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DESIGN AND EVALUATION OF ORO – FLASH RELEASE FILMS OF AMLODIPINE BESYLATE

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Fast dissolving drug delivery, Fast dissolving oral films (FDOFs), Oral thin film (OTF), Oro – Flash release films, Amlodipine besylate, HPMC E5, Solvent casting, Oro - mucosal absorption, Poorly water soluble drugs

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ABSTRACT: This work aimed to formulate amlodipine besylate Oro flash release films by solvent casting method. Various film forming polymers like Hydroxy propyl methyl cellulose (HPMC) E5, HPMC E15, sodium carboxymethyl cellulose, sodium alginate, xanthan gum were used and out of which HPMCE5 was found to be satisfactory. Propylene glycol was used as plasticizer at a range of 13-32%w/w of the film and 31%w/w was found to be the best concentration based on the flexibility and the strength of the film. Optimized formulation contains HPMC E5 as a film forming agent, propylene glycol as a plasticizer, tween 80 as a surfactant, peppermint oil as flavoring agent and aspartame as sweetening agent. Films were prepared by solvent casting method and found to satisfy the mouth dissolving time and other film parameters. 1.5 x 1.5 cm of film is required to be placed on to patient tongue which gets wet by saliva, rapidly hydrates, adheres to tongue and rapidly disintegrates and dissolves to release the drug for the oro – mucosal absorption or allow for gastrointestinal absorption when swallowed. The formulated films exhibited acceptable film endurance. Time required for the film to dissolve and release is 45 seconds and 5 minutes respectively. It can be concluded from the study that the oro flash release film can be a potential novel drug dosage form for poorly water – soluble drugs.

INTRODUCTION: A vast variety of pharmaceutical research is directed at developing new dosage forms.

Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance.

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Among the dosage forms developed for ease of medication, the orally disintegrating systems have been the favorite of product development scientists [1].

Recent developments in this technology have presented viable fast – dissolving oral delivery system as alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or non – compliant patients. Fast – dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing [2]. More recently, fast dissolving films are gaining interest as an alternative to fast – dissolving tablets to definitely

eliminate patient's fear of chocking and overcome patient impediments. Fast – dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot melt extrusion.

Intraoral fast dissolving drug delivery system is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/systemic absorption. Patients suffering from dysphasia, repeated emesis, motion sickness and mental disorders prefer this dosage form as they are unable to swallow large quantity of water. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first – pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect [3]. Different marketed film products were listed in the **Table 1.**

TABLE 1: LIST OF MARKETED FILM PRODUCTS [4, 5]

Distributor	Brand	API	Strength
Del	Orazel	Menthol /pectin	2mg/30mg
Inno Zen	Suppress	Menthol	2.5mg
Novartis	Gas – X	Simethicone	62.5mg
Novartis	Theraflu	Phenylepherine HCl/Dextromethorphan HBr	10mg/20mg
Novartis	Theraflu	Phenylepherine HCl/Dextromethorphan HCl	10mg/25mg
Novartis	Theraflu	Dextromethorphan HBr	15mg
Novartis	Theraflu	Diphenhydarmine HCl	25mg
Novartis	Triamnic	Diphenhydarmine HCl	12.5mg
Novartis	Triamnic	Phenylepherine HCl	2.5mg
Novartis	Triamnic	Phenylepherine HCl/lDiphenhydarmine HCl	5mg/12.5mg
Novartis	Triamnic	Dextromethorphan HBr	7.5mg
Novartis	Benadryl	DiphenylhydramineHCl	12.5mg
Pfizer	Benadryl	DiphenylhydramineHCl	25mg
Pfizer	Suldafed	phenylepherineHCl	10mg
Prestige	Chloaseptic	Benzocaine/menthol	3mg/3mg
Labtec GmbH	Ondensetron Rapid film	Ondensteron	4mg/8mg
Labtec GmbH	Donepzil Rapid film	donepzilHCl	5mg/10mg

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow – channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine inhibits calcium ion influx across cell membrane selectively, with greater effect on vascular smooth muscle cells than on cardiac muscle cells, through specific ion channels [6].

Generally following points are considered for patient compliance in case of anti-angina patients, a rapid onset of action is necessary for immediate pain relief, patient has difficulty to swallow tablet or any other dosage form during pain, geriatrics have difficulty to swallow the dosage form. By considering the above points , patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems one of such approach is fast dissolving drug delivery system. Conventional dosage forms for the anti-angina therapy includes tablets, injections. Injections provide effective rapid relief but, they are painful and very expensive [7].

The main objectives of the present study were to prepare the oral thin films of amlodipine besylate and to evaluate its thickness, folding endurance, moisture content, drug content, *in vitro* disintegration time and *in vitro* dissolution time.

MATERIALS AND METHODS: Amlodipine Besylate was obtained as a gift sample from Hetero Labs, Hyderabad (India). HPMC E5, Sodium carboxymethylcellulose, Microcrystalline cellulose, Xanthan gum, Propylene glycol, Citric acid, Tween 80, Aspartame, Peppermint oil were purchased from Merck and HPMC E15, Sodium alginate from LOBA CHEMIE. All the reagents used were of analytical grade.

Preparation of drug loaded films [8]**:** The polymer (HPMC E5) was weighed accurately and soaked in distilled water overnight. The soaked polymer was made to a uniform dispersion using a homogenizer. The drug was weighed accurately and was dissolved in specific amount of alcohol along with required amount of propylene glycol. The drug solution was added to the dispersion while stirring. Other ingredients such as sweetening agent, flavor and saliva stimulating agent were dissolved in a little amount of water and were added to the dispersion. Distilled water was added up to the required volume. Stirring was continued until a homogenous and bubble free dispersion was obtained. The obtained bubble free dispersion was poured onto a mould and was left for drying on a hot air oven overnight at 40ºC. The dried films were cut in desired size and were evaluated. The composition of the solution used to prepare films is given in the **Table 2**.

TABLE 2: LIST TRIAL FORMULATIONS

Trial	HPMC E5 (g)	HPMC E15 (g)	Xanthan Gum (g)	Na CMC (g)	Na alginate (g)	Propylene glycol (g)	Alcohol (ml)	Water (ml)
F1	0.36	-	0.5	-	-	1	10	30
F2	0.5	-	0.3	-	-	0.5	10	30
F3	0.5	-	-	-	-	0.5	10	30
F4	0.4	-	0.5	-	-	1	10	30
F5	1	-	-	-	-	0.5	10	30
F6	-	-	0.5	-	-	1	10	30
F7	-	0.2	-	--	-	0.5	10	30
F8	-	-	-	0.2	-	0.5	10	30
F9	-	-	-	0.4	-	0.5	10	30
F10	-	-	-	-	0.2	0.5	10	30
F11	-	-	-	0.5	-	0.5	10	30
F12	-	-	-	-	0.3	0.5	10	30
F13	-	-	-	0.6	-	0.5	10	30
F14	1	-	-	-	-	0.5	10	30
F15	-	0.5	-	-	-	0.5	10	30
F16	-	-	-	0.8	-	0.5	10	30

Optimizing Plasticizer Concentration: Plasticizer is vital ingredient of the OTF formulation. It helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the film properties by reducing the glass transition temperature 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 [9].

Hence, selection of plasticizer and its concentration also greatly affects the film properties. In this work propylene glycol was used as a plasticizer. Therefore, after deciding the polymer, the concentration of the plasticizer i.e. propylene glycol to be used in the film formulation in order to have an optimum flexibility and strength was assessed by trial and error means. Films were prepared with different plasticizer concentration as given in the **Table 3.**

TABLE 3: LIST OF TRAILS WITH DIFFERENT PLASTICIZER CONCENTRATION

S. No.	Propylene Glycol (% w/w of dry film)
1	13.6
2	22.7
3	31.8

TABLE 4: FORMULA USED TO PREPARE FILMS (F14)

INGREDIENT	QUANTITY
HPMC E5	1g
Drug	180mg
Alcohol	10ml
Propylene glycol	0.5g
Citric acid	0.1g
Aspartame	0.1g
Tween 80	0.5g
Distilled water	Up to 30ml

Compatibility studies: Compatibility Study was carried out using FT-IR (BRUKER) for (a) pure drug - amlodipine besylate (b) Placebo film (c) amlodipine loaded HPMC E5 film. The specific peaks of drug and the polymers were studied for the interactions and individual spectrum was given in the **Figure 1-3.**

EVALUATION OF ORO – FLASH RELEASE FILMS:

Physical appearance and surface texture: This parameter was generally checked by visual observation and evaluation of texture by feel or touch.

Thickness uniformity: Thickness of the film was measured using screw gauze with a least count of 0.01 mm at different places on the film. The thickness was measured at nine different places on the film and the average was taken.

Folding endurance [10] **:** The flexibility of the film is measured quantitatively in terms of what is known as folding endurance. Folding endurance of the film was determined by repeatedly folding a small strip of the film at the place till it broke. The number of times the film can be folded without breaking gives the folding endurance value.

Drug content uniformity: The films were tested for drug content uniformity by UV – visible spectrophotometric method. Films of require size (1.5 cm x 1.5 cm) were cut at three different places from the casted film. Each cut film was placed in 100 ml volumetric flask and was dissolved using 0.01M HCl. From this 1ml was pipette out and transferred into a 10 ml volumetric flask and the volume was made to the mark with 0.01M HCl. The absorbance of the resulting solution was measured at 239 nm against blank using UV visible spectrophotometer. The percentage drug content was determined using the standard graph.

***In vitro* disintegration test:** As there were no specifications for the disintegration testing of OTFs different researchers proposed and follow different methods. In this work the *in vitro* disintegration time of the film was determined using Slide frame and Petri dish method i.e. a drop of 0.01M HCl was placed on the film and the time taken to form a hole was determined as the *in vitro* disintegration time of the film.

***In vitro* dissolution time:** The *in vitro* dissolution of amlodipine Oro – flash release films was studied in USP type II dissolution apparatus (i.e. paddle) with 500 ml of 0.01M HCl as the dissolution medium. The stirrer was adjusted to rotate at 50rpm. The temperature of the dissolution medium was maintained at 37±0.5ºC throughout the experiment with the film of 1.5 cm x 1.5 cm size in the vessel. Samples of dissolution medium (5 ml) were withdrawn by means of a syringe at regular intervals and were analyzed for drug release at 239 nm. The volume withdrawn each time was replaced with fresh 0.01M HCl in order to maintain sink conditions. Cumulative percent amlodipine released was calculated and plotted against time.

Taste Panel: In order to determine the palatability of the prepared films, a group of students were taken as a panel to determine the mouth feel, *in vivo* dissolution time and taste of the films with and without the sweetening agent, flavor and saliva stimulating agent. The films were given without the drug as the drug was potent.

RESULTS AND DISCUSSION: Drug – excipient compatibility study was carried out using FTIR and the **Figure 4** is the combined spectra of blank film and amlodipine loaded film indicating the functional peaks of the drug was retained in the formulation too proving that drug and the excipients are compatible to each other. Films prepared by using xanthan gum, sodium carboxymethyl cellulose were not elegant as shown in the **Figure 5 and 6** but whereas films prepared using HPMC E5 (**Figure 7**) were elegant and satisfied all the requisite properties and hence the later polymer was found to be most suitable for the reparation of oro flash release films.

Evaluation parameters of films like physical appearance, thickness, folding endurance, drug content uniformity, *in vitro* disintegration time were given in the **Table 4**. The *in vivo* dissolution profile of F14 was given in the **Table 5** and the dissolution rate graph was given in the **Figure 8** showing that within 5 min 100% of drug has been released.

The palatability of the prepared Oro flash release films was determined by a panel and results were given in the **Table 6**. From the results of taste panel, it can be concluded that the prepared films with sweetening agent were more acceptable than those without the sweetening agent. The *in vivo* dissolution time was also better for the films with sweetening agent and saliva stimulating agent.

Finally three trials were carried out in order to determine the precision and the results were given in the **Table 7** and comparative dissolution profile in **Figure 9**. From the results, it was concluded that films formed using the prescribed formula given in the **Table 3** yielded films with required properties with precision.

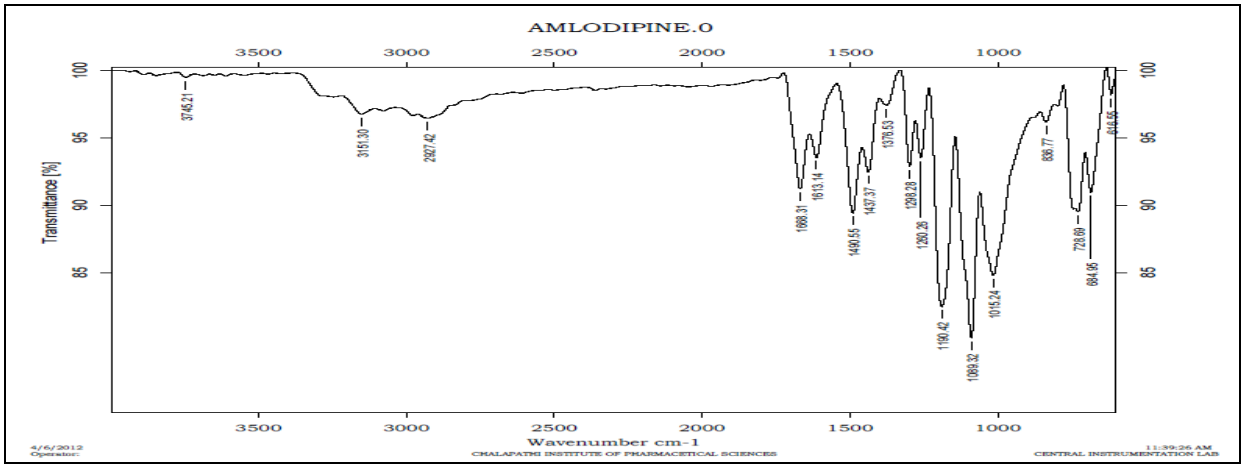

FIG. 1: FTIR SPECTRUM OF PURE AMLODIPINE BESYLATE

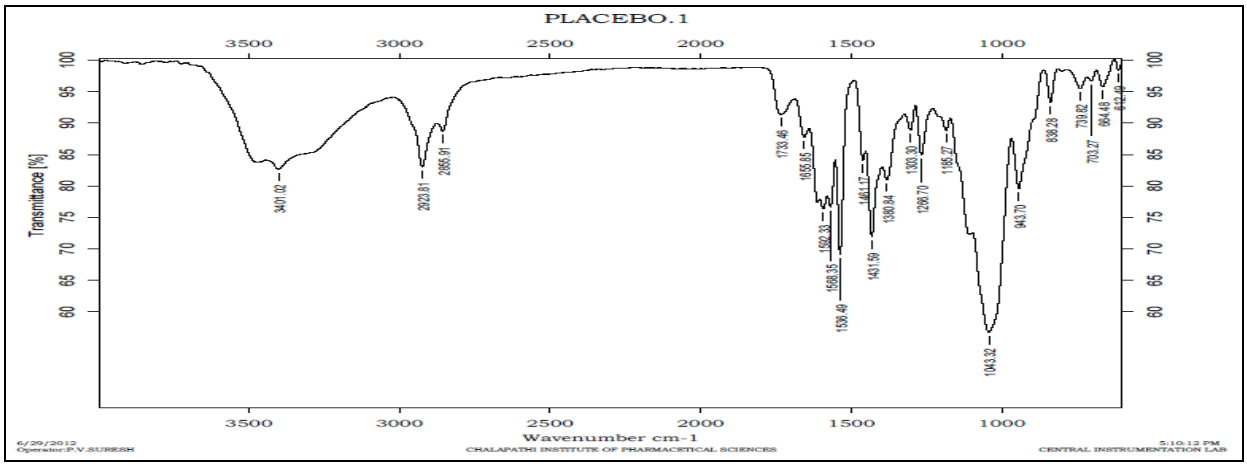

FIG. 2: FTIR SPECTRUM OF PLACEBO FILM

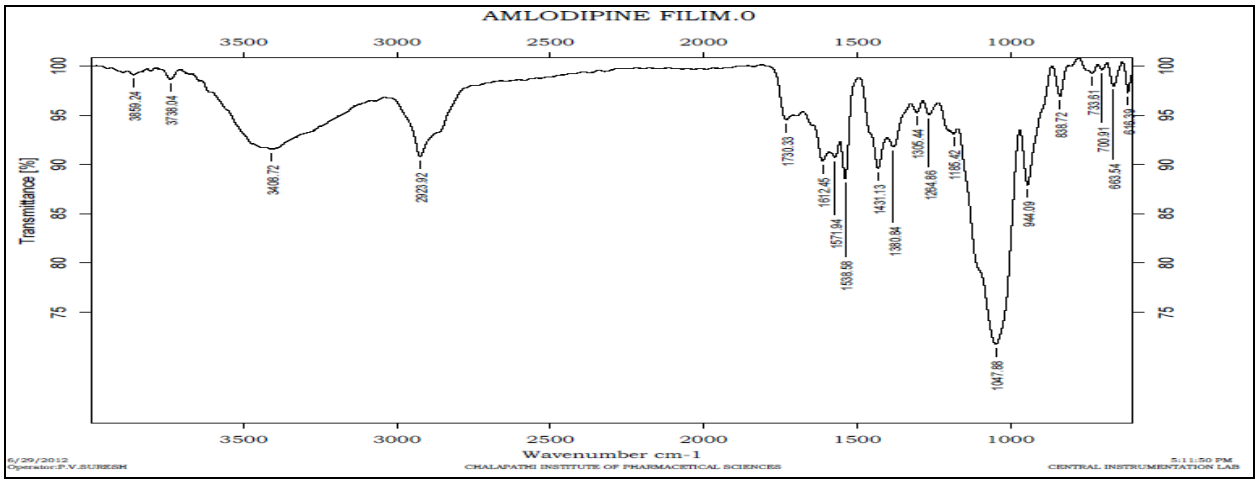

FIG. 3: FTIR SPECTRUM OF AMLODIPINE FILM

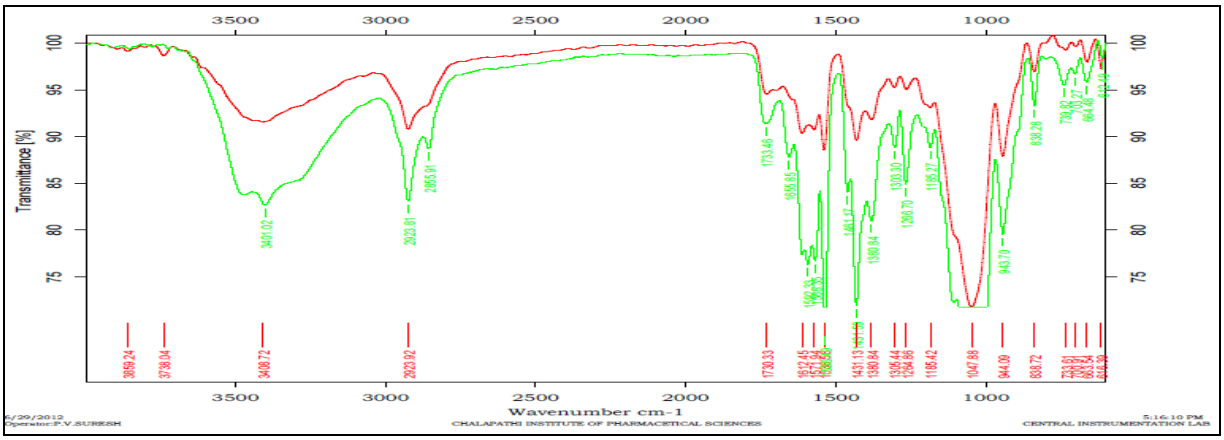

FIG. 4: COMBINED SPECTRA OF ORO – FLASH RELEASE FILMS WITH AND WITHOUT DRUG

FIG. 5: XANTHAN GUM + HPMC E5 FILM

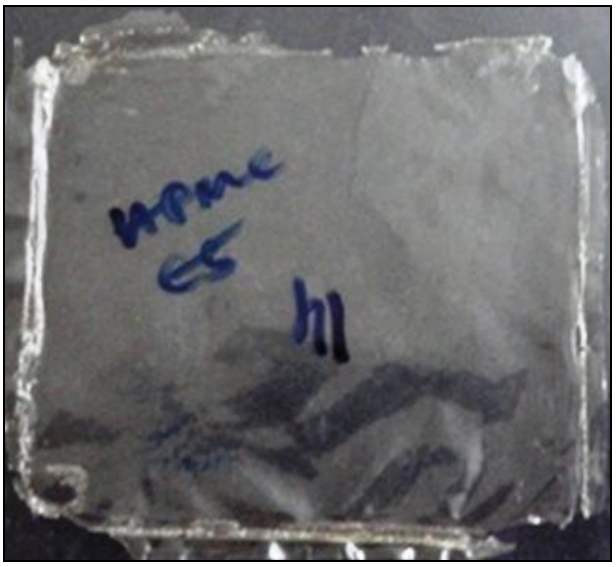

FIG. 7: HPMC E5 FILM (F1)

FIG. 6: SCMC FILM

TABLE 4: EVALUATION PARAMETERS OF THE PREPARED FILM

S. No.	Parameter	Result
1.	Physical appearance	Transparent, elegant, smooth, soft
2.	Thickness uniformity	3.94±0.104mm
3.	Folding endurance	87±10.675
4.	Drug content uniformity	98.65±1.175
5	*In vitro dissolution* time	42±2.516 sec

TABLE 5: *IN VITRO* DRUG RELEASE PROFILE OF F14

Time (mins)	Absorbance	Conc. (µg / ml)	Amount (mg / 500ml)	% Drug dissolved
5	0.318	10.25	5.12	100
10	0.281	9.064	4.53	88.47
15	0.243	7.838	3.919	76.54

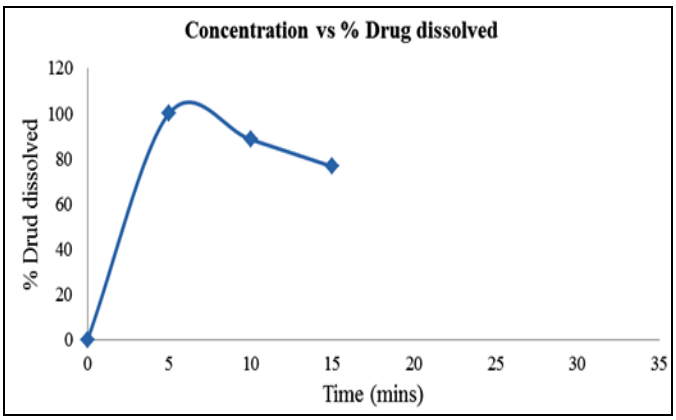

FIG. 8: *IN VITRO* DRUG RELEASE PROFILE OF PREPARED FILM

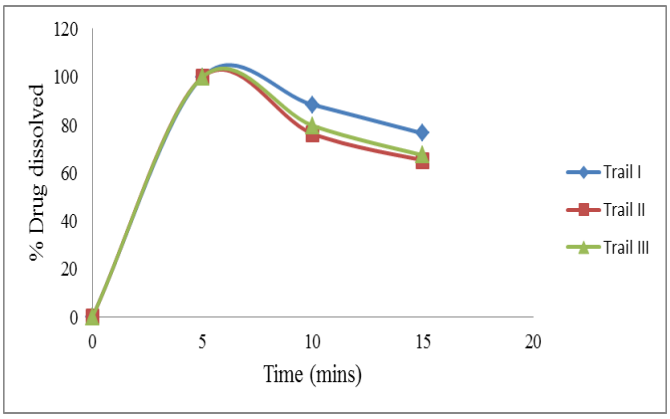

FIG 9: COMPARATIVE DISSOLUTION PROFILES OF OPTIMIZED TRIAL FORMULATIONS

TABLE 6: TASTE PANEL

Volunteer	Taste*		Mouth feel*		*In vivo* dissolution time (sec)	
	F1	F2	F1	F2	F1	F2
Shravan	6	8.5	5	8	19	9
Gulshan	6	8	6	8	20	10
Pranavi	6.5	7	5	7	18	12
Sravan laxmi	7	8.5	7	8	20	15
Vineela	8	7	7	8	15	12
Sasikala	8	7	8	7	15	10
Chandrika	8	7	8	7	20	15
Vara Prasad	6	9	5	8	20	12
Srinivasulu	7	7	5	8	30	15
Shivaram	7	7	6	8	30	15
Darga Babu	8	7	8	6	17	12

Where F1 – film without sweetening agent, flavor and saliva stimulating agent. F2 – film with sweetening agent, flavor and saliva stimulating agent. (* the values were given for 10)

TABLE 7: REPRODUCIBILITY OF THE FINAL FORMULATION

Trail	Thickness (mm)	Assay	Disintegration time (sec)	Folding endurance	Dissolution time for 100 % of Amlodipine to release (min)
I	4.05±0.05	97.15±1.125	45±1.25	89±6.759	5
II	4.03±0.11	98.65±1.264	42±2.257	85±8.454	5
III	3.94±0.104	101.28±0.88	40±3.00	92±5.632	5

CONCLUSION: In the present study, fast dissolving drug delivery system of amlodipine besylate was successfully developed in the form of Oro - flash release films which offered a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Amlodipine was a slightly water soluble drug with an oral bioavailability of 60% and hence this method was useful for improving its bioavailability.

Amlodipine oro – flash release films were prepared using HPMC E5 as the polymer by solvent casting method. From the findings obtained, it was concluded that:

- FTIR studies revealed that there were no interactions between amlodipine and the excipients used in the study.
- The prepared film containing amlodipine was clear and elegant.
- Formulated films gave satisfactory result for various physico – chemical evaluation of films like physical appearance, thickness uniformity, folding endurance, drug content uniformity, *in*

vitro disintegration time and *in vitro* drug release. The low values of standard deviation for drug content and thickness indicated that the drug was equally distributed in uniform thick films.

- The *in vitro* disintegration time was found to be promising as the film disintegrated in about 45 seconds and the *in vitro* drug release studies showed complete drug release in 5 min which was desired.

- From the present study, it could be concluded that the Oro – flash release films of amlodipine besylate can be prepared by solvent casting method using HPMC E5 as the polymer with a dissolution time of 5 minutes for the complete release of the drug from the film.

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REFERENCES:

1. Honey Goel, Parshuram Rai, Vikas Rana, Ashok K, Tiwary: Orally Disintegrating Systems: Innovations in Formulation and Technology. Recent Patents on drug Delivery & Formulation 2008; 2:258-274.
2. Francesco cilurzo: Fast dissolving films made of maltodextrins. European Journal of Pharmaceutics and Biopharmaceutics 2008; 70:895-900.
3. Zhang H, Zhang J, and Streisand J.B: Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. Clinical Pharmacokinetics 2002; 41 (9): 661 – 680.
4. Mital S. Panchal, Hiren Patel, Aarti Bagada, K.R.Vadalia. Formulation and Evaluation of Mouth Dissolving Film of Ropinirole hydrochloride by Using Pullulan Polymers. International Journal of Pharmaceutical Research & Allied Sciences 2012; 1 (3):60-72.
5. Deepak Heer, Geeta Aggarwal, S.L. Hari kumar. Recent Trends of Fast Dissolving Drug Delivery System - An overview of Formulation Technology: Pharmacophore 2013; 4(1):1-9.
6. Available at http://www.drugs.com/pdr/amlodipine-besylate.html
7. Shelke PV, Dumbare AS, Gadhave MV, Jadhav SL,Sonawane AA, Gaikwad DD: Formulation and Evaluation of Rapidly Disintegrating Film of Amlodipine Besylate: Journal of Drug Delivery & Therapeutics2012;2(2):72-76.
8. Francesco cilurzo, Irma E. Cupone, Paola Minghetti, Francesca Selmin, Luisa Montanari. Fast Dissolving Films made of maltodextrins: European Journal of Pharmaceutics and Biopharmaceutics 2008;70:895-900.
9. Gavaskar B, Vijayakumar S, Sharma G and Rao YM: Overview on fast dissolving films. International Journal of Pharmacy and Pharmaceutical Sciences 2010;2(3):29-33
10. Nishimura. M, Mastur. K, Tsukioka. T and Yamashita. H: *In – vitro* and *in – vivo* characteristics of prochlorperazine oral disintegrating film: Int. J. Pharma 2009:38:98-102.

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