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Novel Application Of Mixed Solvency Concept In Formulation And Development Of Fast Dissolving Oral Films Of Poorly Water Soluble Drug, Amlodipine Besylate And Their Evaluations

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ABSTRACT: Aim- The aim of present research is to formulate and develop fast dissolving oral films of amlodipine besylate as small as possible which can be placed on the tongue and also to increase the drug loading. For formulation development, for uniform film casting, it is required that drug should be present in dissolved form. So, to increase the solubility of drug different solubilizers were used in various concentrations. As per the mixed solvency concept proposed by R.K. Maheshwari, each and every substance present in the universe has got solubilizing property i.e., all the liquids, gases and solids possess solubilizing power. As per this concept, each substance is solubilizer. Mixed solvency concept can be used as a tool to reduce the overall concentration of solubilizers needed to produce considerable increase in solubility of poorly water soluble drugs. **Materials and Methods-** For poorly water soluble drug, amlodipine besylate, different combinations of solubilizers such as sodium caprylate, sodium benzoate, PVP K-25 and lysine hydrochloride as mixed solvent systems were used to decrease the overall solubilizer concentration which is required to produce substantial increase in solubility of amlodipine besylate resulting in formulation of oral films by solvent casting method. The procured sample of amlodipine besylate was characterized by UV spectroscopy, melting point and DSC studies. The prepared formulations were evaluated for various properties such as appearance and texture, thickness, folding endurance, surface pH, disintegration time, drug content, TLC studies and dissolution rate studies. **Results and Conclusion-** Fast dissolving oral films of amlodipine besylate were formulated successfully. Mixed solvency concept has been successfully employed for enhancing the drug loading of poorly water soluble drug, amlodipine besylate.

KEYWORDS: Mixed solvency concept,amlodipine besylate, fast dissolving oral films, solubility.

I. INTRODUCTION

The most generally acceptable drug delivery system is oral drug delivery, since it offers multiple benefits compared to other drug delivery systems. But manufacturers bend towards parenteral and liquid orals due to certain drawbacks such as lower drug bioavailability, longer onset time and dysphagia patients. Whereas liquid orals have the issue of specific dosing and are also uncomfortable for the administration of parenteral drugs, which causes patient incompliance. For any drug product, three significant factors are bioavailability, faster action (if necessary) and patient compliance. Each company therefore needs to formulate products that satisfy these three variables according to the need of the patient to increase their market profile[1]. The main objective of any drug delivery system is to have optimum concentration at the drug's site of action in order to reach therapeutic levels and maintain them.

- **Fast dissolving oral film (FDF)**

This novel drug delivery system was created as a replacement for standard oral dosage forms for patients who have trouble swallowing drugs, as well as patients who are bed-ridden, geriatric, and paediatric patients. Orally disintegrating tablets are present in the market, offering one to two minutes of disintegrating time. The invention of mouth dissolving films marked a major development in the oral disintegrating drug delivery system. Much attention is gained by the different avenues explored for the rapid drug releasing product, mouth dissolving film process[2].

The regulatory authorities have recently widened the spectrum of 'oro mucosal preparations' to include oral films and oro dispersible films.

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Mouth dissolving films are referred to as soluble films by the US Food and Drug Administration (USFDA). In its 7.4 edition, including 'mucoadhesive preparation' and 'quick dissolving film', the European Pharmacopoeia monograph on oro mucosal preparations was revised. In the monograph, mouth dissolving films are defined as dispersing single or multilayer sheets of suitable material quickly[3].

Mouth dissolving films contain active molecules that are dissolved or released in the film, putting the film on the patient's tongue where it disintegrates and dissolves in order to release the medication for absorption. The problem of drug administration in some classes of patients, such as paediatrics, geriatrics, bedridden, nauseous, or noncompliant patients, prompted scientists to create new dosage alternatives from the oral route, with mouth-dissolving film being one of the oral route's alternative dosage types.

- **Drug release mechanism ofFDF**

A very thin film applied on the tongue is the mouth dissolving oral film, is immediately wetted by saliva, disintegrates and quickly dissolves to release the drug. Oral mucosa absorbs this released substance directly into the systemic circulation. A possible site for drug administration is oral mucosal drug delivery. It has a quick onset of action, improved drug bioavailability, and bypasses pre-systemic removal in the GI tract. Since the oral mucosa is extremely permeable and has a high blood flow, the drug is absorbed directly into the bloodstream.A very thin film applied on the tongue is the mouth dissolving oral film, is immediately wetted by saliva, disintegrates and quickly dissolves to release the drug. Oral mucosa absorbs this released substance directly into the systemic circulation. A possible site for drug administration is oral mucosal drug delivery. It has a quick onset of action, improved drug bioavailability, and bypasses pre-systemic removal in the GI tract. Since the oral mucosa is extremely permeable and has a high blood flow, the drug is absorbed directly into the bloodstream.In the present research work mixed solvency concept has been employed to formulate fast dissolving oral film of poorly water soluble drug, amlodipine besylate[4].

- **Mixed Solvency Concept**

As per the mixed solvency concept proposed byR.K. Maheshwari, each and every substance present in the universe has got solubilizing property i.e., all the liquids, gases and solids possess solubilizing power. As per his statement, each substance is a solubilizer. A concentrated aqueous solution containing various water soluble substances may act as good solvent for poorly water soluble drugs[5]. By combining various excipients, additive and synergistic solvent actions are expected which has advantage of reducing the toxicities. For a desired solubility enhancement, a single solubilizer may prove toxic for human being but the combination of different excipients in safe smaller concentrations solves the problem of toxicity for the same desired solubility of drug.[6-29]

In the present research work mixed solvency concept has been employed to formulate fast dissolving films of poorly water soluble drug, amlodipine besylate.

II. MATERIALS AND METHOD

MATERIALS

Amlodipine besylate drug was obtained as a gift sample from MCW HealthcarePrivate Limited, Indore. Other chemicals used were of analytical grade. Milli-Q water was used in the study.

METHODS

- **UV spectra of amlodipine besylate**

About 50 mg of amlodipine besylate (accurately weighed) and 400 ml of Milli-Q water (Type 1 ultrapure water) were taken in a volumetric flask of 500 ml capacity. Then, the flask was shaken to dissolve the drug completely. After that, the volume was made with Milli-Q water up to 500 ml to obtain the stock solution of 100 µg/ml concentration. Now, 10 ml stock solution was diluted upto 50 ml with Milli-Q water to achieve a dilution of 20 µg/ml concentration. The resulting solution was scanned between 200-400 nm on Shimadzu-1700 UV spectrophotometer against Milli-Q water. The spectrum is displayed in figure 1.

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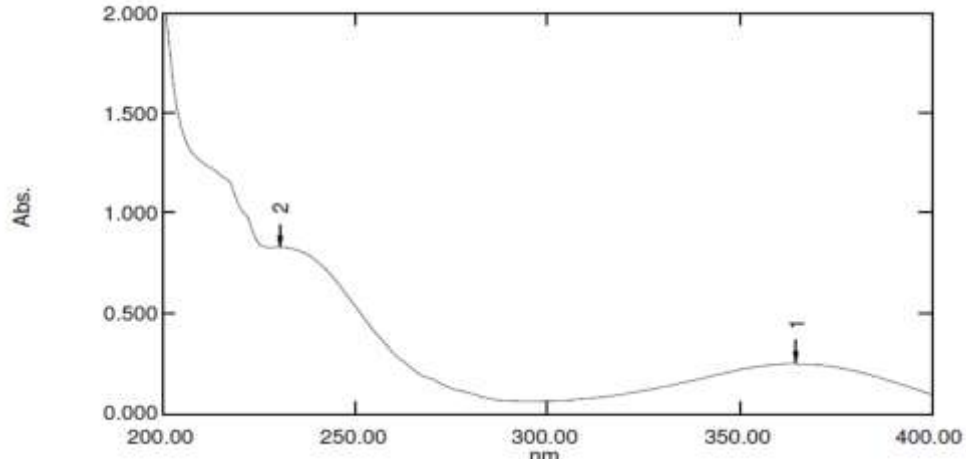

Figure 1: U.V. Spectra of amlodipine besylate in Milli-Q water

- **Melting point determination**

The melting point of the drug was determined by using open capillary method. The drug sample was packed in the capillary and the melting range was determined by Analog melting point test apparatus.

- **Differential scanning calorimetric studies**

Differential scanning calorimetry (DSC) measures the heat loss or gain resulting from physical changes within a sample as a function of temperature. In order to obtain the DSC, the DSC thermograms (perkin elmer DSC 6000), 2.5 mg of drug sample was weighed accurately and placed in aluminium crucible. The crucible was sealed and placed on the heating cell and covered with a glass bell jar. An empty aluminium crucible was used as reference. Heating at the rate of 20 ºC/min with a continuous purge of nitrogen (45 CC/min) was done with recording of energy changes in the sample with respect to the reference in the temperature range of 50-250 ºC. DSC thermogram (melting isotherm) is shown in fig. 2.

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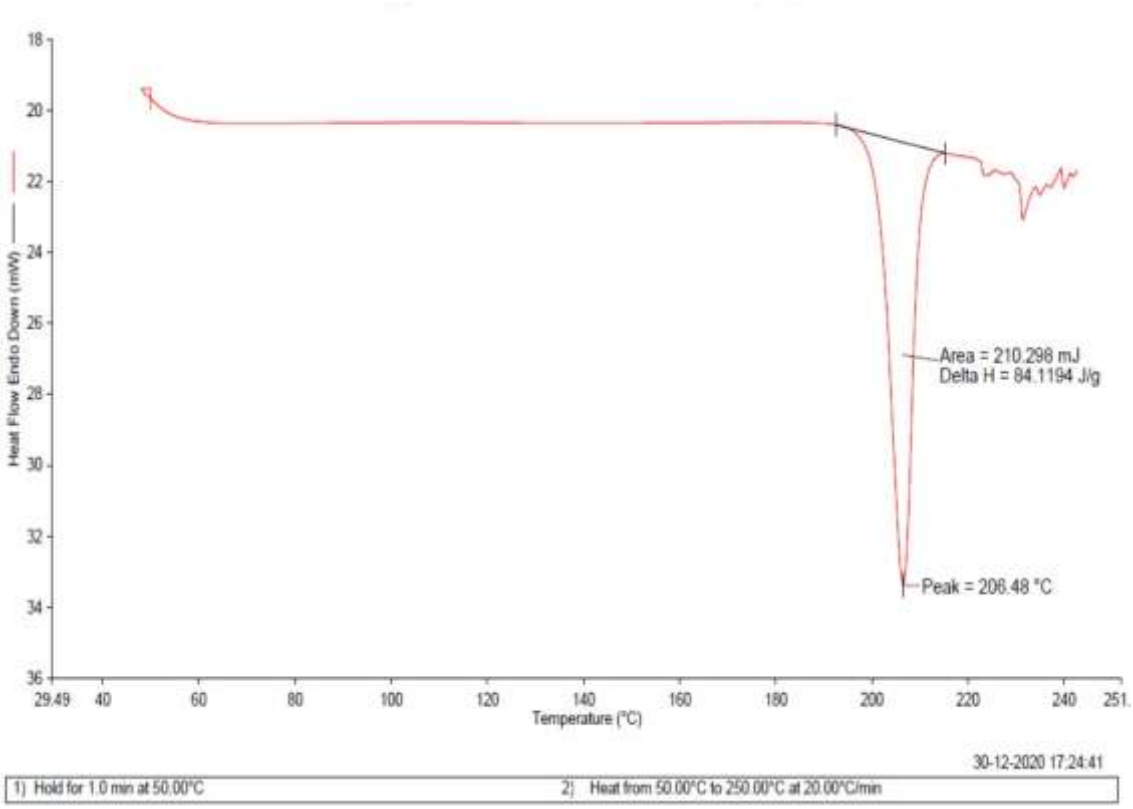

Figure 2: DSC curve of amlodipine besylate

- **Preparation of calibration curve of amlodipine besylate in water (Milli-Q)**

Fifty milligram of amlodipine besylate drug was accurately weighed and transferred to a 10-ml volumetric flask. To this 30% w/v sodium caprylate solution (about 8 ml) was added to dissolve the drug and then volume was made up to 10 ml with 30% w/v sodium caprylate solution so as to obtain resulting solution (stock solution) of 5000 µg/ ml. Appropriate dilutions were made from stock solution with Milli-Q water in concentration range of 20-100 µg/ml. Using a double beam UV visible spectrophotometer (Shimadzu 1700) at 368 nm against the respective reagent blanks, the absorbance of the resulting drug solutions was observed. The data is written down in table 1 and graphically represented in fig 3.

Table 1: Absorbance data for calibration curve of amlodipine besylate in Milli-Q water (n=7)

S.No.	Concentration (µg/ml)	Absorbance (mean ± S.D.)
1	0	0
2	20	0.267 ± 0.0219
3	40	0.521 ± 0.0426
4	60	0.751 ± 0.0403
5	80	0.983 ± 0.0466
6	100	1.213 ± 0.0553

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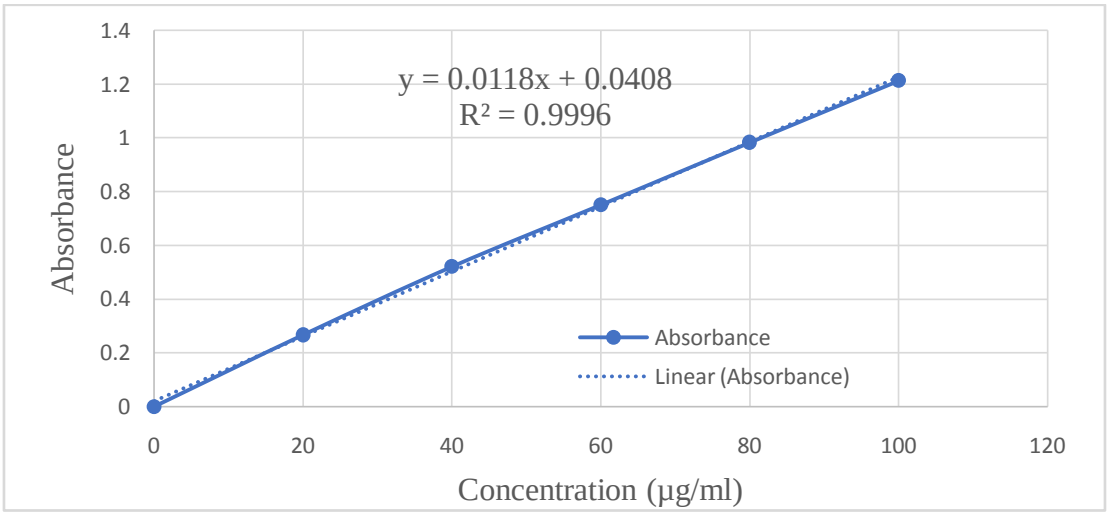

Figure 3: Calibration curve of amlodipine besylate in Milli-Q water at 368nm

- **Preparation of calibration curve of amlodipine besylate in phosphate buffer of pH 6.8**

Fifty milligram of amlodipine besylate drug was accurately weighed and transferred to a 10-ml volumetric flask. To this 30% w/v sodium caprylate solution (about 8 ml) was added to dissolve the drug and then volume was made up to 10 ml with 30% w/v sodium caprylate solution. so as to obtain resulting solution (stock solution) of 5000 µg/ ml. Appropriate dilutions were made from stock solution with phosphate buffer 6.8 in concentration range of 20-100 µg/ml. Using a double beam UV visible spectrophotometer (Shimadzu 1700) at 368 nm against the respective reagent blanks, the absorbances of the resulting drug solutions were observed. The data is written down in table 2 and graphically represented in fig4.

Table 2: Absorbance data for calibration curve of amlodipine besylate in phosphate buffer (n=5)

S.No.	Concentration (µg/ml)	Absorbance (mean ± S.D.)
1	0	0
2	20	0.268 ± 0.0115
3	40	0.511 ± 0.0353
4	60	0.768 ± 0.0382
5	80	0.985 ± 0.0259
6	100	1.219 ± 0.0346

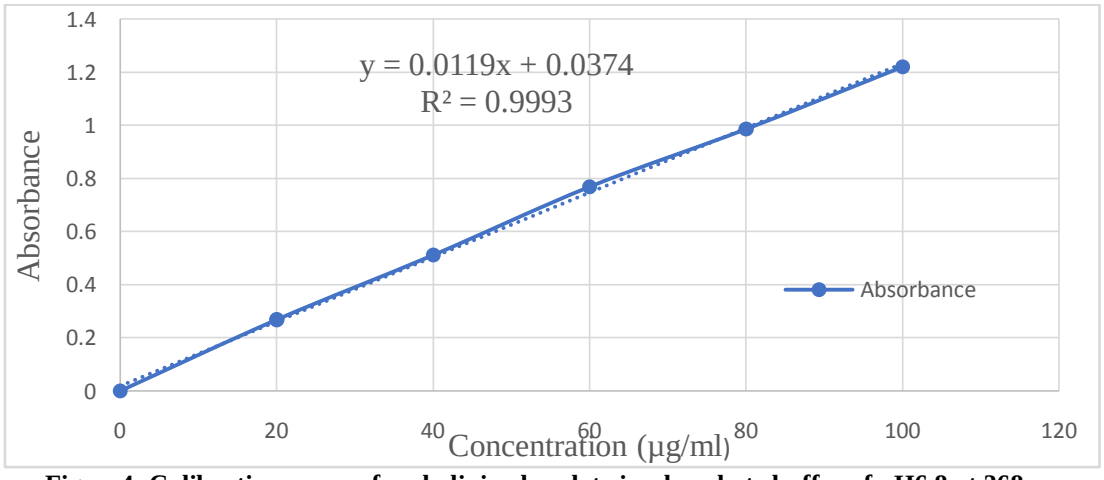

Figure4: Calibration curve of amlodipine besylate in phosphate buffer of pH6.8 at 368nm

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- **Drug solubilizers incompatibility studies**

The compatibility of the drug with excipient was assessed by drug-excipient interaction studies. The drug was mixed with excipient in ratio of 1:1 and properly filled in vials made up of glass, capped and sealed. Both at room temperature and in the refrigerator, the vials of each sample were being kept for 1 month. Every week (1 month), the vials were retrieved and changes were observed (if any) in physical appearance and colour. Results are given in table3.

Table3: Observations of drug solubilizers incompatibility studies

S. No.	Drug solubilizer (1:1 blend)	Initial	Refrigerated condition (2-8 ° C)				Room temperature (25º)			
			1wk	2wk	3wk	4wk	1wk	2wk	3wk	4wk
1.	Amlodipine besylate	WP	UC	UC	UC	UC	UC	UC	UC	UC
2.	Amlodipine besylate + Sodium benzoate	WP	UC	UC	UC	UC	UC	UC	UC	UC
3.	Amlodipine besylate + Lysine hydrochloride	WP	UC	UC	UC	UC	UC	UC	UC	UC
4.	Amlodipine besylate + Sodium caprylate	WP	UC	UC	UC	UC	UC	UC	UC	UC
5.	Amlodipine besylate + PVP K 25	WP	UC	UC	UC	UC	UC	UC	UC	UC
6.	Amlodipine besylate + HPMC E-5	WP	UC	UC	UC	UC	UC	UC	UC	UC
7.	Amlodipine besylate + HPMC E-15	WP	UC	UC	UC	UC	UC	UC	UC	UC
8.	Amlodipine besylate + Glycerine	WS	UC	UC	UC	UC	UC	UC	UC	UC

WP- White Powder, WS- Whitish Suspension, UC- Unchanged

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- **Interference studies of solubilizers in the spectrophotometric estimation of amlodipine besylate**

Different excipients such as sodium caprylate, sodium benzoate, PVP K-25 and lysine hydrochloride were used for the interference study. To determine UV spectrophotometric interference, standard solution of drug was prepared in Milli-Q water alone and also with the excipients. Precisely, 50 mg of the drug was weighed and dissolved in 450 ml of Milli-Q water taken in a 500 ml volumetric flask and heated to 50-60 ºC with rapid shaking until a clear solution was formed and, after cooling, up to 500 ml of Milli-Q water was used to make a stock solution of the drug (100 µg/ml).Then, 10ml of the above solution was taken and diluted up to 50ml with Milli-Q water. This gives a solution of 20µg/ml. Likewise, solutions of excipients were prepared by dissolving 50mg of each solubilizer in 450ml Milli-Q water and volume were made up to 500 ml with Milli-Q water to obtain 100 µg/ml stock solution. From the above solution, 20ml of stock solution of drug (100 µg/ml) and 40 ml of stock solution of excipient (100 µg/ml) were taken in a 100ml volumetric flask and volume was made up to 100ml with Milli-Q water. The absorbances were recorded against water at 368 nm and results are shown in table4.

Table4: Interference studies of drug and solubilizers in the spectrophotometric estimation of amlodipine besylate

Drug	Solubilizer	Concentration of drug (µg/ml)	Concentration of solubilizers (µg/ml)	Wavelength (nm)	Absorbance against water
Amlodipine besylate	-	20	-	368	0.265
Amlodipine besylate	Sodium caprylate	20	40	368	0.267
Amlodipine besylate	Sodium benzoate	20	40	368	0.266
Amlodipine besylate	Lysine hydrochloride	20	40	368	0.259
Amlodipine besylate	PVP K-25	20	40	368	0.268

- **Solubility studies:**

a) Equilibrium solubility determination

Solubility study of amlodipine besylate was carried out in Milli-Q water and phosphate buffer of pH 6.8. Excess drug was weighed and added to 20 ml of Milli-Q water and 20 ml of buffer phosphate of pH 6.8 in vials. Rubber closure and aluminium caps were used to seal the vials. These vials were then kept in the water bath shaker for continuous shaking (Scientech) at room temperature for 24 hrs and then was permitted to stand for 24 hrs uninterrupted. Now, Whatman's filter paper grade no. 41 was used to filter both the drug solutions. Aliquot of the filtrate were suitably diluted with Milli-Q water and the dilutions were analysed on UV-Visible spectrophotometer (Shimatzu 1700). Results are given in table 5.

Table 5: Equilibrium solubility data of amlodipine besylate

S.No.	Solvent systems	Solubility
1.	Milli-Q water	0.111 %
2.	Phosphate buffer of pH 6.8	0.060 %

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b)Approximate solubility study of amlodipine besylate in various aqueous solutions containing individual solubilizers and their blends:

Preparation of different solubilizer solutions:

For preparing solutions of various blends containing different solubilizers (sodium caprylate, sodium benzoate, lysine hydrochloride, PVP K-25), required quantities of solubilizers were weighed and then transferred into 10 ml volumetric flask. Now small amount of Milli-Q water was added and flask was shaken well so that solubilizers get completely dissolved. Finally, volume was made upto the mark i.e., upto 10 ml with Milli-Q water. Then, the solutions were filtered. Solubility studies were performed in these solutions.

For approximate solubility determination, one ml of the above prepared solution of individual solubilizer was placed in a vial of the capacity 10 ml and 2.5 mg of amlodipine besylate (drug) was weighed accurately and then it was added in the one ml of the solution with continuous shaking for 15-20 minutes on vortex shaker (Remi cm 101 plus). If the drug got dissolved, then again 2.5 mg of drug was added and shaking was done likewise. The drug was added in the same way till a saturated solution (nearly) is obtained. This is denoted by the stage when a suspension is obtained even after 20 minutes shaking Now, approximate solubility was determined. Results are shown in table 6.

Table 6: Approximate solubility data of amlodipine besylate in aqueous solutions containing individual solubilizers

S.No.	Solution of solubilizers (w/v)	Approximate solubility (mg/ml)
1.	30 % w/v Sodium caprylate	25
2.	30 % w/v Sodium benzoate	2.5
3.	20 % w/v Lysine hydrochloride	2.5
4.	15 % w/v PVP K-25	7.5

c) Solubility determination of amlodipine besylate in various aqueous solutions of solubilizers (blends)

In order to make 10 ml of blend A, 0.5 gm sodium benzoate, 1.0 gm sodium caprylate, 0.5 gm arginine, 1.0 gm lysine hydrochloride, 0.5 gm poloxomer 407 and 0.3 gm benzoic acid were taken in a 10 ml volumetric flask. About 8 ml of Milli-Q water was added and the flask was completely shaken for about 15-30 minutes on vortex shaker. After complete dissolution of solubilizers, volume was made upto 10 ml with Milli-Q water. Same procedure was followed for preparation of other blends.For solubility determination, one ml of the above prepared blends of solubilizers were placed in a 10 ml vial and 5 mg of amlodipine besylate (drug) was weighed accurately and then it was added gradually in one ml of the solution with continuous shaking for 15-20 minutes on vortex shaker (Remi cm 101 plus). If the drug got dissolved, then again 5 mg of drug was added and shaking was done likewise. The drug was added in the same way till a saturated solution (nearly) is obtained. This is denoted by the stage when a suspension is obtained even after 20 minutes shaking Now, approximate solubility was determined. Now, approximate solubility was determined. The solubility of amlodipine besylate in the mixed blends of solubilizers is represented in table 7.

Table 7: Approximate solubility data of amlodipine besylate in blends

S.No.	Blend code	Composition of blends (% w/v)	Approximate solubility (mg/ml)
1.	Blend-A	10% w/v Sodium caprylate 5% w/v Arginine 5% w/v Lysine HCl 5% w/v Poloxomer 407 3% w/v Benzoic acid	25
2.	Blend-B	10% w/v Sodium caprylate	25

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		5% w/v Sodium benzoate 5% w/v Lysine HCl 5% w/v Poloxomer 407	
3.	Blend-C	10% w/v Sodium caprylate 10% w/v Poloxomer 407 5% w/v Lysine HCl	25
4.	Blend-D	15% w/v Sodium caprylate 5% w/v Lysine HCl	25
5.	Blend-E	10% w/v Sodium caprylate 5% w/v Sodium benzoate 5% w/v Lysine HCl 5% w/v PVP K-25	45
6.	Blend-F	10% w/v Sodium caprylate 5% w/v PVP K-25 5% w/v Lysine HCl	35
7.	Blend-G	5% w/v Sodium caprylate 10% w/v Arginine 5% w/v Valine 5% w/v Benzoic acid	20
8.	Blend-H	5% w/v Sodium caprylate 5% v/v Sodium benzoate 5% v/v Sodium citrate 10% w/v Arginine 5% w/v Poloxomer 407 10% v/v Lysine HCl	30

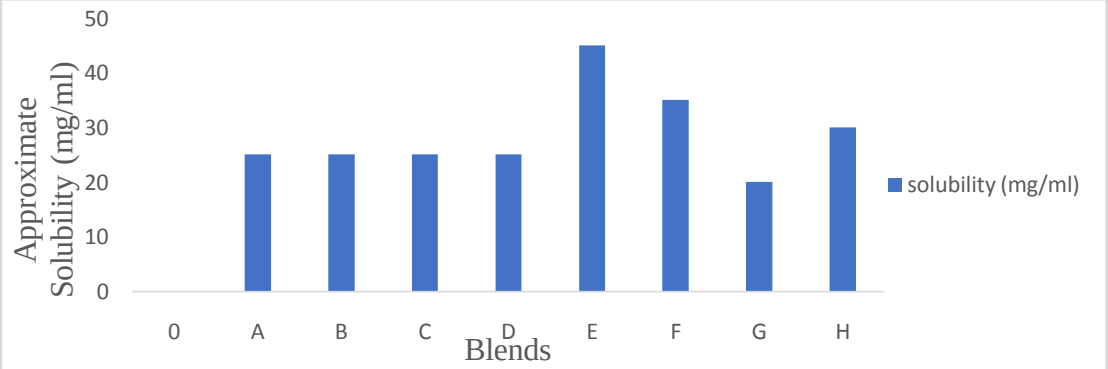

Figure 5: Graphical representation of solubility of amlodipine besylate in various aqueous solutions of solubilizers (blends)

- **Selection of polymers:**

Water soluble polymers were selected for the preparation of films. For development of fast dissolving oral film, water soluble polymer is one of the most important ingredients. Polymer properties affect the properties of film. For selecting film forming water soluble polymers, various kinds of polymers were used and properties of polymers were evaluated. The main purpose of polymer is to give mechanical strength and also to decrease its disintegration time. The polymers were selected on the basis of physical strength and also disintegration time as they are crucial optimization parameters for a film.

Table 8: List of polymers used for study

S.No.	Name of polymer used for film formation
1.	HPMC E-5
2.	HPMC E-15
3.	HPMC E-50
4.	Sodium alginate

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5.	Gelatin
6.	PVA
7.	CMC

HPMC- hydroxy propyl methyl cellulose, PVA- polyvinyl alcohol, CMC- carboxymethyl cellulose

Procedure:

Approximately 9.2 ml of a blend containing 15 percent glycerine as a plasticizer was picked and placed into a 10 ml vial for the preparation of polymeric films. Polymer (0.75 gm) is added and dissolved by shaking. The preparation was correctly stirred and held for 5-6 hrs. undisturbed. Now this polymer solution was spread over petriplates and allowed to dry for 24 hours at 40 ºC in a hot air oven. Now the film was peeled from the petriplate and then stored in aluminium foil by wrapping it. The films were then tested for their characteristics.

Evaluation of casted polymeric films

a) Disintegrationtime

Disintegration time was determined visually in a Petri dish containing 25 ml of phosphate buffer (pH 6.8) and a film was placed in it. n every 10 seconds, the buffer was swirled manually. As the time of disintegration, the time needed to fully split and disperse the film was noted.

b) Foldingendurance

The endurance of film was calculated by folding the film in one place repeatedly before it splits. The folding endurance value is the value at which number of times films can be folded without breakage.

c) Thickness

The film's thickness was calculated using a micrometer in 5 locations (centre and four corners), with the average thickness being determined (Digimetric micrometer, Mitutoyo, Tokyo, Japan).

Table 9: Evaluation of the properties of films of different polymers

S.No.	Polymer used	Film's appearance	Thickness (mm)	Disintegration time (seconds)
1.	HPMC E-5	Transparent, smooth, thin, non-sticky, easy removal from petriplate	0.09	25
2.	HPMC E-15	Transparent, smooth, thin, non-sticky, easy removal from petriplate	0.11	22
3.	HPMC E-50	Transparent, smooth, thick, non-sticky, easily remove from petriplate	0.25	90
4.	Sodium alginate	Opaque, powdered on scrapping	-	-
5.	Gelatin	Yellowish translucent, gummy film, sticky and tacky	-	-
6.	PVA	Translucent to opaque	0.31	74
7.	CMC	Opaque, hard, brittle	-	-

HPMC- hydroxy propyl methyl cellulose, PVA- polyvinyl alcohol, CMC- carboxymethyl cellulose

- **Optimization of polymer concentration:**

Four batches each of different concentrations of selected polymers i.e., HPMC E-5 and HPMC E-15 were prepared. Now studies of different properties of film were done.

Table10: Properties of various HPMC E-5 concentrations

S.No.	Selection factor	2.5% w/v HPMC E-5	5% w/v HPMC E-5	7.5% w/v HPMC E-5	10% w/vHPMC E-5
1.	Pourability	Poured	Poured	Pourable	Difficult to pour

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		easily	Easily		
2.	Viscosity	Less viscous	Less viscous	Viscous	Highly viscous
3.	Appearance of the film	Transparent	Transparent	Transparent	Transparent
4.	Folding parameter	Easily breakable	Little folding capacity	High folding capacity	Breaks easily
5.	Uniformity	Uniform	Uniform	Uniform	Non-uniform
6.	Thickness	0.08 mm	0.11 mm	0.09 mm	0.18 mm

Table 11: Properties of various HPMC E-15 concentrations

S.No.	Selection factor	2.5% w/v HPMC E-15	5% w/v HPMC E-15	7.5% w/v HPMC E-15	10% w/v HPMC E-15
1.	Pourability	Easily pourable	Pourable	Less Pourable	Difficult to pour
2.	Viscosity	Less viscous	Viscous	Viscous	Highly viscous
3.	Appearance of the film	Transparent	Transparent	Transparent	Transparent
4.	Folding parameter	Easily breakable	High folding capacity	Little folding capacity	Easily breakable
5.	Uniformity	Uniform	Uniform	Uniform	Non-uniform
6.	Thickness	0.09 mm	0.08 mm	0.12 mm	0.17 mm

- **Selection of plastizers and superdisintegrants**
- **Selection of plastizers**

Five different batches each of HPMC E-5 (7.5% w/v) and HPMC E-15 () were prepared using different plasticizers having concentration 15% v/v. The films prepared were tested for film characteristics.

Table12: Effect of various plasticizers in polymeric casted films

S.No.	Polymer Used	Plasticizer used (15% v/v)	Appearance	Thickness (mm)	Folding endurance	Disintegration time (seconds)
1.	HPMC E-5	Propylene glycol	Thin, translucent and uniform	0.14	84	48
2.	HPMC E-15	Propylene glycol	Thin, translucent and uniform	0.13	72	45
3.	HPMC E-5	Glycerine	Transparent, smooth and flexible	0.09	131	22
4.	HPMC E-15	Glycerine	Transparent, smooth and flexible	0.08	124	18
5.	HPMC E-5	PEG 200	Transparent, smooth, thickness is greater	0.16	98	42
6.	HPMC E-15	PEG 200	Hazy, smooth, thickness is greater	0.15	88	44
7.	HPMC E-5	PEG 400	Non-uniform, transparent, thickness is greater	0.19	115	58

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8.	HPMC E-15	PEG 400	Non-uniform, transparent, thickness is greater	0.20	108	57
9.	HPMC E-5	PEG 600	Non-uniform, white, thickness is greater	-	-	-
10.	HPMC E-15	PEG 600	Non-uniform, white, thickness is greater	-	-	-

- **Optimization of plastizers concentration**

Five batches of each HPMC E-5 (7.5% w/v) and HPMC E-15 (5% w/v) with different concentrations of selected plasticizer (glycerine) ranging from 5% to 25 % v/v were prepared and were tested for film characteristics.

Table 13: Impact of various plasticizer concentrations in polymeric film characteristics:

S.No.	Polymer used	Glycerine concentration (% v/v)	Appearance of film	Thickness of film (mm)	Folding endurance	Disintegration time (seconds)
1.	HPMC E-5	5%	Brittle and hard	0.11	29	29
2.	HPMC E-15	5%	Brittle and hard	0.10	26	26
3.	HPMC E-5	10%	Hard, transparent and uniform	0.09	71	25
4.	HPMC E-15	10%	Hard, transparent and uniform	0.10	79	28
5.	HPMC E-5	15%	Soft, transparent, smooth and uniform	0.08	135	21
6.	HPMC E-15	15%	Soft, transparent, smooth and uniform	0.07	128	18
7.	HPMC E-5	20%	Soft, transparent and sticky	0.12	114	33
8.	HPMC E-15	20%	Soft, transparent and sticky	0.14	110	32
9.	HPMC E-5	25%	Soft and very sticky	0.18	103	43
10.	HPMC E-15	25%	Soft and very sticky	0.16	106	41

- **Selection of superdisintegrant**

For selecting superdisintegrant, films were prepared with various superdisintegrants in both HPMC E-5 and HPMC E-15. Thickness and disintegration time of the casted film were studied.

Four individual Polymeric solutions of formulations each of HPMC E-5 (7.5%) and

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HPMC E-15 (5%) were made using 15 % v/v glycerine as plasticizer. Now, in each of these respective solutions, 0.5% w/v superdisintegrants were then mixed and casting of films were done in petriplates. After drying at 40 ºC for 24 hrs., films were then peeled and then different properties of film were evaluated.

Table14: Impact on the properties of polymeric film by superdisintegrants:

S.No.	Polymer	Plasticizer	Superdisintegrant Used	Thickness (mm)	Disintegration time (seconds)
1.	HPMC E-5	Glycerine	Croscarmellose sodium	0.09	23
2.	HPMC E-15	Glycerine	Croscarmellose sodium	0.08	22
3.	HPMC E-5	Glycerine	Crosspovidone	0.11	31
4.	HPMC E-15	Glycerine	Crosspovidone	0.12	34
5.	HPMC E-5	Glycerine	Microcrystalline cellulose	0.16	58
6.	HPMC E-15	Glycerine	Microcrystalline cellulose	0.14	55
7.	HPMC E-5	Glycerine	Sodium starch glycolate	0.18	49
8.	HPMC E-15	Glycerine	Sodium starch glycolate	0.17	48

- **Optimization of superdisintegrant concentration**

Four individual polymeric solution formulations each of HPMC E-5 (7.5% w/v) and HPMC E-15 (5% w/v) were prepared using 15 % v/v glycerine as plasticizer. Now, in all of these respective solutions, selected superdisintegrant i.e., croscarmellose sodium were then mixed and casting of films were done in petriplates. After drying at 40 ºC for 24 hrs., films were then peeled and then different properties of film were evaluated.

Table 15: Impact on polymer film properties of different concentrations of the selected superdisintegrant:

S.No.	Polymer	Plasticizer	Crosspovidone concentration used (% w/v)	Thickness (mm)	Disintegration time (seconds)
1.	HPMC E-5	Glycerine	0.3 %	0.07	31
2.	HPMC E-15	Glycerine	0.3 %	0.06	29
3.	HPMC E-5	Glycerine	0.4 %	0.08	27
4.	HPMC E-15	Glycerine	0.4 %	0.07	28
5.	HPMC E-5	Glycerine	0.5 %	0.10	22
6.	HPMC E-15	Glycerine	0.5 %	0.09	24
7.	HPMC E-5	Glycerine	0.6 %	0.13	33
8.	HPMC E-15	Glycerine	0.6 %	0.11	32

- **Formulation of fast dissolving oral films of amlodipine besylate:**

According to the preliminary studies and the excipient selection studies, six batches have been optimized. For making these batches, three blends (blend D, blend E and blend F) were optimized on the basis of greater solubility enhancement of drug and less individual concentration of solubilizers.

Table 16: Composition of blends used for the development of formulations

S.No.	Blend code	Blend composition
1.	Blend D	15% w/v Sodium caprylate 5% w/v Lysine HCl
2.	Blend E	10% w/v Sodium caprylate

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		5% w/v Sodium benzoate 5% w/v PVP K-25 5% Lysine HCl
3.	Blend F	10% w/v Sodium caprylate 5% w/v PVP K-25 5% Lysine HCl

Table 17: Optimized batch formulas for fast dissolving films

S. No.	Batch code	Drug (amlodipine besylate) (mg)	Blends	Polymer used (% w/v)	Plasticizer (glycerine) (% v/v)	Superdisintegrant (croscarmellose sodium) (% w/v)	Volume made up by Milli-Q water
1.	F1	250	blend D	7.5% HPMC E-5	15%	0.5%	10 ml
2.	F2	250	blend D	5% HPMC E-15	15%	0.5%	10 ml
3.	F3	250	blend E	15% HPMC E-5	15%	0.5%	10 ml
4.	F4	250	blend E	5% HPMC E-15	15%	0.5%	10 ml
5.	F5	250	blend F	7.5% HPMC E-5	15%	0.5%	10 ml
6.	F6	250	blend F	5% HPMC E-15	15%	0.5%	10 ml

- **Method of preparation of fast dissolving oral film of amlodipine besylate**

250 mg of amlodipine besylate was weighed accurately and was dissolved in 8.5 ml of respective solubilizer blends (blend D, blend E, blend F)containing 15% w/v glycerine as plasticizer and then 50 mg (0.5% w/v) of croscarmellose sodium was added as superdisintegrant. Now, 750 mg (7.5% w/v) of HPMC E-5 was added as film forming polymer and volume was made upto 10 ml with blend. Preparation was then suitably mixed and stirred properly using magnetic stirrer until the polymer (HPMC E-5) got completely dissolved. Now, this drug containing polymeric preparation was sonicated to remove trapped air bubbles and then kept undisturbed for 5-6 hrs for swelling of polymer. Now, the measured polymeric preparation volume was then spread evenly over the petriplate and dried in the oven for at least 24 hours. After proper drying, film was carefully peeled from petriplate, checked for any imperfections and then cut according to required size. Finally, the film was wrapped and stored for further examination in an aluminium foil with a plastic sealing bag.

Same procedure was repeated for polymer HPMC E-15 % (5 % w/v)

Calculation of dosage of drug:

Petriplate external diameter = 8 cm

Petriplate internal diameter = 7.75 cm

Petriplate internal radius = 3.875 cm

Internal area of petriplate = Area of circle = πr^2

$= 3.14 \times (3.875)^2$

$= 47.1490\ cm^2$

10 ml of polymer preparation contains 250 mg of drug.

Thus, 2 ml of polymer preparation carries 50 mg of the drug.

This 2ml polymer preparation was then spreaded over 47.1490 cm^2 area of petriplate.

Thus, 50 mg drug is present is present in 47.1490 cm^2 area of petriplate.

So, 5 mg drug is present in… = (47.1490 cm^2/50 mg) × 5 mg

$= 4.7145\ cm^2$ area

Area of circle = area of square = a^2

$a^2 = 4.7145\ cm^2$

$a^2 = \sqrt{4.7145}\ cm^2$

$a = 2.17$ cm

So, according to this calculation 5 mg dose of drug is present in 2.17 × 2.17 cm^2 area of film.

- **Evaluation studies of fabricated fast dissolving oral film**

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a) Appearance and texture: The prepared film was visually inspected for colour, flexibility, smoothness and texture was evaluated by touch or feel of the film. The films were off-white and semi-transparent in appearance and surface texture of films was smooth.

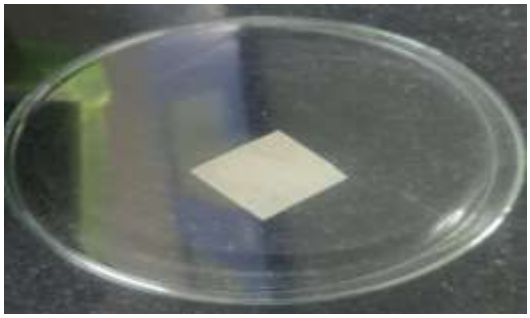

Figure 6: Photograph of prepared fast dissolving oral film

b) Thickness: The film's thickness was calculated using a micrometer in 5 locations (centre and four corners), with the average thickness being determined (Digimetric micrometer, Mitutoyo, Tokyo, Japan). Results are shown in table 18.

Table 18: Thickness studies for formulated film batches

S.No.	Batch code	Mean thickness (mm)
1.	F1	0.12
2.	F2	0.07
3.	F3	0.09
4.	F4	0.08
5.	F5	0.10
6.	F6	0.07

Figure 7: Graphical representation of thickness of formulated film batches

c) Folding endurance: The endurance of film was calculated by folding the film in one place repeatedly before it splits. The folding endurance value is the value at which number of times films can be folded without breakage. The results are shown in table 19.

Table 19: Folding endurance studies for formulated film batches

S.No.	Batch code	Folding endurance
1.	F1	121
2.	F2	118
3.	F3	144

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4.	F4	137
5.	F5	131
6.	F6	128

Figure 8: Graphical representation of folding endurance of formulated film batches

d) Surface pH: Prepared dose of film was taken and was placed in the petriplate containing 5 ml water. The film was allowed to wet and then pH was checked on the surface of film using pH paper. The results are shown in table 20.

Table 20: Surface pH studies for formulated film batches

S.No.	Batch code	pH
1.	F1	6.5-7
2.	F2	6.5-7
3.	F3	6.5-7
4.	F4	6.5-7
5.	F5	6-6.5
6.	F6	6-6.5

e) Disintegration time: In vitro disintegration was determined was visually in a petriplate containing 25 ml of pH 6.8 phosphate buffer with swirling every 10 seconds. The disintegration time is the time when film starts to break or disintegrate.The results are shown in table 21.

Table 21: Disintegration time studies for formulated film batches

S.No.	Batch code	Disintegration time (seconds)
1.	F1	25
2.	F2	22
3.	F3	21
4.	F4	16
5.	F5	30
6.	F6	34

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Figure 9: Graphical representation of disintegration time of formulated film batches

f) Drug content:A single film, consisting theoretically 5 mg of drug, was taken into a 100 ml volumetric flask and 80 ml of Milli-Q water was added to it further. The flask was shaken until the film dissolved completely and then volume was made upto 100 ml with Milli-Q water. The solution was filtered and evaluated by UV-spectrophotometer. Absorbance of the resulting solution was measured at 368 nm against Milli-Q water. Results of this study are shown in table 22.

Table 22: Drug content of formulated oral films

S.No.	Batch code	Drug content	Percentage drug content
1.	F1	4.77 mg	95.4 %
2.	F2	4.94 mg	98.8 %
3.	F3	4.86 mg	97.2 %
4.	F4	4.89 mg	97.8 %
5.	F5	5.12 mg	102.4 %
6.	F6	5.22 mg	104.4 %

g) TLC studies: In order to determine the possibility of interaction between drug and solubilizers, thin layer chromatography studies were performed. A plate of silica gel GF 254 was activated at 110 ºC for 1 hour and then used. Methanolic solution of amlodipine besylate pure drug was prepared and methanolic solution of formulated film were prepared and both were spotted with the aid of capillary tube. Then, the plates were left in air for sufficient time (about 15 minutes) to dry and then were transferred to a saturated jar with the solvent system 20 % w/v sodium caprylate solution as mobile phase.The mobile phase was allowed to run for about 4.5 cm. Finally, the plates were allowed to air dry and were observed for visualization of spots by iodine chamber. The respective R_f values were determined and recorded in table 23.

Table 23: TLC analysis of pure drug and for drug present in formulated oral film

S.No.	Mobile phase	R_f values		Inference
		Drug	Oral film	
1.	20 % w/v Sodium caprylate solution	0.35	0.36	No significant change in $R_f$values, hence no interaction between drug and solubilizers

h) Dissolution rate studies: The in-vitro dissolution analysis was performed using films containing 5 mg amlodipine besylate. Studies of dissolution have been performed according to USP II apparatus (paddle type) with 50 rpm and with a dissolution medium pH 6.8 of 300 ml of phosphate buffer. This has been sustained at a temperature of 37 ± 0.5 ºC. Ten ml of samples were taken at regular intervals and spectrophotometrically analysed (Shimadzu 1700) at 368 nm. Absorbance of each sample were noted against their individual reagent blank (placebo). Immediately after each sample removal, an equivalent quantity of new dissolution media was replaced. Results are shown in table 24.

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Table 24: Dissolution profiles of different batches of fast dissolving oral films of amlodipine besylate in phosphate buffer pH 6.8

S.NO.	Time (min.)	% Cumulative drug dissolved						
		F1	F2	F3	F4	F5	F6	Pure drug
1.	1	10.74	18.77	56.52	34.31	11.70	46.60	1.42
2.	2	30.07	65.21	78.04	72.41	67.90	76.06	17.92
3.	5	80.27	87.35	78.47	79.87	73.25	79.70	31.17
4.	10	84.37	94.26	79.36	82.21	74.88	80.48	36.86
5.	15	93.16	97.23	81.91	82.89	79.06	83.53	39.42
6.	30	99.50	97.36	82.22	83.47	80	84.17	45.34
7.	45	99.58	97.51	82.34	84.15	81.13	84.36	57.52
8.	60	99.65	97.88	83.60	84.82	82.55	88.78	59.38

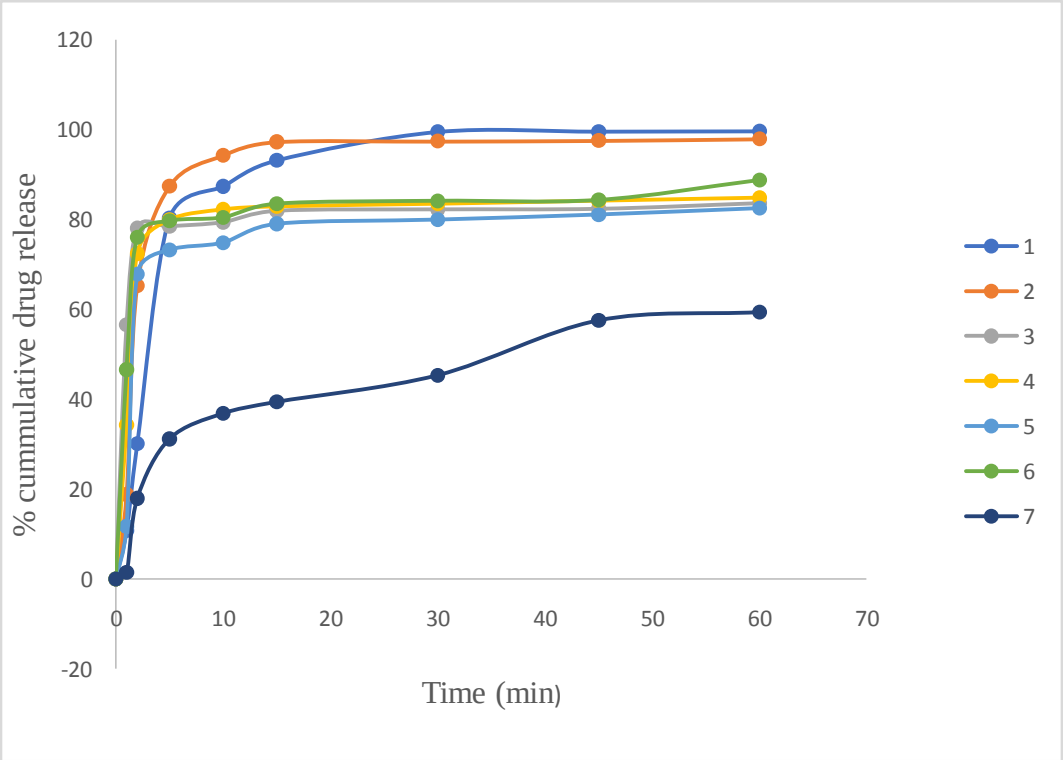

Figure 10: Graphical representation of % cumulative drug release v/s time plot in phosphate buffer pH 6.8

Result and discussion: Dissolution rate studies of formulated oral films of amlodipine besylate and pure drug were performed and it was observed that the release of formulated oral films was much significantly higher when compared with release of pure drug.

III. RESULTS AND DISCUSSION

For drug identification and drug characterization, UV spectrophotometric analysis, differential scanning calorimetry and melting point determination of drug sample were performed. The UV spectrum was scanned between 200 and 400 nm for amlodipine besylate drug sample.The melting point range of drug sample was found to be 202-207 ºC.DSC curve of the crystalline form of amlodipine besylate showed a sharp peak at 206.48 ºC. The drug showed peaks at 231 nm and 368 nm.The drug sample was analysed and the observed data was same as reported in literature. The drug sample showed same results as reported in literature the calibration curve of the amlodipine besylate was prepared in Milli-Q water and phosphate buffer of pH 6.8. The linearity of calibration curve showed that the beer lambert's law was obeyed in concentration range of 20-100

µg/ml at 368 nm. Preformulation study of amlodipine besylate was carried out. The equilibrium solubility of amlodipine besylate was found to be 0.111% w/v in water and 0.060% w/v in phosphate buffer of pH 6.8. Drug excipient physical compatibility study was performed, observing any physical changes in the blends of drug and excipients visually for one month. UV interference study for drug estimation was also performed taking drug concentration 20 µg/ml and excipient concentration 40 µg/ml against respective reagent blank. These studies showed no physical and chemical incompatibility and no UV interference. In order to choose solubilizers to improve the solubility of the drug amlodipine besylate, solubility tests were carried out at room temperature in a variety of solubilizer-containing solutions or in a combination of solubilizer blends. The solubility of amlodipine besylate was increased up to 2.5% (w/v) in solubilizer in blend D (15% w/v Sodium caprylate + 5% w/v Lysine HCl), in blend F (10% w/v Sodium caprylate + 5% w/v PVP K-25 + 5% w/v Lysine HCl) upto 3.5% (w/v) in blend E (10% w/v Sodium caprylate + 5% w/v Sodium benzoate+ 5% w/v Lysine HCl +5% w/v PVP K-25) upto 4.5% (w/v) that was maximum among all blends. Solubilizer blends have been tried to give the expected solubility in order to minimize the possible toxic effects of the individual solubilizer at a high concentration. In selected final blends, solubilizer blends of total strength 20 % w/v and 25 % w/v, 2.5% w/v were used to obtain sufficient expected solubility. In a blend containing sodium caprylate, sodium benzoate, PVP K-25, lysine HCl, the maximum synergistic effect was observed.Different film forming polymers, plasticizers and superdisintegrants were being evaluated for the production of fast dissolving oral film. HPMC E-5 (7.5% w/v), HPMC-15 (5 % w/v) were chosen as film forming polymers, Glycerine (15 % v/v) was chosen as plasticizer and croscarmellose sodium (0.5 % w/v) was chosen as superdisintegrant. They were chosen and configured according to the mechanical properties and time of film disintegration. TLC that showed no interaction between drug and excipients. Six batches of fast-dissolving oral film containing 5 mg dose per 2.17 cm^2 of selected and optimized ingredients were developed and profile.

IV. CONCLUSION

It was concluded from all of the above studies that the approach of the mixed solvency concept is novel, safe, cost-effective and user-friendly. Fast dissolving oral films of amlodipine besylate wereevaluated for thickness, folding endurance, disintegrating time, in vitro dissolution. Italso eliminates the toxicity problem associated with high concentrations of water soluble solubilizers. Thus, it may be used in future for the development of drugs in a dosage form where rapid action is required.

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