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FABRICATION AND EVALUATION OF FAST DISTINTEGRATING ORAL HYBRID FILMS OF NEW MOIETY OF COUMARIN

Bhavana Madupoju*[1], Usha rani Peddaboina[2], Dr. Krishna Reddy. Y[1], Srikanth Gurram[1], Vijay Medi[1]

[1]Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda.

[2]Department of Pharmacy, University College of Technology, Osmania University, Hyderabad.

Abstract:

The main aim of this investigation is to develop fast disintegrating oral films of new moiety of coumarin by using Pectin and synthetic polymers. The coumarin moiety loaded oral-dispersible films were formulated by using HPMC , pectin, ethyl cellulose as film forming polymers. The selected polymers were natural and synthetic water soluble polymers. Generally solvent casting method was used in the manufacture of the mouth dissolving films. The formula which incorporates pectin ,HPMC , EC and also other varying ratio of solvents(DMSO, water, Ethanol) were used in the formulation of Oro-dispersible films. Citric acid was used as a salivary stimulating agent. The prepared films were subjected to the analysis of various evaluation tests such as weight variation, tensile strength, thickness, surface pH, and drug content. The significant parameters such as disintegration and dissolution profiles also studied in detail since the product was prepared for fast dissolving in the oral cavity. Based on all combinations of formulation one ideal formulation i.e, F4 is selected which acts as promising tool for systemic delivery of new moiety of coumarin.

Corresponding author:

M. Bhavana,
Assistant professor,
Department of Pharmaceutics,
Nalanda College of Pharmacy,
Cell no: +918501051606

QR code

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INTRODUCTION:

A variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication . Oral route of drug administration is considered to be most effective and acceptable form due to its better therapeutic efficacy. Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue[1]. Fast dissolving drug delivery system (FDDS) is fitted for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and as well accomplish it cost effective[2].

The advantages of sublingual delivery of drugs via oral films include larger surface area, enhanced safety, high precision during dose administration compared to liquid forms, high levels of patient compliance, and quicker relief[3]. Buccal, or sublingual delivery through thin films therefore provides a way to circumvent swallowing through rapid dissolution in the oral cavity, thereby causing quick onsets of action at a lower dosage. As the oral film releases the drug instantly, this dosage form can be formulated for to treat diseases, such as pain, allergies, sleep disturbances, anxiety and gastric problems, which require a fast onset of action[4].

Coumarins are of great interest due to their biological properties, physiological, bacteriostatic and anti tumour activities which make these compounds attractive for their backbone derivertization and screening as novel therapeutic agents. Coumarins and its metabolite 7-hydroxycoumarin have anti- tumour activity against several tumour human lines. Both coumarin and its derivatives have shown as promising potential inhibitors of cell proliferation in various carcinoma cells[5].

The objective of this study was to prepare fast-dissolving oral films of coumarin for rapid dissolution in the oral cavity. The films were prepared using a solvent casting method and are optimized using the various polymer combinations (HPMC,EC and Pectin) and different solvents (water, DMSO, Ethanol). The drug was incorporated into the polymer network and evaluated for *In Vitro* drug release studies. The prepared films were characterized for other parameters like disintegration, thickness, folding endurance, surface pH, percent elongation and tensile strength.

MATERIALS AND METHODS:

Materials

A new moiety of Coumarin was received as a gift sample from Usha Peddaboina, Research scholar, Department of pharmacy, osmania university, Hyderabad. Hydroxy Propyl Methyl Cellulose, Pectin, Ethyl cellulose, DMSO, Ethanol, Methyl paraben, Citric acid, PG, were purchased from S.D. Fine Chemicals Ltd., India. All the chemicals were of analytical grade. Distilled water was used whenever required.

Methods

Preparation of films Preparation of Polymeric films :

Drug containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of polymer was dissolved in 5ml of solvent and stirrer continuously for 1 hour, optimized amount of sweetener, and Plasticizer, flavour were dissolved in little other portion of solvent and then added to the polymeric solution. The optimized amount of drug was dissolved in 2ml of solvent and kept on sonication for proper dispersion. The drug solution was then added to the polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition untill the entrapped air bubbles were removed. The aqueous solution was casted in a plastic Petridish and was dried at controlled room temperature (25° - 30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the Petridish and was cut into size required for testing. The films were stored in air tight plastic bags till further use. Same procedure were be followed for the preparation of HPMC, Pectin , EC films and combination of solvent[6,7]. The composition of drug loaded film is shown in table no. 1.

Table.1: Composition of drug loaded oral thin films

INGREDIENTS(mg/ml)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
DRUG	2	2	2	2	2	2	2	2	2	2	2	2
HPMC	300			300			300			300		
EC		300			300			300			300	
PECTIN			300			300			300			300
CITRIC ACID	25	25	25	25	25	25	25	25	25	25	25	25
PG	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
METHYL PARABEN	10	10	10	10	10	10	10	10	10	10	10	10
FLAVOURING AGENT	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
DMSO+WATER	10	10	10									
WATER				10	10	10						
DMSO							10	10	10			
ETHANOL										10	10	10

Evaluation Tests [8- 13]

Weight variation

For weight variation three films of every formulation were taken weighed individually on digital balance then average weight was calculated.

Thickness

Randomly 3 films were selected and thickness was measured using a digital screw gauge, (Digimatic outside micrometer, Mitutoyo, Japan). The individual film was placed between two anvils of the screw gauge and sliding knob was rotated until the film was fitted. The digital reading displayed was noted.

Surface pH

The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 1hr. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition.

Folding endurance

The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Dissolving time

The dissolving time was determined by placing the film in a beaker containing 50 ml of phosphate buffer (pH 7.4). Time required by the film to dissolve completely was noted.

Drug content estimation

A circular film of 2.5cm diameter was cut and placed in a beaker containing 100 ml of phosphate buffer pH 6.8 solutions. The contents were stirred in magnetic stirrer to dissolve the film and the contents were transferred to a 100ml volumetric flask. The absorbance of the solution was measured against the corresponding blank solution at 457 nm. As the absorbance noted above 1mcg/ml, 1ml of the stock was further diluted to 10ml of phosphate buffer solution (pH 7.4) and absorbance was measured at 457nm.

Disintegration time

It was determined by using disintegration test apparatus. $1cm^2$ film was placed in the basket, raised and lowered it in such a manner that complete up and down movement at a rate to achieve equivalent to thirty times a minute. Time required by the film to achieve no trace of film remaining above the gauze was noted.

In-vitro drug dissolution studies

The dissolution studies were conducted using phosphate buffer pH 6.8 are shown in table 3. Each film strip (containing drug equivalent to 5 mg) was then submerged into the dissolution medium. The dissolution study was carried out using dissolution test apparatus USP type-II at 37^0C, at 50 rpm, using 900 ml phosphate buffer (pH 7.4) as dissolution medium. Test samples were withdrawn at different time intervals and analyzed spectrophotometrically at 457 nm. The absorbance values were transformed into concentration using standard graphic.

RESULTS AND DISSCUSSION:

All the prepared films were found to be non-tacky. Three films each of 1 cm^2 were cut at three different places from the casted film and weight variation was determined. Weight variation varies from 43mg to 70 mg. It was observed that in-vitro disintegration time varies from 36 to 46 sec for all the formulations.

In-vitro disintegration time of the films was found to be increased with change in the type of the polymer as well as solvent. Folding endurance of film was found to be in the range of 77 to 208. The prepared film formulations were assayed for drug content. Results of drug content showed the uniformity of the drug varies as per type of solvent and polymer used. The surface pH of the films was ranging from 6.1 to 7.1. The surface pH of the films was found to be neutral.

The *In-Vitro* drug release profiles of the formulations in phosphate buffer pH 7.4 show differences depending on their composition. From the data obtained from evaluation parameters, it is evident that formulations F1, F4, F7, F10 were found to be satisfactory in all the aspects among them the most preferred is the formulation F4 as the solvent used is water and shows almost similar properties as with that of F1, F7, F10 where DMSO: water, DMSO, ethanol were used as solvents.

Coumarin and its derivatives well highly soluble in DMSO, Ethanol but slightly soluble in water but its solubility can be increased by using hot water. Hence in the present study a combination of solvents and polymers were used in the preparation of coumarin loaded oral thin films. Among all combinations F4 found to be most satisfactory in terms of all the evaluation parameters and also in terms of least side effects as the polymer used is HPMC and solvent used is water.

Table 2: Evaluation Parameters

Formulation code	Weight varaition (mg)	Thickness(mm)	Surface PH	Folding endurance	Drug content estimation(%)	Disintegration (sec)
F1	43.6	0.067	7.0	220.5	95	36.5
F2	40	0.042	6.5	90.5	39.5	47.5
F3	66.6	0.762	6.2	220	89.5	38.5
F4	50	0.079	6.8	200.2	87.5	26
F5	33.6	0.090	7	77.9	58.5	40.5
F6	70.6	1.09	5.7	198.3	75.5	36
F7	47.6	0.078	7.0	231	87.5	24
F8	41	0.053	6.2	80.5	47	43.5
F9	67.3	0.097	5.1	200.5	69.5	36.5
F10	51	0.065	6.5	208.5	90.5	44
F11	39	0.053	6.8	79	45.5	46
F12	63.6	0.933	7.1	198.5	67.5	40

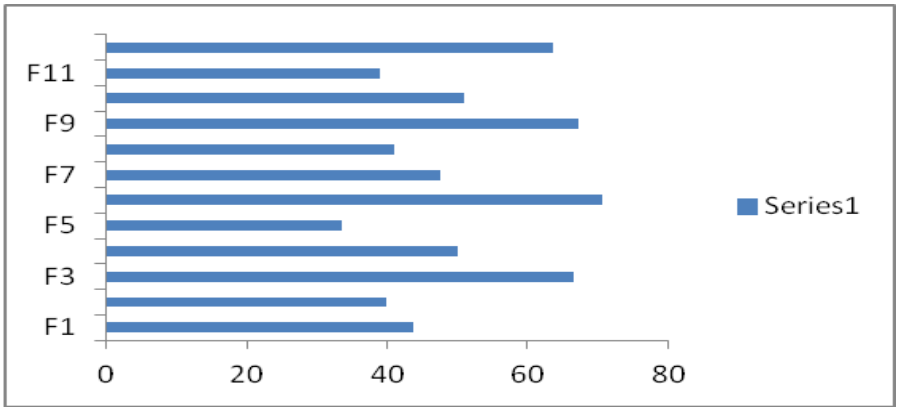

Fig.1 Weight Variation

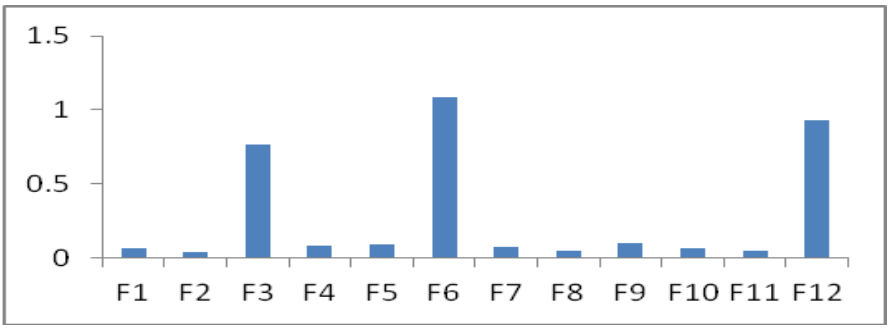

Fig.2: Thickness

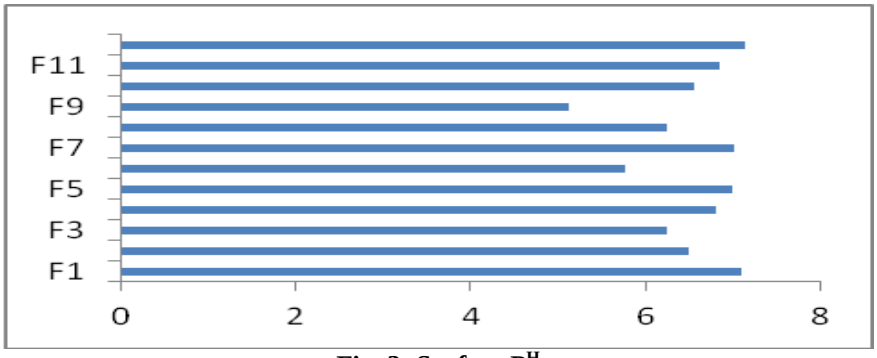

Fig .3: Surface P^{H}

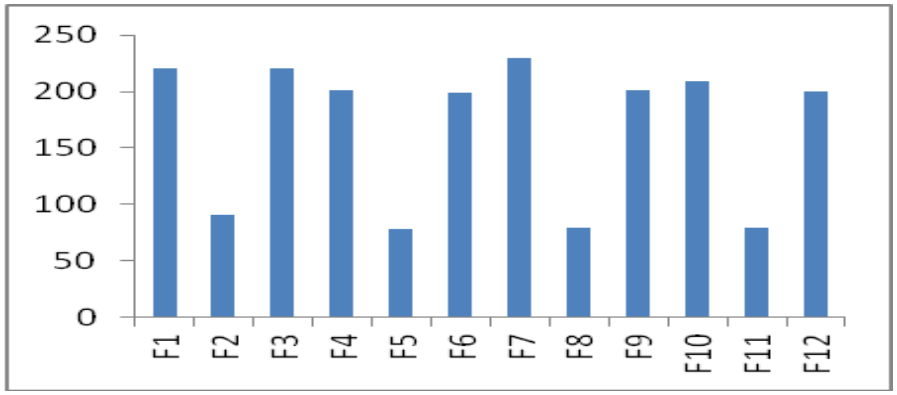

Fig.4: Folding Endurance

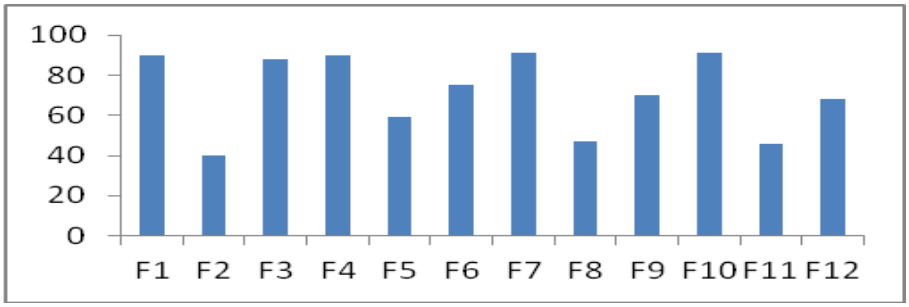

Fig.5: Drug Content Estiamation

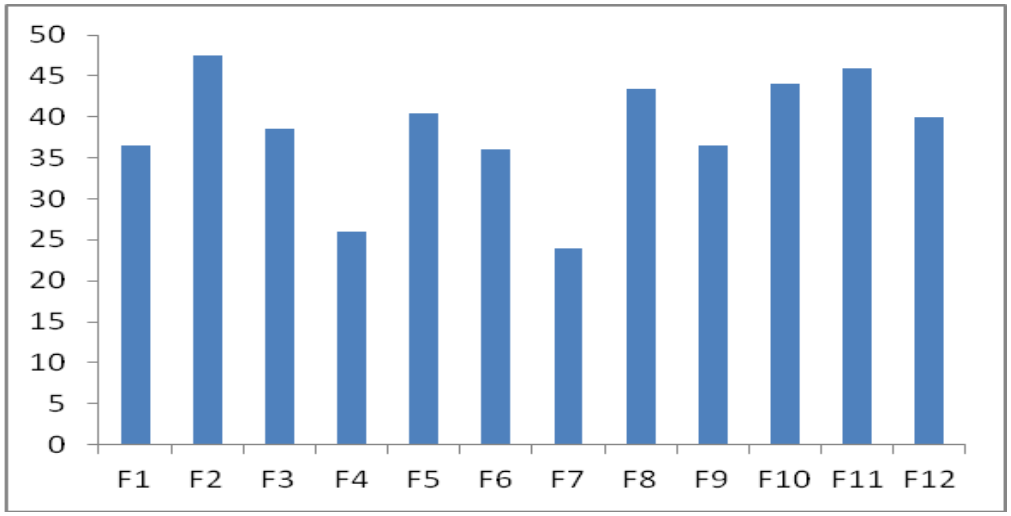

Fig.6: Disintegration

Table 3: caliberation curve of drug in phosphate buffer 6.8

Concentration(ug/ml)	absorbance
0	0
1	0.137
2	0.218
3	0.309
4	0.468
5	0.527
6	0.684

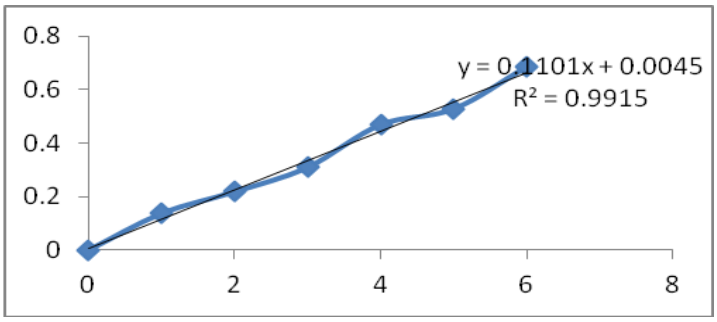

Fig.7: calibration curve of drug in phosphate buffer 7.4

Table 4: *In Vitro* dissolution data of the coumarin loaded oral thin films.

Time (sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
30	4.5	3.6	4.1	10.5	9.6	15.6	11	10.5	15.6	10.5	16	8
60	17.4	15.6	8.2	14.6	16	20.2	14.6	15.6	25.7	16	25.7	14.6
180	25.7	26.6	16	21.1	20.6	27.5	28.9	25.2	32.1	24.3	37.1	24.3
240	55.1	32.1	32.14	32.1	24.7	37.1	37.1	32.6	37.1	42.2	40	29.3
360	62.4	42.2	36.2	41.3	47.2	42.2	41.3	38.5	46.3	46.8	45	42.4
480	71.6	52.3	42.2	61.5	51.8	51.8	56.9	67	52.3	52.3	52.3	46.8
600	76.2	67	60.6	80.8	61.5	56.9	82.6	74	67	80	75	67

CONCLUSION:

The present study shows that it is possible to formulate fast dissolving films of coumarin with the intention of obtaining better therapeutic efficiency with increasing bioavailability and improving patient compliance, thereby avoiding the hepatotoxic activity of coumarins. Plasticizer used resulted in better films in respect to physicochemical parameter like, tensile strength, % elongation, folding endurance and flexibility. Formulation F7 shows maximum drug release(82.6%) in 10 min in comparison to other formulations. F4 was the best formulation showed 80.8% drug release in 10 min as the solvent is water rather than DMSO. In the present study DMSO and Ethanol were used as solvents so as to compare the drug content and *In Vitro* dissolution time of the oral films when water is used as a solvent. F4 formulation showed almost similar properties as that of F1, F7, F10 formulations where DMSO & water(3:7),DMSO, ethanol were used as solvents in which the coumarins are highly soluble. Although the drug is slightly soluble in water the drug loading and drug release parameters were found to be similar to that of other formualtions. Hence F4 formulation is considered as ideal formulation. Oral thin films were found to be a promising tool for delivering of Anti-tumour properties of coumarins to systemic circulation thereby avoiding the hepatotoxic activities.

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