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RESEARCH ARTICLE

Formulation and Evaluation of Gastroretentive drug delivery system 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. Twevel 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 formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms. Among all the formulations, formulation F12 containing drug prepared with HPMC K4M and carbopol, showed promising result releasing 98.8% of drug in 12 hrs with a floating lag time of 56 seconds and duration of floating time is 12hrs.

Keywords : Amlodipine Besylate, HPMC K100M,

INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968 [1]. It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include, floating drug delivery systems (FDDS), high density DDS, muco-adhesive systems, swelling and expanding DDS, modified shape systems, and other delayed gastric devices. Floating drug delivery systems, also called as hydrodynamically balanced system, is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of small intestine, drugs acting locally in the stomach and for the drugs that are poorly soluble or unstable in the intestinal fluid.

Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate. 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. one daily and adjusted to maximum dose 10 mg one daily dose of Amlodipine is

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given orally. Amlodipine has maximum solubility in acidic pH. Amlodipine has some adverse effect such as nausea, abdominal pain. Effervescent floating tablet of Amlodipine besylate retain in stomach improves solubility, bioavailability, reduces drug waste and decrease side effect such as gastric irritation and nausea [2].

Materials and Methods:

Amlodipine Besylate, Hydroxy Propyl Methyl Cellulose, K100M, Hydroxy Propyl Methyl Cellulose, K4M, Carbopol, Xanthanegum, Polyvinyl Pyrrolidine was provided as a kind gift from Sun Pharmaceuticals, Chennai. Lactose and Talc were purchased from E Merck (India) Ltd, Mumbai. Magnesium stearate, sodium bicarbonate and citric acid were purchased from SD Fine Chem. Ltd. Mumbai, India. All other ingredients used were of laboratory grade.

Preparation of the Amlodipine Besylate floating tablets

All the ingredients (except glidents and lubricant) as shown in Table 1 were weighed separately, mixed thoroughly in poly bag for 10 minutes to enusure uniform mixing and the mixture was passed through sieve no.60. Granulation was done with a solution of calculated quantity of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through sieve no. 12, and dried at 45-55°C for 2 hours. The dried granules were sized by sieve no. 18 and mixed with magnesium stearate and talc. The blend thus obtained was compressed (8 mm diameter, flat punches) using a single station compression machine (Cadmach, Ahmedabad, India).

Flow properties of granules

Angle of repose was determined using fixed funnel method. A glass funnel is held in place with a clamp on a ring support over a glass plate. Approximately 1gm of power is transferred in to funnel keeping the orifice of the funnel blocked by the thumb. When the powder is emptied from funnel, the angle of the heap to the horizontal plane is measured. Granules were poured gently through a glass funnel in to a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the equations given below [3].

Post compressional studies of the prepared floating tablets

The prepared tablets were tested as per standard procedure for weight variation (n=20), thickness (n=20), hardness (n=6), friability and drug content. Thickness of the tablets was measured by digital micrometer; hardness of tablet was determined by using tablet hardness tester (EH-01, Electrolab, Mumbai); friability test was conducted using Roche friabilator [4,5,6] .For

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estimation of drug content, ten tablets were randomly selected and powdered. A quantity of powder equivalent to 50 mg of Amlodipine Besylate was accurately weighed and transferred into a volumetric flask and dissolved in 100 ml of 0.1N hydrochloric acid (HCl). The flask was shaken on a flask shaker for 24 h and the solution was filtered through 0.45µ membrane. 1 ml of the above solution was transferred to a volumetric flask and diluted suitably with 0.1N HCl. The absorbance of resulting solution was measured at 254 nm using UV/visible spectrophotometer.

In vitro buoyancy study

The *in vitro* buoyancy was determined as per the method described by Rosa *et al*. The test was performed by placing each of the tablets in a 250 ml beaker, containing 200 ml of 0.1N HCl with Tween 20 (0.02% w/v), pH 1.2, maintained at 37±0.5°C. The time between introduction of the dosage form and its buoyancy on the 0.1N HCl (lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were determined visually [6].

In vitro dissolution study

The release rate of Amlodipine Besylate from floating tablets was determined using *United States Pharma-copeia (USP)* 24 Dissolution Testing Apparatus 2 (paddle method). The dissolution test was per-formed using 900 ml of 0.1N HCl, at 37±0.5°C and 75 rpm. A sample (5 ml) of the solution was with-drawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 254 nm using a UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability study

To assess the drug and formulation stability, stability studies were done according to Interna-tional Conference on Harmonisation (ICH) guidelines. The floating tablets were stored at 40±2°C/75±5% relative humidity (RH) in closed high-density polyethylene bottles for a period of 6 months. Tablets were analyzed at specified time intervals for the drug content, *in vitro* dissolution and buoyancy behaviour. The differences in parameters from floating tablets were evaluated using unpaired t-test. In t-test, a probability value of $p < 0.05$ was considered to be statistically significant.

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RESULTS AND DISCUSSIONS

Table 1. Formulation of Amlodipine Besylate Floating Tablets

S.NO	Ingredients	Formulations of Amlodipine Besylate floating Tablets Quantity (mg)												
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
01	Amlodipine besylate	10	10	10	10	10	10	10	10	10	10	10	10	-
02	HPMC K100M	40	60	80	-	-	-	-	40	60	80	-	-	-
03	HPMC K4M				40	60	80	-				40	60	-
04	Sodium bicarbonate	80	80	80	80	80	80	80	80	80	80	80	80	-
05	PVP K30	20	20	20	20	20	20	20	20	20	20	20	20	-
06	lactose	235	215	195	235	215	195	285	235	215	195	235	215	-
07	Talc	5	5	5	5	5	5	5	5	5	5	5	5	-
08	Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10	-

Table 2. Evaluation of powder blend of Amlodipine Besylate

FORMULATIONS	PARAMETERS				
	ANGLE OF REPOSE (θ)	BULK DENSITY (gm/cc)	TAPPED DENSITY (gm/cc)	COMPRESSIBILITY INDEX (%)	HAUSNER'S RATIO
F1	$32^0 64' \pm 0.05$	0.507 ±0.01	0.572 ±0.01	11.3 ± 0.76	1.12 ± 0.15
F2	$33^0 02' \pm 0.03$	0.614 ±0.05	0.690 ±0.06	11.0 ± 0.54	1.12 ± 0.28
F3	$32^0 24' \pm 0.02$	0.624±0.06	0.706 ±0.04	11.6 ± 0.64	1.13 ± 0.12
F4	$33^o 10' \pm 0.02$	0.592±0.09	0.676 ±0.05	12.4 ± 0.33	1.14 ± 0.87
F5	$32^0 07' \pm 0.02$	0.554±0.06	0.625 ±0.07	11.36 ±0.54	1.12 ± 0.35
F6	$32^0 64' \pm 0.03$	0.568±0.05	0.640 ±0.09	11.25 ±0.72	1.12 ± 0.54
F7	$34^0 55' \pm 0.03$	0.509±0.05	0.576 ±0.08	13.16 ±0.76	1.13 ± 0.48
F8	$32^0 24' \pm 0.02$	0.453±0.04	0.576±0.03	11.2±0.45	1.12±0.564
F9	$33^o 10' \pm 0.02$	0.534±0.03	0.645±0.05	12.2±0.24	1.13±0.23
F10	$32^0 07' \pm 0.02$	0.512±0.05	0.597±0.08	12.1±0.43	1.14±0.13
F11	$32^0 64' \pm 0.03$	0.423±0.07	0.496±0.04	11.3±.13	1.14±0.23
F12	$34^0 55' \pm 0.03$	0.538±0.05	0.644±0.05	12.3±0.34	1.12±0.31

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

Table 3. Evaluation of Floating Tablets of Amlodipine Besylate

S.No	PARAMETERS	PHYSICAL CHARACTERS OF AMLODIPINE BESYLATE FLOATING TABLETS*											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
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	6.0 ± 0.20	6.1 ± 0.25	6.0 ± 0.34	6.0 ± 0.20	6.2 ± 0.42
2	Thickness (mm)	3.5 ± 0.05	3.6 ± 0.03	3.2 ± 0.04	3.5 ± 0.02	3.6 ± 0.04	3.3 ± 0.03	3.6 ± 0.05	3.5 ± 0.02	3.6 ± 0.04	3.3 ± 0.03	3.6 ± 0.05	3.2 ± 0.04
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	400± 2.08	400± 0.57	398± 1.00	399± 2.05	400± 0.57
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	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	99.9± 0.25	93.18± 0.49	96.15 ±0.35	99.99 ±0.64	98.60 ±0.36
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	56 ± 3.47	90 ± 5.10	120 ± 5.03	30 ± 4.58	120 ± 5.03
7	Duration of Buoyancy (hrs)	>20	>20	>20	>16	>16	>16	Upto2hrs	>20	>20	>16	>16	>16
8	Swelling Index (%)	64 ± 0.23	66 ± 0.48	69 ±0.65	51 ± 0.38	56 ± 0.45	59 ± 0.37	32 ± 0.44	64 ± 0.23	66 ± 0.48	69 ± 0.65	51 ±0.38	56 ± 0.45

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

Table 4. *In-Vitro* drug release studies of 12 formulations (DISSOLUTION STUDIES)

Time (hrs)	Formulation code											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
1	52.4	12.47	10.62	9.55	25.10	25.10	14.18	12.23	8.974	22.50	15.49	30.14
2	93.4	17.24	14.78	13.70	37.83	37.83	23.31	17.12	15.97	35.70	26.7	42.89
3		21.26	18.64	17.56	48.62	48.62	29.21	21.37	21.21	52.35	32.31	54.01
4		27.57	23.72	21.41	62.33	59.40	42.56	25.62	33.4	62.35	44.69	65.61
5		32.82	28.96	25.42	70.37	68.73	48.65	32.47	38.20	69.72	49.31	74.93
6		46.50	40.80	36.49	76.58	72.23	58.59	52.00	45.05	76.58	58.11	81.32
7		52.71	47.46	44.22	81.98	78.06	66.45	58.29	57.27	82.14	69.69	88.67
8		58.88	53.48	49.94	88.67	86.37	82.74	72.94	68.71	88.67	82.75	94.39
12		76.09	71.62	67.45	96.99	94.54	92.90	84.72	77.06	96.9	94.52	98.33

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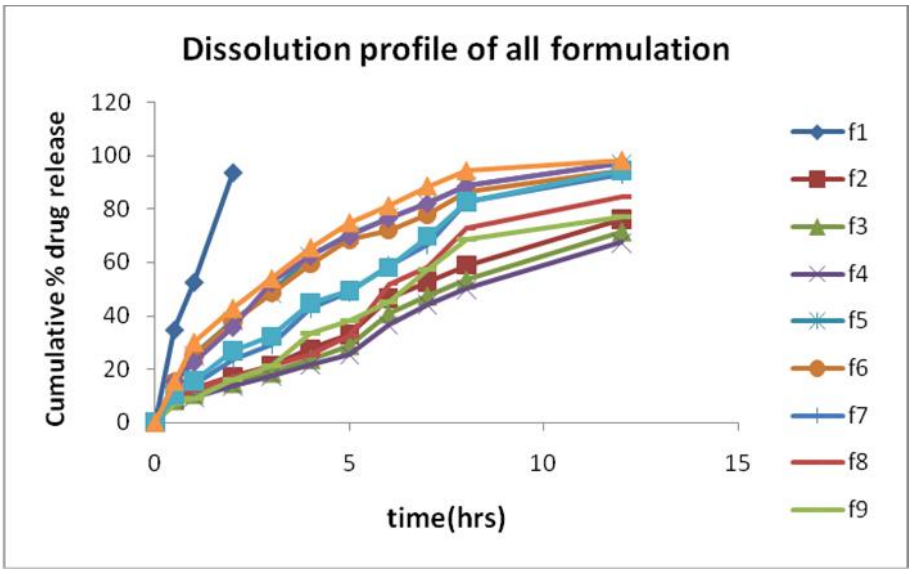

Fig 1: ***In-Vitro*** **drug release profile of F1-F12 formulation**

Table 5 : Curve Fitting Analysis

Formulation code	Zero order		First order		Higuchi		Korsmeyer-peppas		Drug release mechanism
	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Diffusion exponent (n)	
F-1	0.978		0.826	-0.175	0.991	34.67	0.987	0.499	fickian transport
F-2	0.978	6.451	0.861	-0.112	0.982	30.13	0.965	0.456	fickian transport
F-3	0.985	6.051	0.822	-0.125	0.990	29.87	0.939	0.389	fickian transport
F-4	0.984	5.682	0.915	-0.124	0.988	30.39	0.978	0.497	fickian transport
F-5	0.866	7.906	0.951	-0.097	0.992	28.86	0.978	0.460	fickian transport
F-6	0.869	7.592	0.852	-0.086	0.985	26.35	0.964	0.429	fickian transport
F-7	0.954	8.113	0.845	-0.103	0.951	28.35	0.962	0.548	Non-fickian transport
F-8	0.959	7,544	0.856	-0.098	0.959	27.39	0.952	0.572	Non-fickian transport
F-9	0.974	6.093	0.874	-0.057	0.937	23.09	0.958	0.525	Non-fickian transport
F-10	0.946	7.257	0.752	-0.143	0.996	26.35	0.935	0.575	Non-fickian transport
F-11	0.926	7.257	0.865	-0.094	0.923	27.39	0.986	0.523	Non-fickian transport
F-12	0.975	6.075	0.836	-0.059	0.943	27.09	0.9745	0.508	Non-fickian transport

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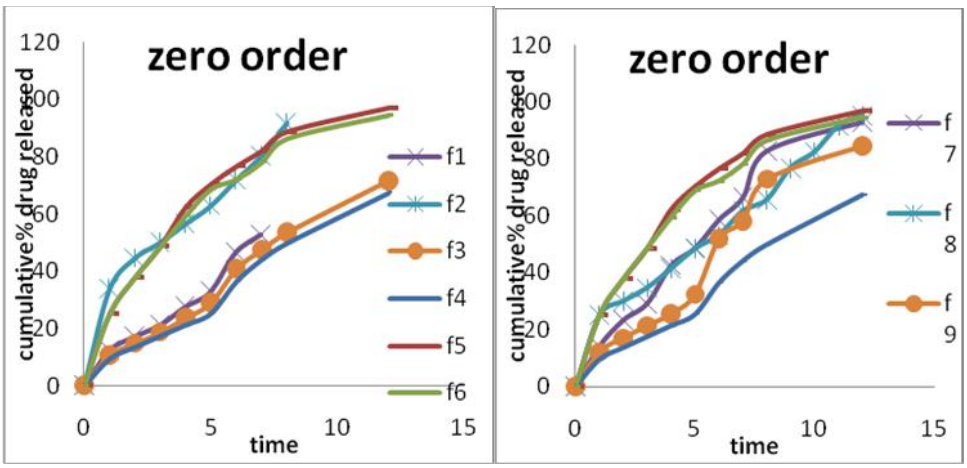

Fig 2: **Zero order release from Amlodipine Besylate Floating**

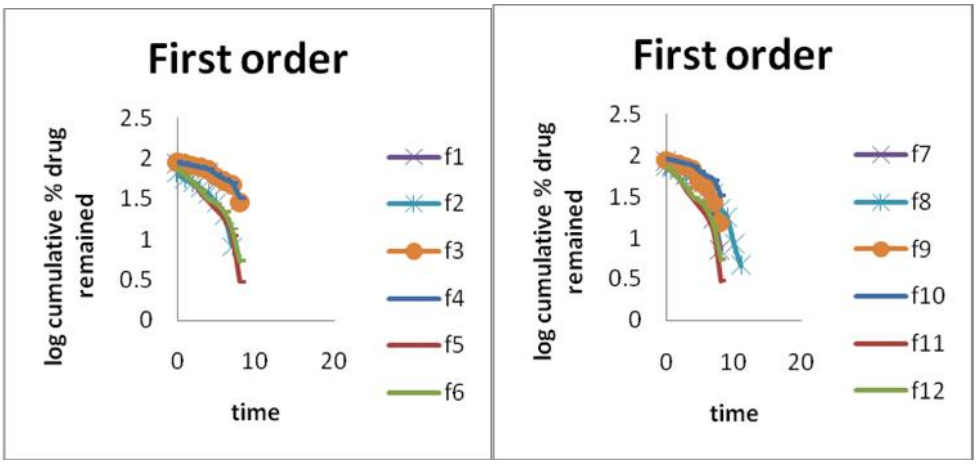

Fig 3 : **First Order Release Profile from Amlodipine Besylate**

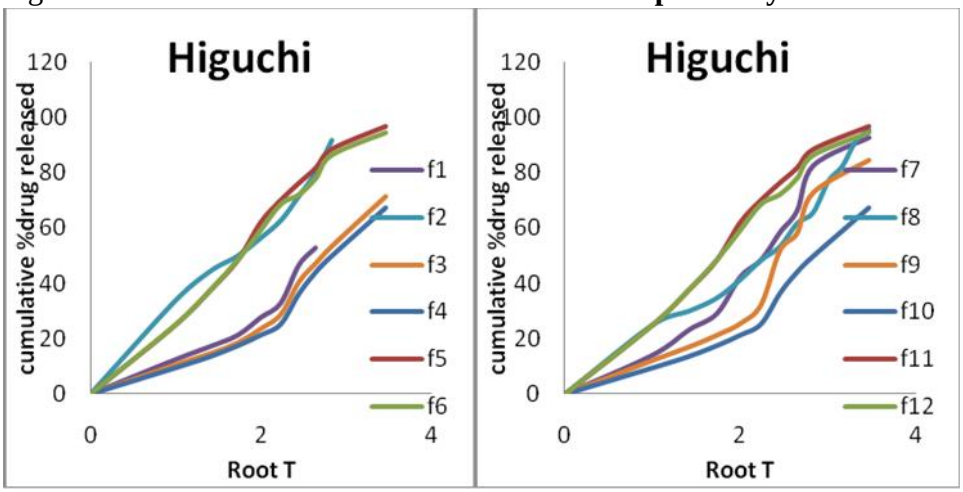

Fig 4 : **Higuchi's release profile from amlodipine besylate**

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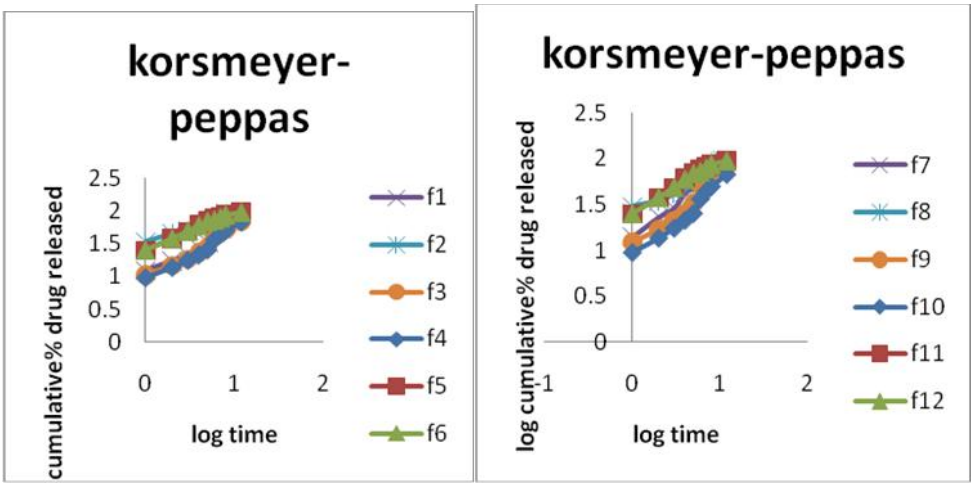

Fig 5 : **Korsmeyer- peppas profile from Amlodipine Besylate**

Table 6 : Stability studies of cumulative Percentage of Drug Release From Floating tablets of Amlodipine Besylate F12 formulation (optimized formulation)

S.NO	Time (in hrs)	Percentage of drug release (%) at different time interval*								
		4°±2°C			27°±2°C			40°±2°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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Table 7: Stability Studies of Amlodipine Besylate Floating Tablets Drug Content Estimation

PERCENTAGE DRUG CONTENT OF AMLODIPINE BESYLATE FLOATING TABLET (F12)*								
4°C±2°C			**27°C±2°C**			**40°C±2°C**		
15 days	30 days	45 days	15 days	30 days	45 days	15 days	30 days	45 days
95.88±0.01	94.73±0.01	95.82±0.05	96.02±0.03	95.94±0.02	95.84±0.04	95.79±0.05	96.62±0.04	95.93±0.05

*All the values are expressed as mean ± standard deviation

The present study was to formulate Amlodipine Besylate floating tablets in different batches F1 to F12 using polymer Hydroxy propyl methyl cellulose of two different grades (HPMC K100M and HPMC K4M), xanthanegum and carbopol 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, in vitro-drug release studies and stability studies were carried out. All results are presented in appropriate tables and figures.

The angle of repose of all the formulations was within 35^0. The result showed that the angle of repose was $32^007'$-$34^055'$. It proved that the flow properties of all formulations are good. 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 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. 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. 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 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, carbopol and xanthanegum in different ratios. The drug release was compared with the marketed sample of Amlodipine Besylate and control (i.e drug without polymer). From the dissolution profile it was observed that Invitro dissolution studies of formulations F1 to F12 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 F2 to F4 showed slower drug release (76.9%,71.2%,67.6%) when compared to the

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formulations with lower HPMC viscosity grades (HPMC K4M) i.e F5 to F7 (96.8%, 94.5% and 92.2%). This may be due to less water permeability of HPMC K100M than HPMC K4M. The combination of carbopol and xantanegum with the HPMC K100M than HPMC K4M results i,e from F8 to F12 (84.9%, 76.2%,96.5%, 94.2% and 98.3%). The percentage drug release of control F1 (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 98.3% in 90 minutes. Among all the formulations, formulation F12 containing drug prepared with HPMC K4M and carbopol, showed promising result releasing 98.8% of drug in 12 hrs with a floating lag time of 56 seconds and duration of floating time is 12hrs. 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 (Davis 1968). Floating properties of the tablets could be improved with gas generating agent which is sodium bicarbonate. It generates gas when it comes in contact with an acidic environment of the stomach. This gas entraps into the matrix of water soluble polymers and the formulation floats in acidic environment of the stomach. 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 [7] . The results of dissolution studies revealed that the formulation F12 showed retarded drug release (98.3%) in controlled manner upto 12 hours. The optimal formulation is F12 which exhibited optimal release pattern of drug (98.3%) upto 12hrs with afloating lag time of 56 sec and total floating time of 24 hrs was considered as the best optimized formulation among other formulations. Drug release from the optimized formulation (F12) followed zero order kinetics.

The results of in-vitro drug release data of all the formulations obtained from dissolution studies were fitted to four models namely. Zero-order kinetic model (cumulative percentage drug release verses time), First-order kinetic model (log cumulative percentage drug remaining verses time), Higuchi's equation (cumulative percentage drug release verses square root time), Korsmeyer's equation (logncumulative percentage drug release verses log time) and presented in Table No.4 and Figures 2 - 15.

According to the data (Table No:4) the release of drug was both diffusion and erosion controlled mechanisms. Release of the drug from matrix tablet containing hydrophilic polymers involves factors of both diffusion and erosion. Diffusion is related to transport of drug from the dosage form into the in vitro fluid depending on the concentration [8]. In the present study in vitro release profile of the optimized formulation F3 was expressed by korsmeyer-Peppas equation showed good linearity (R2=0.9707), and n value is below 1 indicates drug release is first order release followed by diffusion mechanism of the drug release. From the korsemeyer plot it was known that the drug release of the best formulation (F3) showed n (slope) value was >0.85 indicates first order and Non-Fickian release mechanisms [9].

Amlodipine Besylate floating tablets of optimized formulation (F12) 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.6. There was no colour change and the drug content was 95.93%. There was no change in drug content (Table No.7) and in vitro release (Table No.6) . The result proved that the optimized formulation (F3) stored at different temperatures was stable.

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CONCLUSION

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 hydrophiliccontrolled release polymer HPMC K4M and carbopol 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 Retensive Drug Delivery System. Such work can be further extended using some other controlled release polymers for drug delivery.

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