drug release from the optimized formulation (F3) followed zero order kinetics.

Stability Studies

Amlodipine Besylate floating tablets of optimized formulation (F3) were stored at refrigerator temperature ($4^{o}\pm2^{o}C$), room temperature ($27^{o}\pm2^{o}C$) and in accelerated temperature ($40^{o}\pm2^{o}C$) in stability chamber for 45 days.

At the end of 15, 30 and 45 days of storage, the tablets were observed for any changes in physical appearance, analyzed for drug content and subjected to in vitro release studies and the results are presented in Table No.10. There was no color change and the drug content was 95.93%. There was no change in vitro release (Table No.9). The results proved that the optimized formulation (F3) stored at different temperatures were found to be stable

Table No 9: Stability Studies Of Cumulative Percentage Of Drug Release From Floating Tablets Of Amlodipine Besylate F3 formulation (0ptimized Formulation)

S.NO	Time (in hrs)	Percentage of drug release (%) at different time interval*								
		$4^{o}\pm2^{o}C$			$27^{o}\pm2^{o}C$			$40^{o}\pm2^{o}C$		
		15 days	30days	45days	15days	30days	45days	15days	30days	45days
1	1	9.2±0.04	8.9±0.03	8.6±0.02	9.7±0.02	8.6±0.03	9.1±0.03	8.9±0.03	7.6±0.02	8.3±0.04
2	2	13.1±0.03	12.4±0.03	12.6±0.05	13.5±0.04	13.2±0.02	12.9±0.04	12.8±0.05	12.6±0.03	12.5±0.05
3	3	17.1±0.03	15.6±0.04	16.6±0.05	17.6±0.03	16.3±0.04	16.1±0.02	16.9±0.03	16.6±0.04	16.3±0.05
4	4	20.8±0.05	20.5±0.05	20.2±0.03	20.1±0.03	20.9±0.03	20.8±0.03	21.5±0.02	20.2±0.04	19.8±0.03
5	5	25.1±0.05	24.8±0.03	24.5±0.04	24.4±0.04	23.2±0.02	24.9±0.04	24.9±0.04	24.5±0.05	24.3±0.04
6	6	36.4±0.03	36.04±0.03	35.9±0.04	36.7±0.05	35.4±0.03	36.2±0.02	36.1±0.04	36.2±0.05	35.6±0.03
7	7	44.1±0.03	43.9±0.03	43.6±0.05	42.3±0.04	43.7±0.04	43.5±0.04	43.9±0.03	43.6±0.04	42.2±0.04
8	8	49.1±0.04	48.8±0.03	48.5±0.03	48.5±0.02	47.2±0.03	49.01±0.04	48.7±0.03	46.4±0.05	46.1±0.05
9	12	67.4±0.02	72.4±0.04	69.03±0.03	65.6±0.03	66.4±0.03	65.9±0.04	66.1±0.02	66.8±0.05	67.2±0.04

*All the values are expressed as mean ± standard deviation , n=3

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Figure No 7: Zero order release from Amlodipine Besylate Floating Tablets

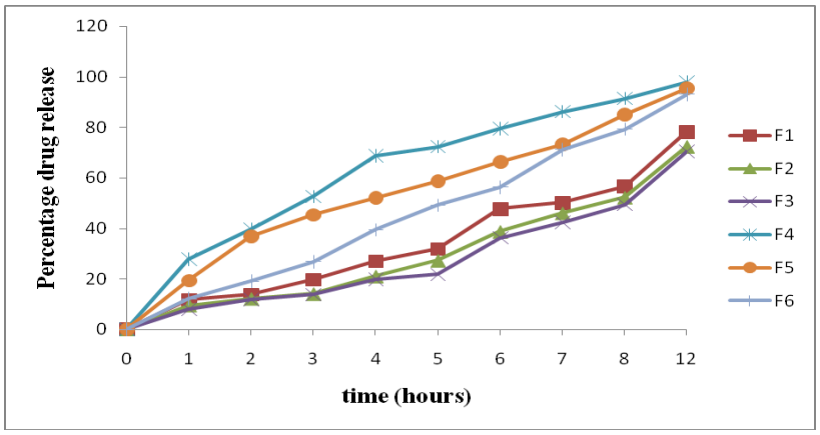

Figure No 8 : First Order Release Profile from Amlodipine Besylate Floating Tablets

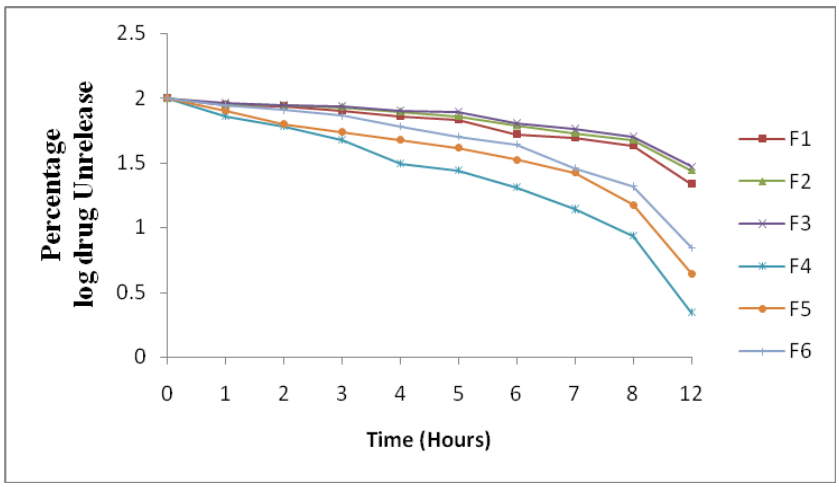

Figure No 9: Higuchi's release profile from amlodipine besylate floating tablets

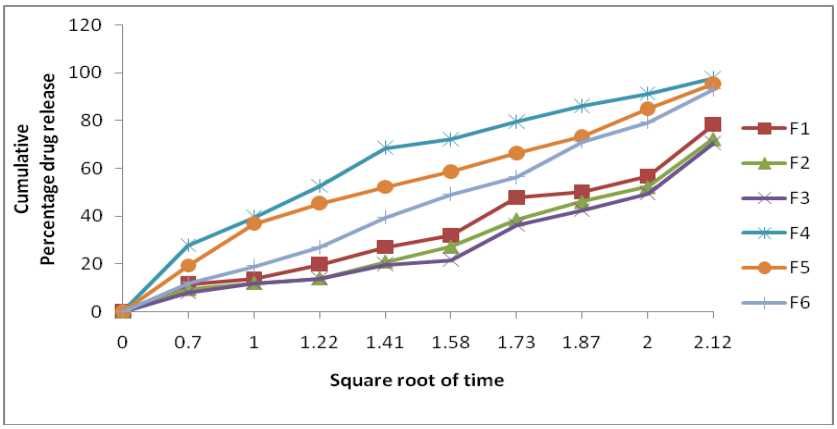

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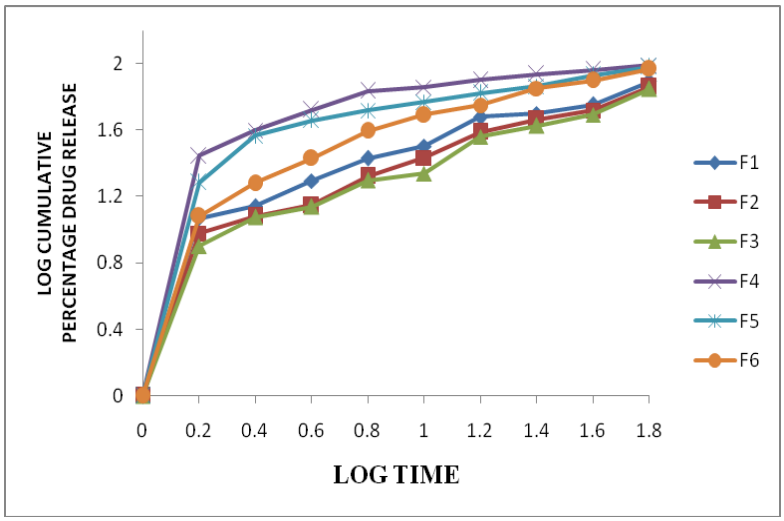
Figure No 10: Korsmeyer- peppas profile from Amlodipine Besylate Floating Tablets



SUMMARY AND CONCLUSION

The objective of present study was to develop floating tablets of Amlodipine Besylate in order to achieve an extend retention in the stomach which may provide increased absorption and thereby increase the bioavailability.

- Tablets were prepared by direct compression and evaluated for hardness test, friability test, thickness test, uniformity of weight, drug content estimation and swelling index. All the parameters were passed the test.
- All the formulations showed the buoyancy lag time of 30-180 sec and duration of buoyancy was greater than 24 hours in F1-F3 and greater than 16 hours in F4-F6 . It was found that all formulations showed good floatability.
- When comparing all the formulations, F3 with polymer HPMC K 100M showed a better controlled drug release of 67.6% at the end of 12 hours when compared to all other formulations.

CONCLUSION

There has been a number of floating drug release systems for various drugs investigated to improve the bioavailability and compliance. Clinical evaluation generally showed improvement in treatment with extended release dosage forms.

In the present investigation, floating tablets of Amlodipine Besylate can be developed to enhance gastric residence time and thereby improve its bioavailability. More over the frequency of administration can be reduced. It was observed that Amlodipine Besylate floating tablets prepared by using hydrophilic controlled release polymer HPMC K100M can able to float for maximum duration of time and released the drug at a slow and controlled manner. The percentage of drug release rate depends on the percentage of polymer used. The developed system offers a simple and novel technique for Gastric retentive drug delivery system. Such

work can be further extended using some other controlled release polymers for drug delivery. Further, clinical investigation of Amlodipine Besylate floating tablets in human volunteers may prove the suitability of floating typed formulations. Such an attempt will be useful to release Amlodipine Besylate floating drug delivery system in the market in the near future.

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