International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.4, pp 334-344, 2017

Design, Development and Evaluation of Fast Dissolving Film of Amlodipine Besylate

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Abstract : The present work aimed at preparing films of amlodipine with the reason of developing a dosage from for a very fast onset of action, which is beneficial in managing servere conditions of hypertension, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and using water. Amlodipine is a calcium channel blocker that dilates (widens) blood vessles, improves blood flow hence used to treat chest pain (angina) and other conditions caused by coronary artery disease. The films were prepared by a solvent casting method with polymers hydroxypropyl methylcellulose (HPMC) and superdisintegrants SSG. Compatibility study between drug and physical mixture was performed by FT-IR and DSC. The films were characterized for various physiochemical properties such as, physical appearance, surface texture, weight uniformity, thickness, drug content, swelling index, moisture content, in vitro study and stability study etc. Compatibility study showed no any kind of interaction between ingredients used. It was observed that concentration of polymer showed effects on physical parameter and dissolution time of formulation. A marked increase in the disintegration time was exhibited by fast-dissolving film containing low concentration of HPMC and highest concentration of superdisintegrants when compared with other films. Fast dissolving films of amlodepine can be considered suitable for clinical use in the treatment of heart disease and other conditions of coronary artery disease, where a quicker onset of action for a dosage form is desirable along with the convenience of administration

Keywords: Amlodipine besylate, fast dissolving film, physical charcterization, disintegration study, in vitro release profile.

Introduction

The pharmaceutical industry is no unfamiliar to the use of thin polymeric films for delivery of API, as many recommendations given by practitioner and over-the-counter treatments come in the form of transdermal patches/films. Because the drug given by oral route mostly the favored way for administering pharmaceutical active agents, however, the design of the orally-dissolving film as a drug delivery has fascinated substantial interest in recent years. The delivery of drug, orally is at present the gold standard in the pharmaceutical industry, where it is believed as the most suitable, secure and economical route of delivery of many pharmaceuticals. But still it requires some advancement because of its some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. To overcome various problems related to swallowing, chewing, chocking Fast Dissolving Tablets (FDTs) were designed in early 19th century. Mouth dissolving drug delivery systems were first developed in the late 1970s as an alternative to

tablets, capsules, and syrups. Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. The earliest developed fast dissolving technology existed in the tablet form and the rapid disintegrating properties resulted from special process or formulation modification Fast dissolving films are gaining popularity as an alternative to fast dissolving tablets as they eliminates patient's fear of chocking and overcome patient impediments[1].

Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions. Fast dissolving films generally consists of plasticized hydrocolloids or blends which can be laminated by using techniques such as hot -melt extrusion and solvent casting. Additionally they also provide easy delivery of drug under emetic condition. Mouth dissolving films are the new drug delivery system for delivery of drugs through oral cavity and were developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which when placed on the patient's tongue or any oral mucosal tissue gets instantly wet by saliva and rapidly hydrates and adheres onto the site of application. Film then rapidly disintegrates and dissolves to release the medication for absorption through or mucosal route or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets. [2]

Amlodipine besylate 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 dose10 mg one daily dose of Amlodipine besylate is given orally. Amlodipine besylate is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolitesexcreted in the urine. Amlodipine besylate have some adverse effect such as nausea, abdominal pain. Buccal patches of Amlodipine besylate retain in oral cavity thus increase bioavailability, reduces drug waste and decrease side effect such as gastric irritation and nausea [3].

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wetgranulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling [4].

Plasticizer is a essential constituent of the fast dissolving films. Plasticizer helps to get better flexibility of the film and trim down the brittleness of the films. It considerably improves the film forming properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients [5].

The prime aim of study was to develop fast dissolving film of Amlodipine besylate using different concentrations of hydroxyl propyl methyl cellulose, SSG, PVP and Polyethylene glycol 400 etc. Buccal patches of Amlodipine besylate are intended to facilitate administration of drug to those suffering from nausea or vomiting and also to patients with an upper gastrointestinal tract disease/infection or surgery which affects GIT absorption or having complexity in swallowing per oral drug.

Materials and Method

Material:

Amlodipine besylate was received as a gift sample from Macleod's Pharma, vapi, India, Hydroxy Propylmethyl Cellulose (E5) and PEG 400 obtained from Loba chemicals, Mumbai and Sodium starch glycolate (Loba chemicals, Mumbai) was purchased from local supplier. All the other reagents were used of analytical grade.

Experimental:

Drug – Excipients interaction study

The pure drug (amlodipine besylate), a mixture of amlodipine besylate with polymers HPMC E5 were mixed separately with IR grade KBr in the ratio of 1:100 and corresponding pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over a wave range of 4000 to 500 cm-1.in FT-IR instrument (8400 S Shimadzu) [6].

Differential scanning Colorimetry (DSC)

The DSC measurements were performed on a differential scanning calorimeter (DSC 822c, Mettler Toledo) with a thermal analyzer. Under nitrogen flow of 20 ml/min, 2 mg of amlodipine besylate film were placed in a sealed aluminium pan, and heated at a scanning rate of 50 ºC /min from 20 ºC to 200 ºC. An empty aluminium pan was used as reference [6].

Dose calculation

Amount of drug present in one film = 1.25 mg of amlodipine besylate.
Diameter of the proposed film = 0.7 cm.
Therefore area of the proposed film = 5 cm2
Diameter of plate = 8.8 cm.
Area of plate = 60.79 cm2
Number of films present in proposed area of the plate = 60.79/6
= 10.13 films
For this purpose the concentration of drug in formulation should be 12.5 mg.

Preparation of films:

The formulations of amlodipine besylate were prepared in the laboratory by solvent casting method using polymer such as HPMC and polyvinyl pyridine, sodium starch glycolate as a super disintegrant with the use of plasticizer (PEG-400). Amlodipine besylate was dissolved in 100 ml distilled water and then added 1.5 ml acetic acid, then agitated it, by using magnetic stirrer for atleast 2 h for complete dissolution of drug and exipients. Then, HPMC was dissolved in above mixture and then plasticizer PEG-400 was added at different concentrations 10% and 15% so as to form a flexible film. Sodium starch glycolate as a superdisintegrant 0.2-0.4% was also added into it. After complete stirring, solution was casted on a petridish by using mercury as a substrate (diameter 8.8cm) and films were dried at room temperature for 24 h. The film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose containing of 1.25 mg of drug. The samples were stored in desiccator atrelative humidity 30-35% until further analysis [7].

Table 1: Composition of different formulations containing amlodipine besylate

Formulation code	Drug (mg)	HPMC (%)	Polyethylene Glycol (%)	PVP (%)	SSG (super Disintegrant %)
F1	1.25	1	10	0.2	-
F2	1.25	1	10	0.4	-
F3	1.25	1	10	0.2	0.2
F4	1.25	1	10	0.4	0.4
F5	1.25	1.5	15	0.2	-
F6	1.25	1.5	15	0.4	-
F7	1.25	1.5	15	0.2	0.2
F8	1.25	1.5	15	0.4	0.4

Evaluation of Formulations

Physical appearance & Surface Texture:

This parameter was checked by doing visual inspection of films and texture of films is evaluated [8].

Determination of pH of Film:

For the determination of surface pH of the patch a small area of the film was cut and was allowed to swell by keeping it in distilled water for 1 h in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the film and allowing it to equilibrate for 1 min. The average of three determinations for each formulation was done [9].

Thickness Uniformity:

The thickness of the film was measured by using micrometer at three different points (Mitutoyo, Japan) and the mean value was calculated. The standard deviation of thickness was computed from the mean value [10].

Uniformity in Weight:

The weight variation test was carried out by weighing three films individually using digital balance (Shimadzu Inc., Japan). The mean weight of film was noted. The standard deviations of weight variation were computed from the mean value [11]..

Folding endurance

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2.5 cm × 2.5 cm (6.25 cm^2) was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed, and the values were reported [12].

Swelling property of film:

Film swelling studies is conducted using simulated saliva solution. A patch of 10 mm size diameter from every batch was weight on a pre-weight cover slip. It was kept in petridish and 10 ml phosphate buffer, pH 6.8 was added. After one hour, the cover slip was removed and measures the weight. The difference in the weight gives the weight increase due to absorption of water and swelling of patch. [13] The degree of swelling was calculated using formula;

$$\propto = \frac{wt - wo}{wt}$$

Where: wt is weight of film at time t, and wo is weight of film at time zero.

Percentage Moisture loss Test:

Percentage moisture loss test was determined by keeping the films in a desiccator containing anhydrous calcium chloride. After 3 days, the films were taken out, re-weighed and the percentage moisture loss was calculated using the following formula [14]

$$\%Moisture\ Loss = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Drug Content Uniformity:

To check the uniformity of the drug in the film three films were taken out from each batch. Each film was then placed in volumetric flask containing 10ml of distilled water and shaken to extract the drug from film. One milliliter of above resulting solution was withdrawn, after suitable dilution with distilled water then

analyzed UV- spectrophotometrically at 239 nm using distilled water as blank. The mean and standard deviation of drug content of three randomly selected films were calculated. The same procedure was adopted for all the batches and drug content was noted [15].

Disintegration Test:

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films strips [16].

In vitro dissolution studies:

In vitro release of drug from all formulations was determined using USP apparatus type II (Paddle method). The following conditions were followed to study the in-vitro dissolution study of Amlodipine Besylate mouth dissolving film [13]

1. Dissolution apparatus: USP Type II (Paddle method)
2. Volume of dissolution medium: 900 ml
3. Temperature: 37±0.200C
4. Dissolution medium: simulated salivary fluid (pH6.8)
5. Sampling interval: 2 min
6. Quantity of sample withdrawn: 5ml

Samples were assayed spectrophotometerically at 239 nm. Three trials were carried out for all the samples and the average value was taken. The percentage of the drug dissolved at various time intervals was calculated and plotted against time.

Stability Study

Stability studies were carried out on formulation F3, according to ICH guidelines by storing replicates of strips (packaged in aluminium foil) in a humidity chamber, with a relative humidity of 75± 5% and a temperature of 40±0.5 °C. At periodic intervals the samples were taken out at 0,15, 45 and 90 days and the period for their degradation of the strip was checked. Samples were also analyzed for drug content [17].

Result and Discussion

Several methods were described in the methodology for the development and evaluation of film containing amlodipine besylate as a drug. These formulations were intended to produce immediate release of drugs in the buccal region. The result and discussion are described under different heading as follows. Fast-dissolving films of amlodipine besylate were evaluated for various parameters. In the present study, eight formulations were prepared by varying the polymer concentration, and by using different polymers

Drug-Excipients compatibility studies:

As described in the methods, FT-IR studies were carried out on pure drugs and along with the polymer. There were no any kind of interaction was observed between drug and excipients used in the development of films. IR spectra of amlodipine besylate, HPMC E5 combinations are shown below;

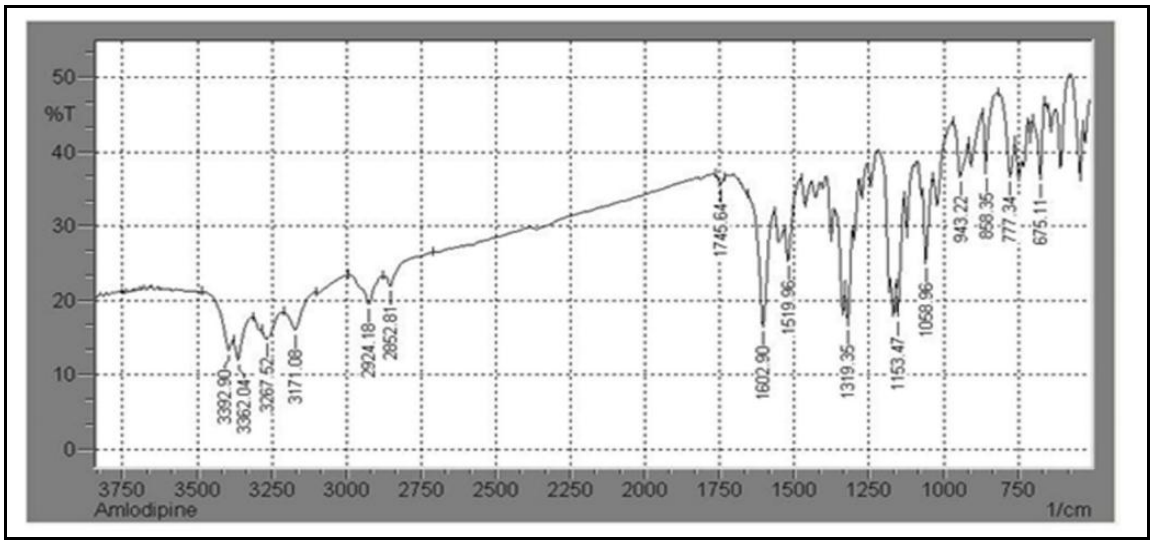

Fig. 1: FTIR Spectra of amlodipine besylate

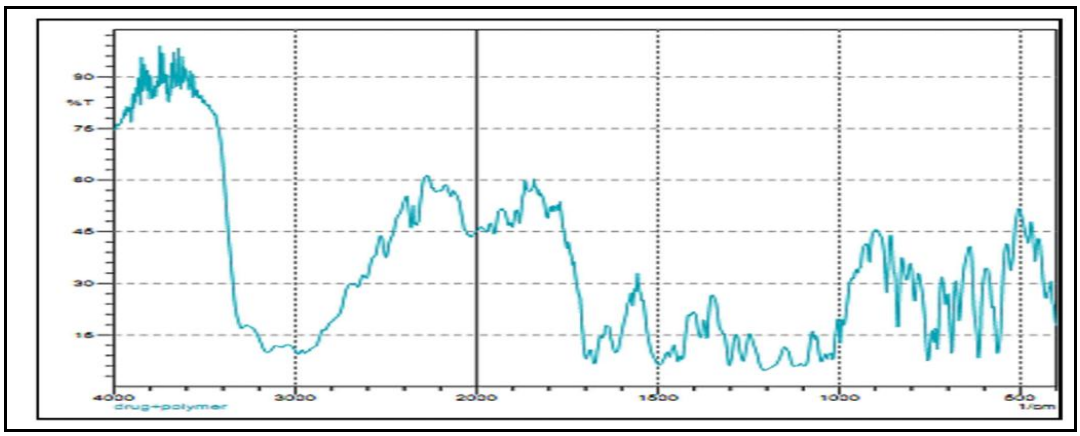

Fig. 2: FTIR Spectra of amlodipine besylate + HPMC E5

Table 2: Peak and chemical group present in IR spectra of amlodipine besylate

Peak (cm-1)	Chemical Group
3392.90	NH2 stretching mode
2924.18	CH3 stretching mode
1745.64	O-C=O stretching mode
1319.36	O stretching mode
1602.90	C=C stretching (in ring) aromatics
1153.47	C-N stretching Aliphatic amines

Differential Scanning Colorimetry (DSC):

The DSC thermogram of pure drug and polymer utilized in the system of formulations are presented in following figure;

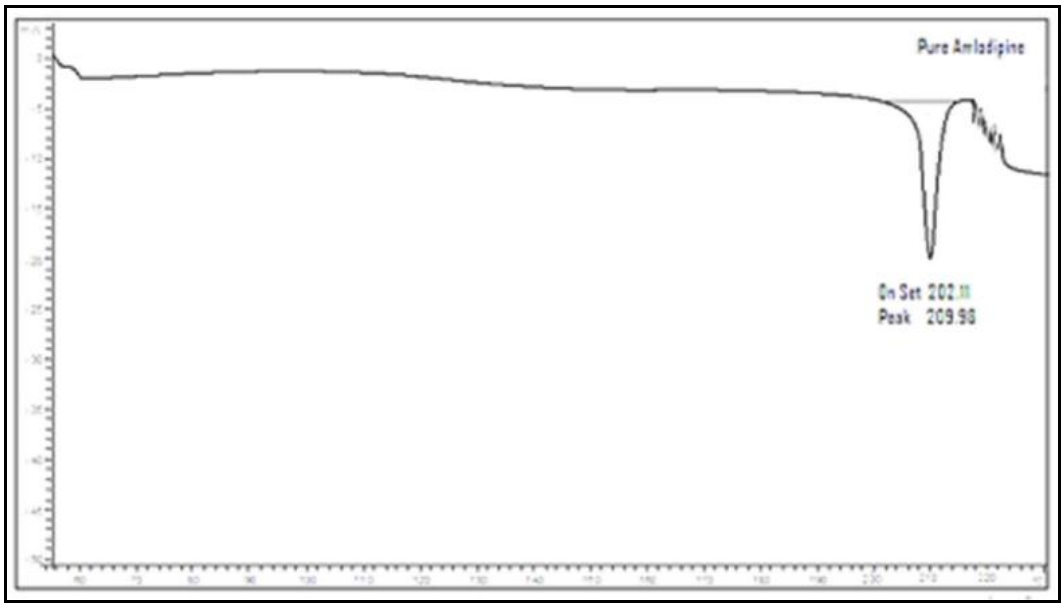

Fig. 3: DSC thermogram of Amlodipine besylate

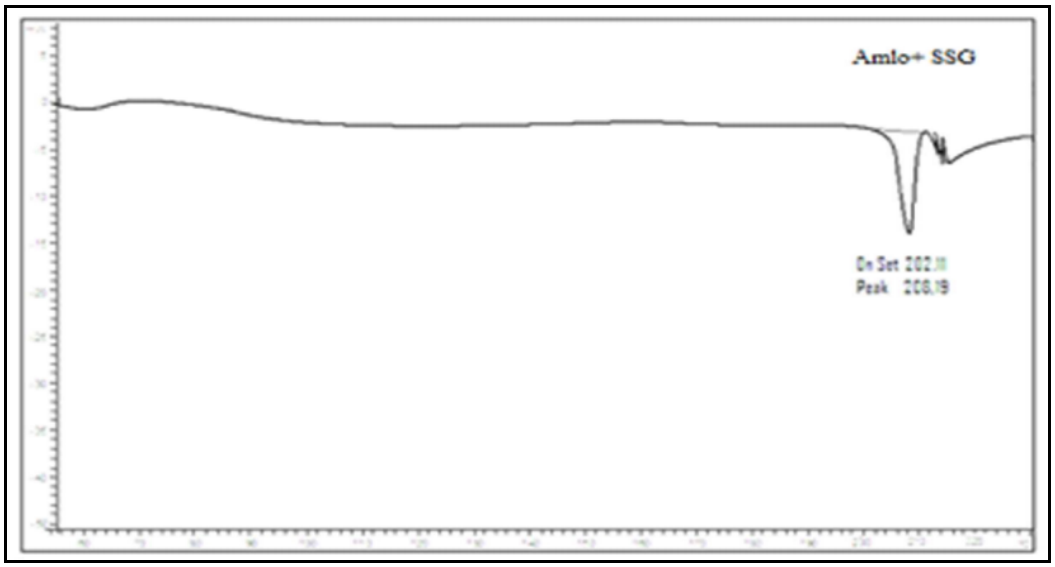

Fig. 4: DSC thermogram of amlodipine besylate + Sodium starch glycolate

Physical appearance and Surface texture of developed patches along using different concentration of HPMC showed that films were found to be smooth with somewhat different apperance when observed. All the films prepared with different polymer concentrations were found to be flexible, transperparant, smooth, non-sticky, and homogeneous.

Drug loaded film was tested for uniformity of weight and the results are given in the table 3. The weight of all the prepared batches was found to quite uniform. Weight of all the film ranged between 12.32 and 15.88 mg. The change in the concentration of polymers and plasticizer could significantly show the difference in the weight of film.

The surface pH was found to be in the range of 6.0-6.7, which is close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients

The thicknesses of drug-loaded film were measured with the help of Digimatic Caliper. The mean values are shown in the table. The drug loaded film of amlodipine besylate did not show any significant change in the thickness of film. But the marginal difference in the thickness was observed among each group indicated

that more the amount of polymer, higher the thickness values. It was observed that there was no significant difference in the thickness among the films, which indicated that the films were uniform.

All the films, showed good folding endurance (near to 200), indicated that the films have good flexibility. The percentage moisture loss was determined in triplicate. When the formulations were kept at very dry condition, the moisture loss had been occurred. Formulation F1 showed the maximum amount of moisture loss 7.38 % and formulation F8 had shown less amount of moisture loss 4.88%. Percentage moisture loss was decreased by increase in film thickness. The lower value in all the formulations indicated that, the integrity of the film was maintained at dry conditions and it was viewed by observing the films after percentage moisture loss test.

The content uniformity test is commonly employed for unit dosage forms. In order to make sure about the uniform dispersion of drug in film, the drug content was carried out. The drug content was analyzed at 239 nm by using suitable blank. All the formulations showed more than 90% of the drug loading indicating much of the drug is not lost. The results were expressed in table 4 . The results indicated that the drug was uniformly dispersed.

The swelling index study was carried out in pH 6.8 phosphate buffer solution. The swelling index of the formulations F1 to F8 was mentioned in table. Among these six formulations F8 showed high swelling index and F1 showed low swelling index. Among these six formulations F8 showed high swelling index and F1 showed low swelling index as shown in table 4. Formulations containing max concentration of HPMC & superdisintegrants showed high swelling index due to the more water absorption as compared to the other formulations.

Table:3 Evaluation parameters of oral fast dissolving film of Amlodepine

Film code	Surface Texture	Transperancy	Thickness (mm)	Avg. weight (mg)	Moisture loss (%)	Folding Endurance
F1	++-	Best	0.130	12.32	7.38	169
F2	++	Best	0.147	13.9	6.30	154
F3	+++	Best	0.151	13.82	5.12	149
F4	+++	Best	0.157	14.12	5.44	167
F5	++	Good	0.165	14.38	5.62	189
F6	++	Good	0.167	14.36	5.51	175
F7	++-	Good	0.172	15.61	4.95	194
F8	++	Good	0.176	15.88	4.88	178

(+) Indicates Smooth Surface, (-) Indicate Rough Surface. Each value is the mean, n = 3 determinations

Table: 4 Evaluation parameters of oral fast dissolving film of Amlodepine

Film code	Surface pH	Disintegration Time (sec)	Drug content (%)	Sweling Index
F1	6.7	32	94.07	56.45
F2	6.5	29	96.09	59.11
F3	6.4	24	98.23	78.56
F4	6.1	19	99.20	72.34
F5	6.0	55	89.38	69.75
F6	6.2	59	97.07	57.54
F7	6.7	46	99.54	88.45
F8	7.0	38	96.93	86.64

Each value is the mean, n = 3 determinations

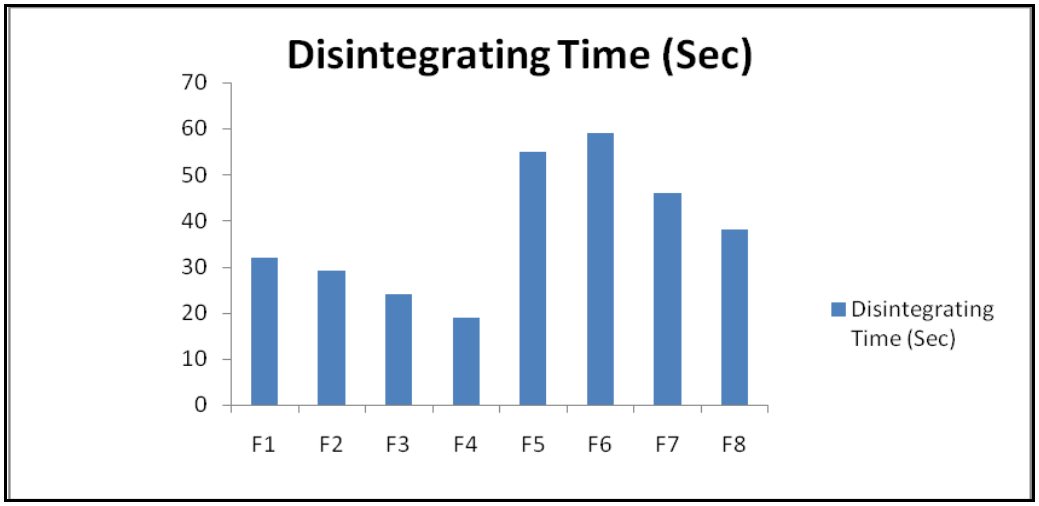

Fig. 5: Disintegration time (sec) of prepared formulations

In-vitro dissolution study:

In-vitro drug dissolution study of various formulations was carried out in PBS pH 6.8; the release data of formulations are shown in table: The optimized formulation F4 was selected for stability studies on the basis of in-vitro disintegration time and results of pysicochemical parameter. Dissolution time was found to be increased by decreasing the concentration of SSG. As it was also observed that the concentration of HPMC also have effect n release of drug from films.As the concentration of HPMC is low along with max concentration of SSG release was greater as compared to other formulations. Drug released was found to be highest for F4 with minimum time and release rate was decreased as the concentration of HPMC is high without any superdisintegrants. The results were tabulated as follows;

Table: 5 In-vitro dissolution study of selected formulations

Time (min)	F2	F3	F4	F6	F7	F8
0	0	0	0	0	0	0
2	7.46±0.12	14.58±0.16	17.65±0.12	11.45±0.15	13.25±0.2	12.46±0.5
4	16.58±0.68	29.64±0.13	39.48±0.45	25.12±0.11	27.45±0.6	28.14±0.13
8	40.15±0.42	59.78±1.2	64.78±0.21	34.89±0.27	38.86±0.12	40.12±0.12
12	65.24±0.31	74.15±0.54	78.12±0.16	54.23±0.22	54.19±0.4	56.32±0.14
16	76.47±0.12	91.68±0.64	97.96±0.1	70.12±0.26	69.42±0.34	79.52±0.24
20	89.45±0.3			81.36±0.74	92.78±0.16	98.45±0.23
24				96.23±1.2		

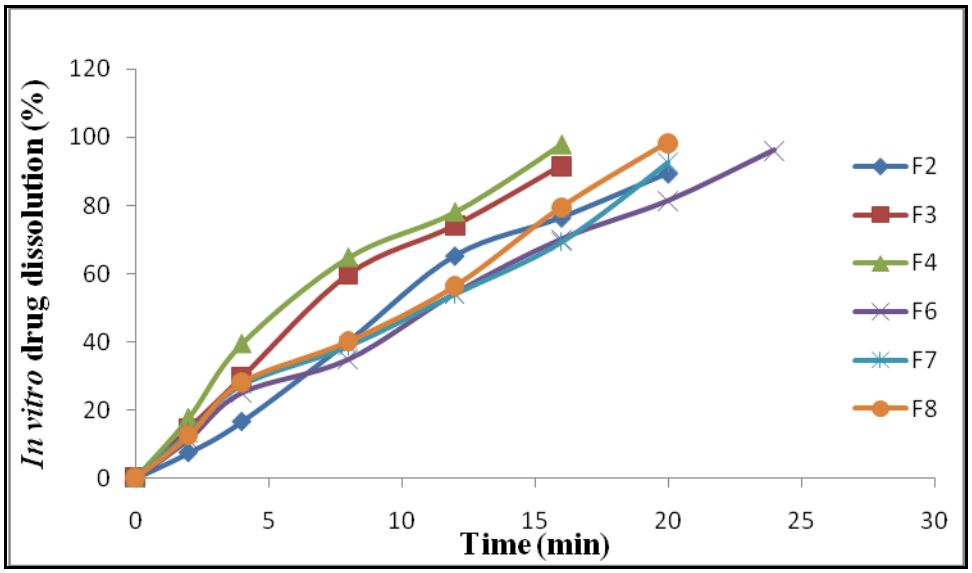

Figure: 6 In-vitro dissolution study of selected formulations

Stability studies

The optimized formulation F4 was evaluated at the time interval of 30 and 60 days for all the parameters like Appearance, Weight, Thickness, % and drug content. The observations of stability studies of optimized formulation F4 are shown in table 14 and 15 and it did not show any significant change in these parameters after stability studies. This confirms the stored film formulation were stable for the storage period.

Table 6: Characterization of Films after stability study (F4)

Duration	Visual Appearance	Weight of film (mg)	Thickness of films(mm)	% Drug Content
0 days	Transparent	14.12	0.157	99.20
30 days	Transparent	14.09	0.151	98.85
60 days	Transparent	13.98	0.149	98.12

Table 7: In- vitro release of drug after stability study (F4)

% CDR of F4 formulation after stability study			
Time (min)	**0 days**	**30 days**	**60 days**
2	17.65	16.20	18.45
4	39.48	36.56	31.78
8	64.78	59.52	59.63
12	78.12	72.45	71.12
16	97.96	96.69	94.56
20			

Conclusion

In this study, Amlodipine Besylate fast dissolving films were prepared using polymer HPMC (E5) by solvent casting method. The eight preliminary batches arranged/prepared to obtained final optimized batch. It was observed that concentration of polymer effects the formation of film and dissolution time of the formulations. FTIR and DSC study indicated that there is no interaction between the drug and excipients. The quality control tests results were within the acceptable limits. In this study best formulation was chosen from

each polymer based on release parameters. F4 formulation is considered as the best according to the obtained results with disintegrating time of 19 sec and complete drug release in 16 min. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. As the concentration of SSG was increased, both the disintegration and the drug release rates increased. The disintegration and release rates were found to be faster for films prepared with lowest concentration of HPMC alongwith maximum concentration of superdisintegrants.

Acknowledgement:

The authors would like to acknowledge the Principal, R C Patel Institute of Pharmaceutical Education and Research Shirpur, for providing the necessary facilities to carry out the research work.

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