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FORMULATIOM AND EVALUATION OF GASTRORETENTIVE AMLODIPINE BESYLATE CAPSULE

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ABSTRACT

The purpose of this research is to develop a novel expandable gastroretentive dosage form (GRDF), based on unfolding mechanism. It consists of a drug loaded bilayer polymeric film, folded into a hard gelatin capsule. Gastric retention is achieved due to unfolding of the dosage form within 15-20 min. Amlodipine besylate is selected as the drug candidate for this work. Amlodipine has to be administered to the upper parts of the intestine in order to maintain sustained therapeutic levels. This may be achieved by a GRDF. Films were prepared by solvent-casting technique using Ethyl cellulose, HPMC E15 and Eudragit RLPO as polymers and dibutyl phthalate as the plasticizer in both layers. The film with zigzag folding in the capsule was shown to unfold in the gastric juice and provide drug release up to 12 h in the acidic medium. The films were evaluated for weight & thickness variation, mechanical properties, *in vitro* drug release and unfolding behavior based on the mechanical shape memory of polymers. Absence of drug polymer interaction and uniform drug dispersion in the polymeric layers was revealed by FT-IR, DSC studies.

INTRODUCTION:

Oral route is the most preferred route of drug delivery due to ease of administration and greater patient compliance [1], although studies revealed that this route is subject to two physiological influences, a short gastric residence time (GRT) and variable gastric emptying time (GET), which may lead to unpredictable bioavailability and times to achieve peak plasma levels. Furthermore, the brief GET in humans, which normally averages 2-3 h through the major absorption zone (stomach and upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose. Thus, control of placement of a drug delivery system in a specific region of the gastro intestine (GI) tract offers numerous advantages like improved bioavailability and therapeutic efficacy, local delivery of drug and possible reduction of dose size. All these considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Gastroretentive systems can remain in the gastric region for several hours and significantly prolong the gastric residence of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, improve solubility of drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine [2-4]. Amlodipine besylate is an angioselective calcium channel blocker used in hypertension and angina. It is also acts an antiretroviral drug of protease inhibitor class, used to treat human

immunodeficiency virus (HIV). Amlodipine is listed in World Health Organization (WHO) model list of essential medicines as antihypertensive medicine in the dose range of 2.5-15 mg. Oral (acidic pH) bioavailability of Amlodipine besylate is around 60% and having a half life of 30 to 35 h. It was found that the aqueous solubility of the amlodipine besylate in distilled water was 2.6 mg/ml. It has some adverse effect such as nausea, abdominal pain. In recent studies effervescent floating tablets of Amlodipine besylate retain in stomach improves solubility, bioavailability, reduces drug waste and decrease side effect such as gastric irritation and nausea [5-9].

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

EXPERIMENTAL

MATERIALS

Amlodipine besylate was procured from Dr. Reddy's; Hyderabad as a gift sample. Ethyl Cellulose, HPMC E 15, Eudragit RLPO, Di butyl pthalate, DCM & Methanol and other chemicals and solvents were of analytical grade/IP/equivalent grade and procured from laboratory.

METHODS

Preparation of Films

Preparation of primary layer

Expandable GRDFs were prepared by solvent casting method. Weighed quantity of EC, HPMC E15 and Eudragit RLPO were taken in a boiling tube. To this, 25 ml of solvent mixture of dichloromethane: methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps. The boiling tube was set-aside for 6 hours to allow the polymers to swell. After swelling, measured quantity of di butyl phthalate was added to this mixture and vortexed. Finally weighed quantity of solid dispersion (1:3) of Amlodipine with povidone was dissolved in 10 ml of solvent mixture, added to the polymer solution and mixed well. It was set-aside for some time to exclude any entrapped air and was then transferred into a previously cleaned anumbra petriplate. Drying of these patches for 8 hrs was carried out in oven (at 40ºC) placed over a flat surface. The patches formed were removed carefully, placed in a vacuum oven and vacuum was applied to remove traces of solvent if any.

Preparation of secondary layer

Weighed quantity (2 g) of EC was taken in a boiling tube. To this, 25 ml of solvent mixture of dichloromethane: methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps. The boiling tube was set-aside for 1 hour to allow the polymer to dissolve. After that, measured quantity (1 ml) of di butyl phthalate was added to this mixture and vortexed. It was set-aside for some time to exclude any entrapped air and was then poured onto primary layer, which leads to formation of a bilayered film. For the preparation of GRDFs the composition of secondary layer is same for all formulations. Drying of these patches for 8 hrs was carried out in oven (at 40°C) placed over a flat surface. The patches formed were removed carefully, placed in a vacuum oven and vacuum was applied to remove traces of solvent if any. On removal of the films they were checked for possible imperfections before being cut into 4cm×2cm rectangles and micro crystalline cellulose (MCC) was applied on to the film on both sides. These films are filled into hard gelatin size 00 capsules by folding in a zigzag manner. The area of the petriplate used in the preparation of both layers is 64cm^2.

Optimization of GRDFs

The GRDFs were optimized for folding and unfolding patterns, drug release and integrity as described below.

Unfolding behaviour of GRDFs- in vitro

Films were folded by two methods. In both methods Avicel-101 was used as anti adherent agent. In the first method the film was rolled in a single direction, in the second method the film was folded in a zigzag manner and both films were inserted into individual capsule. In each case six capsules were taken for in vitro dissolution study in 900mL aqueous hydrochloric acid pH 1.2 at 37ºC ± 0.5ºC using the USPXXIII Apparatus1 (basket) at 100 rpm. Baskets were removed after 5, 10, 15, 20, 30, 60, 120, 240, 480 and 720 min and the films were examined for their unfolding behaviour.

Integrity of GRDFs

Initial trials were made with different grades of Eudragit and HPMC polymers with different ratios of solvent, plasticizer and anti adherent agents. Finally the films with EC (as secondary layer), HPMC E15, EC and Eudragit RLPO (as primary layer) got very good integrity for 12 hrs *in vitro*. Among the polymers used to prepare the film, EC plays an important role to maintain the integrity of the primary layer in combination with secondary layer.

Drug release: Initial trials were made without Eudragit RLPO, but there was no control over the drug release i.e., total drug was released in 4 hrs only. Drug release was prolonged by optimizing the EC concentration and inclusion of Eudragit RLPO in the primary layer. There was no drug in the secondary layer, but it gives good integrity and unfolding behaviour to the GRDF.

Solubility enhancement: To improve the solubility of the drug, solid dispersions were prepared by two methods i.e., physical mixing and solvent evaporation. In both methods the ratio of drug and polymer (povidone) varies from 1:1 to 1:3. Physical mixture was prepared by simply mixing the recrystallized drug and polymer in a motor with care to avoid any grinding action. In the solvent evaporation technique drug and polymer in different ratios were dissolved in methanol (Table.1). The solvent was removed under reduced pressure in a rotary evaporator at 70°C. The dispersions were vacuum dried for 48 h in a desiccators at room temperature. The residue was ground and the particle size fraction was obtained by sieving. Good solubility enhancement was observed in case of 1:3 solid dispersion prepared by solvent evaporation technique (Table. 3). The solubility was increased from 24 µg/ml to 120 µg/ml in 0.1 N HCl (pH 1.2). In this work the term solid dispersion is the mixture of drug and polymer prepared by solvent evaporation technique.

Characterization of GRDFs

Weight variation test:

Each formulation was prepared in triplicate and ten patches each equivalent to 4cm×2cm was cut from each plate. Their weight was measured using Shimadzu digital balance. The mean ± SD values (**Table 5**) were calculated for all the formulations.

Thickness variation test

The thickness of the patches was measured by digital screw gauge (Digimatic outside micrometer, Mitutoyo, Japan). The mean ± SD values. (**Table 5**) were calculated for all the formulations.

***In vitro* drug release studies**

Drug release from the formulations was studied by using USP dissolution tester XXIII Apparatus1 (basket) at 100 rpm in 900mL aqueous hydrochloric acid pH 1.2 at 37ºC ± 0.5ºC. The procedure is repeated for the marketed product LASIX ® 20 mg Tablets (Sanofi aventis, Canada), compared with optimized formulation. The in *vitro* drug release pattern was interpreted by using 'PCP Disso v2.08' soft ware and the data was fitted in various kinetic models and the values of the correlation coefficients were compared.

Measurement of mechanical properties

Mechanical properties of the GRDFs were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25 kg load cell. Film strip with the dimensions 60 x 10 mm and free from air bubbles or physical imperfections, were held between two clamps positioned at a distance of 3 cm. A cardboard was attached on the surface of the clamp to prevent film from being cut by the grooves of the clamp. During measurement, the strips were pulled by the top clamp at a rate of 2.0 mm/s to a distance till the film broke. The force and elongation were measured when the films were broken. Results from film samples, which were broken at end and not between the clamps were not included in observations. Measurements were run in six replicates for each formulation. The following equations were used to calculate the mechanical properties of the films.

Tensile strength ($kg.mm^{-2}$) =

Force at break (kg)/ Initial cross sectional area of the sample (mm^2) and

Elongation at break ($\%mm^{-2}$) =

[Increase in length (mm)] 100/ [Original length] [Cross sectional area (mm^2)]

RESULTS AND DISCUSSIONS

Preformulation studies:

Identification of drug:

The change in principle peaks of amlodipine besylate and excipients were found. The IR spectra of amlodipine besylate, HPMC, EC, Eudragit. Pure amlodipine besylate spectra showed sharp characteristic peaks at 3300.20, 3158.50, and 1651.08 cm^{-1}. All the above characteristic peaks appears in the spectra of Films at same wave number indicating no modification or interaction between the drug and carrier.

Melting point determination:

Thermal behaviour of Amlodipine besylate, PVP K-30, PEG 4000 and solid dispersion of Amlodipine besylate with PVP K-30 and PEG 4000 are depicted in Fig.6, 7, 8, 9. The DSC curve of Amlodipine besylate profiles a sharp endothermic peak (Tpeak = 204.54°C) corresponding to its melting, indicating its crystalline nature.

Compatibility Studies:

The vials containing samples were observed 2^{nd} and 4^{th} week and compared with vials kept at 4^0C as control. They were compared for incompatibility like lump formation and color change. From the results it was observed that there is no change as shown in **table 2**.

Drug polymer compatibility studies using Fourier Transform Infrared Spectroscopy (*FT-IR*):

Compatibility studies of pure drug with excipients were carried out prior to the preparation of compression coated tablets. I.R spectra of pure drug and combination of drug and excipients were obtained, which are shown in **Figure.1** and **2**. All the characteristic peaks of Amlodipine were present in Spectra thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

Differential scanning calorimetry

However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity, in solid dispersion. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data also indicate there seems to be no interaction between the components of solid dispersion. No significant difference in DSC pattern of solid dispersion suggests that even the kneading process could not induce interaction at the molecular level and solid dispersion contains highly dispersed drug crystals in carrier (**Figure.3** and **4)**.

Polymer content

In case of primary layer, EC content of less than 500 mg was insufficient to retard the drug release and retain the integrity. So formulations were prepared by keeping EC content constant and varying the contents of HPMC E 15 and Eudragit RLPO from 200 to 300 mg. In case of secondary layer, EC content of less than 2g was insufficient to retain the integrity and mechanical shape memory (**Table 4**).

Plasticizer content

For secondary layer, plasticizer (DBP) concentration of less than 0.5mL was insufficient to form film. Plasticizer concentration of 1mL yielded more flexible films. Further increasing the concentration of plasticizer above 1mL resulted in enormous increase in the drying time. In case of primary layer 0.5mL of DBP yielded more flexible films.

Solvent volume

For secondary layer, solvent volume of 25mL was sufficient to cast the film. In case of primary layer, solvent volume of 14-20mL resulted in viscous solution; hence complete transfer of the solution could not be ensured. Solvent volume of 25-35 mL was sufficient to solubilize the drug and cast the films. Increasing the solvent volume above 35 mL resulted in the formation of patches with entrapped air bubbles.

Characterization of GRDFs

The results of weight variation test for various formulations were shown in **Table 5**. Results of weight variation test indicated uniformity in weight of the patches, as evidenced by SD values. In thickness variation test (**Table. 5**), the thickness was found to be uniform.

Table.1: Solubility studies of Amlodipine:

Solvent	Amlodipine
Water	Soluble
0.1N HCl	0.38 mg/mL
6.8 pH buffer	0.11mg/mL
4.5 pH buffer	0.31 mg/mL

Table.2: Drug and Excipients compatibility studies

S.no	Ingredients	Ratio	Physical Description		
			Initial	55°C (2 weeks)	40±2°C /70±5 % RH(4 weeks)
1	API (Amlodipine)	--	White Colour	No change	No change
2	API+ HPMC K100M	1:1	white	No change	No change
3	API+ Ethyl Cellulose	1:1	white	No change	No change
4	API+ Eudragit	1:1	Off white	No change	No change

Figure.1: *FT-IR* Spectra of Amlodipine

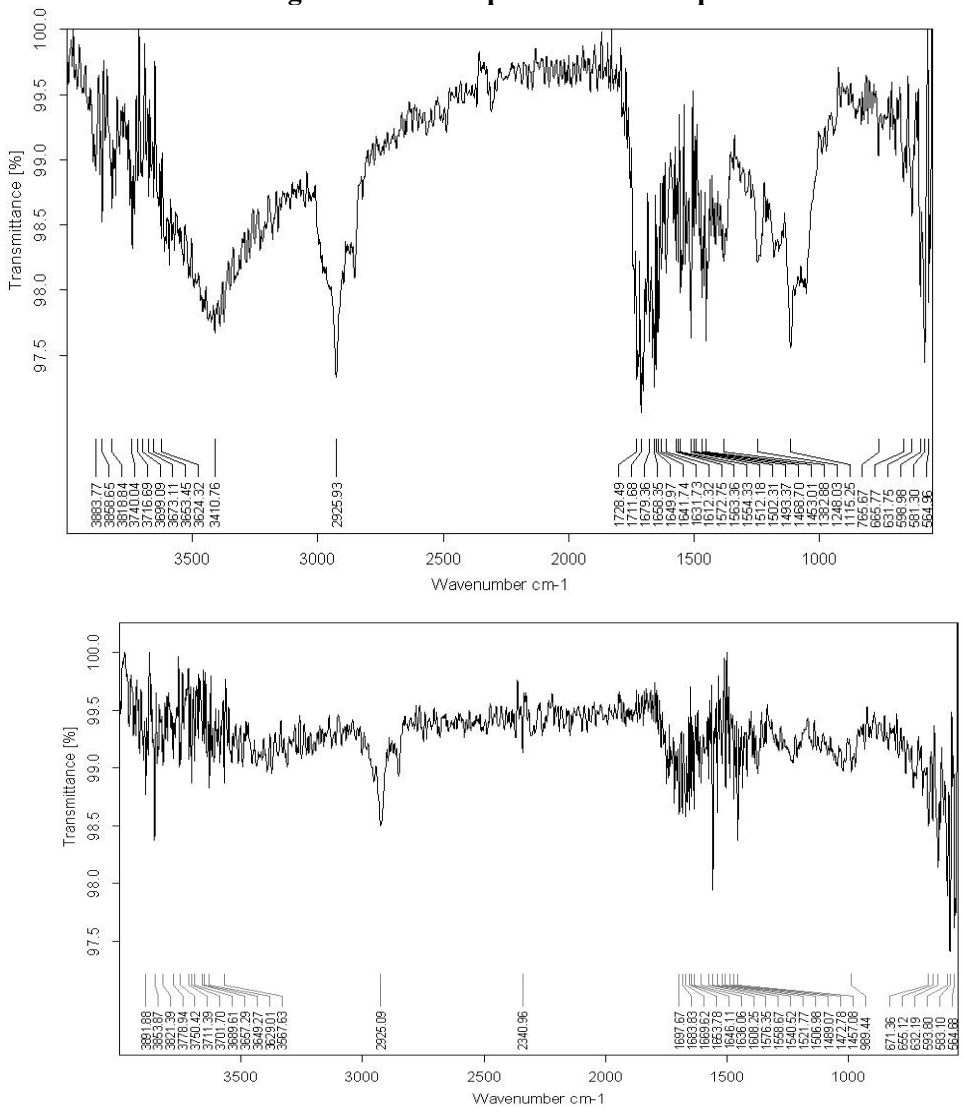

Figure. 2 : *FT-IR* Spectra of optimized formulation (F3)

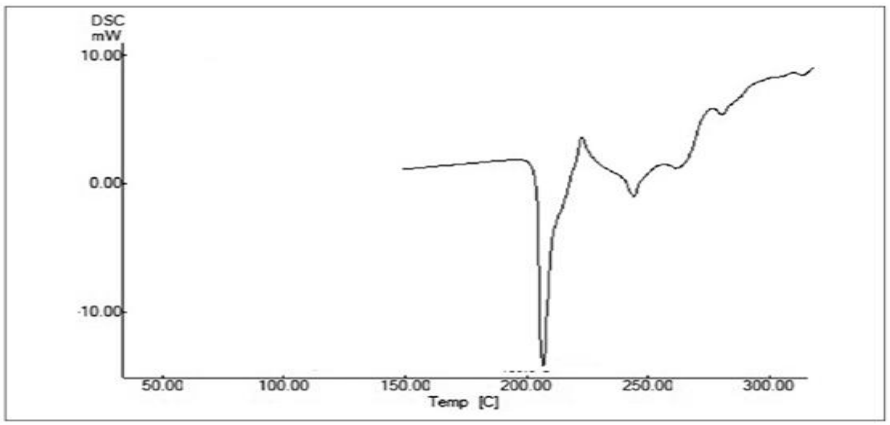

Figure.3: DSC of Pure Amlodipine

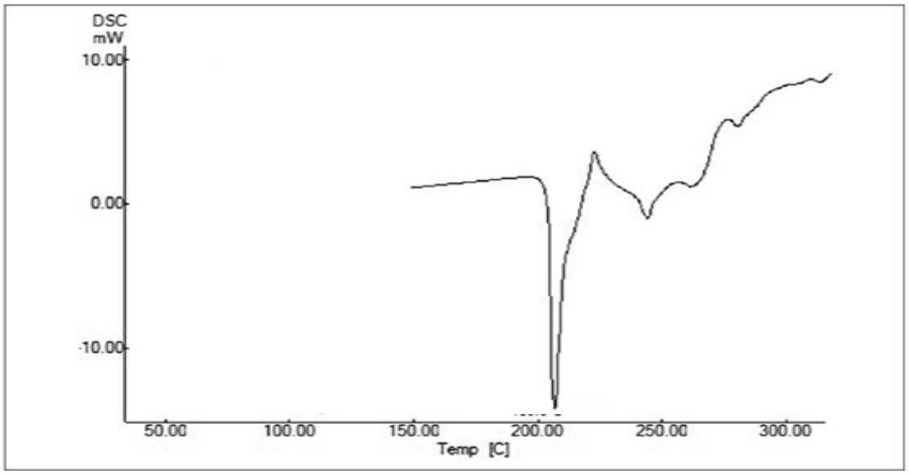

Figure.4: DSC of Amlodipine (F3)

Concentration (µg/ ml)	Absorbance in 0.1 N HCl
5	0
10	0.164
20	0.344
30	0.442
40	0.535
50	0.716
60	0.873

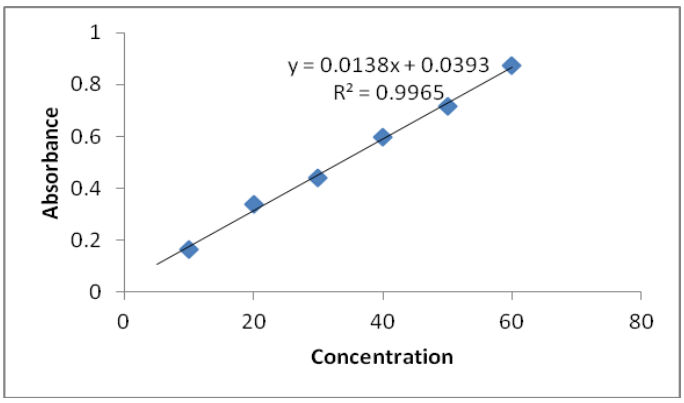

Figure.5: Plot of standard graph of Amlodipine besylate in 0.1 N HCl

Table.4. Formulation Ingredients of Amlodipine GRDFs

Formulation	Drug* (mg)	EC (mg)	HPMC E 15 (mg)	Eudragit RLPO (mg)	di butyl phthalate (µl)	DCM& Methanol (1:1) (ml)
F1	10	350	300	200	500	35
F2	10	350	275	225	500	35
F3	**10**	**350**	**250**	**250**	**500**	**35**
F4	10	350	225	275	500	35
F5	10	350	200	300	500	35

**Solid dispersion equals to 10 mg of the drug*

Table.5. Evaluation of the GRDFs

F. code	Weight (mg)	Thickness (µm)	Tensile Strength(kg/mm^2	Elongation at break (%mm^{-2})
F1	**350±3.66**	480±1.59	26.48±3.62	0.22±0.08
F2	362±3.98	489±2.64	29.62±2.27	0.46±0.09
F3	356±4.96	485±1.66	22.44±4.66	0.42±0.06
F4	370±3.64	483±2.42	24.62±4.62	0.38±0.08
F5	365±4.29	484±2.17	27.82±6.89	0.28±0.04

F.Code: Formulation Code; All values indicate mean±Standard Deviation

Table.6: *In vitro* drug release studies Amlodipine besylate

S. No	Time (h)	Cumulative release (%)				
		F1	F2	F3	F4	F5
1.	0	0	0	0	0	0
2.	0.5	7.11±1.30	8.62±1.73	7.90±1.94	7.69±1.80	8.75±1.40
3.	1	18.34±1.27	18.75±1.35	19.11±1.95	19.16±1.21	19.29±1.37
4.	2	32.82±1.36	33.67±1.54	35.12±1.87	29.11±1.43	31.29±1.47
5.	4	43.59±1.58	44.17±1.26	45.21±1.37	41.26±1.94	43.89±1.34
6.	6	61.23±1.48	62.12±1.93	61.21±1.32	59.89±1.33	60.29±1.30
7.	8	67.11±1.64	67.29±1.23	68.77±1.30	62.25±1.54	63.75±1.94
8.	10	72.11±1.24	73.20±1.89	73.34±1.2	72.28±1.37	72.71±1.37
9.	12	74.21±1.23	75.11±1.97	76.12±1.37	76.16±1.20	77.29±1.98
10.	14	80.12±1.45	82.09±1.52	83.74±1.91	84.23±1.54	85.96±1.20

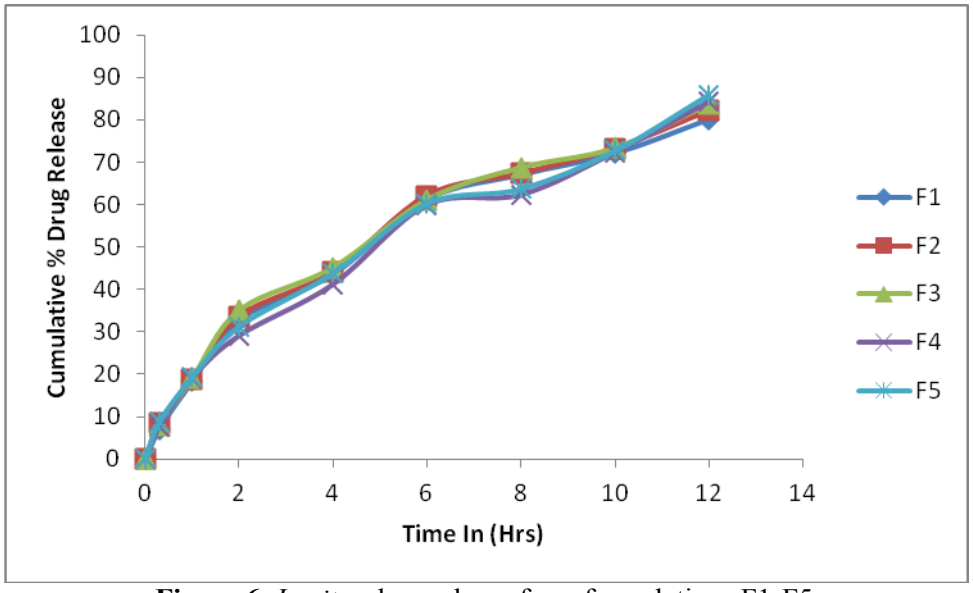

Figure.6. *In vitro* drug release from formulations F1-F5

***In vitro* drug release studies:**

Drug release was studied for all formulations from F1-F5. Based on the in vitro drug release, unfolding behaviour and mechanical properties, the formulation F3 was selected as the optimized formulation. Was studied and compared with formulation F3 (**Figure.6**). Formulation F3 showed that it was a controlled release formulation (**Table 6).** Releasing the drug up to 12 hr and followed first order release (R^2=0.992) with diffusion control mechanism (Higuchi model, R^2=0.991).

***In vitro* drug release from formulations**

Mechanical properties of films

The results of the mechanical properties i.e., tensile strength and elongation at break are presented in **Table 5** and values indicated that no statistical difference was observed in tensile strength and elongation at break values between the formulations.

Unfolding behaviour: GRDFs prepared by both methods were evaluated for their *in vitro* unfolding behaviour. The GRDFs prepared by first method have not unfolded properly, but the GRDFs of second method unfolded within 15-20 min. Apart from folding pattern, for proper unfolding of a film, mechanical shape memory (resiliency to restore its original shape) is required. Such shape memory polymers may have the glass transition (*Tg*) at about room temperature. The selection of plasticizer for GRDFs is very important because, only the plasticizers of similar solubility parameter ($MPa^{0.5}$) to that of EC (20 $MPa^{0.5}$) will have a greater effect on Tg suppression [10]. Initial trials were made with various plasticizers like Dibutyl phthalate (19 $MPa^{0.5}$), Diethyl phthalate (20.5 $MPa^{0.5}$), Triethyl citrate (20.4 $MPa^{0.5}$). But satisfactory results were obtained with only DBP.

CONCLUSION: The current research work demonstrates the successful development of a GRDF for a drug (Amlodipine) with a narrow absorption window. It consists of a drug loaded bilayer polymeric film, folded into a hard gelatin capsule. Gastric retention is achieved due to unfolding of the dosage form in the stomach within 15-20 min of administration. The polymers used in the development of GRDFs were safe and proper combination of these polymers will yield a novel expandable GRDF with good *in vitro* drug release in acidic media, mechanical properties, and unfolding behaviour. In fasting condition the myoelectric migrating contractions force the contents to duodenum from stomach.

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REFERENCES:

1. Garg S, Sharma S. Gastroretentive drug delivery systems. *Business Briefing: Pharmatech*. 2003, 5, 160-6.
2. Singh BN, Kwon H. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. *J Control Release*. 2000, 63, 235-59.
3. Dave BS, Gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and *in vitro* evaluation. *AAPS Pharm Sci Tech*. 2004, 5, e34.
4. Arora S, Ali J, Ahuja A, Khar RK, Baboota A. Floating drug delivery system: A review. *AAPS Pharm SciTech*. 2005, 6, 47.
5. Gutierrez-rocca J, Omidian H and Shah K. Progress in gastroretentive drug delivery system" *Bussiness Briefing, Pharmatech*. 2003, 152-156.
6. Hou SY, Cowles VE and Berner. Gastric retentive dosage forms: A review, Crit. Rev. Ther. *Drug Carrier Syst*. 2003, 20(60), 459-497.
7. Ritesh Kumar, Anil Philip. Gastroretentive dosage forms for prolonging gastric residence time. *lnt J Pharm Med*. 2007, 21(2), 157-171.
8. Garima Chawla, Piyush Gupta, Vishal Koradia and Arvind K Bansal. Gastroretention: A means to address regional variability in intestinal drug absorption. *Pharma technology*. 2003, 27(2), 50-68.
9. Mathiowitz, Edith ed., Encyclopedia of controlled drug delivery, Vol-I, New York Wiley; 1999, 9-11.
10. H G Shivkumar, D Vishakante, Gwdaand T and M Pramod Kumar. Floating controlled drug delivery systems for prolong gastric residence. *IJPER*. 2004, 38(4), 172-179.