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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF ORAL DISSOLVING FILMS OF APREPITANT

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ABSTRACT

The present investigation was undertaken with an objective of formulating oral dissolving films (ODFs) of Aprepitant by solvent casting technique to enhance convenience and compliance of the elderly and pediatric patients for better therapeutic efficacy. Film formers like hydroxy propyl methyl cellulose E5 (HPMC E5), HPMC E15 and Poly vinyl alcohol along with plasticizers like Glycerol, PEG400, and Isopropyl alcohol (IPA), Dichloromethane as solvents were evaluated. The prepared films were evaluated for film thickness, average weight, folding endurance, %drug content and content uniformity, tensile strength, percent elongation, *in vitro* disintegration time and *in vitro* dissolution studies. The optimized formulation F4 prepared using HPMC E15 (drug to polymer ratio of 1:1) showed minimum disintegration time (49±2 sec), highest dissolution rate i.e. 99.98% of drug within 15 min and satisfactory physicomechanical properties. Release kinetics data reveals that drug release follows first order. Results of FTIR data of optimized formulation (F4) revealed that there was no incompatibility observed between the drug and excipients used in the formulation. These findings suggest that the fast dissolving oral film containing Aprepitant is considered to be potentially useful for the treatment of nausea where quick onset of action is desirable when compared with the standard Emend conventional capsule.

INTRODUCTION

Despite of tremendous advancement in drug delivery the oral route of drug administration is the most important method of administration of drug for systemic effect. About 60% of all dosage forms available are the oral solid dosage form. The liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance.

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Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form.

The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as traveling patients who may not have ready access to water [1] So many pharmaceutical companies 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 or buccal cavity. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. Although oral disintegrating tablets have an advantage of administration without choking and fast disintegration; the disintegrated materials contained in them are insoluble and remain same until swallowing. In such cases formulation of fast dissolving film will be advantageous [2, 3]. Fast dissolving films (FDF), a type of drug delivery system for the oral delivery of the drug, was developed based on the technology of the transdermal patch. This delivery system consists of a thin film, which is simply placed on the patients's tongue or mucosal tissue, instantly wet by saliva, the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for mucosal absorption[4]. The RDFs are essentially prepared using water soluble and fast disintegrating polymers which also possess good film forming properties like hydroxy propyl methylcellulose (HPMC), polyvinyl alcohol (PVA), hydroxy propyl cellulose (HPC), along with plasticizers like glycerol, PEG400. **Aprepitant** (brand name: **Emend** is an antiemetic chemical compound that belongs to a class of drugs called substance P antagonists (SPA). It mediates its effect by blocking the neurokinin 1 (NK1) receptor. APRI is used for short-term (usually about two to six weeks) treatment of emesis related to cancer chemotherapy. APRI is available as pellets filled in capsules to be taken to prevent emesis due to anti cancer drugs. The drug is practically insoluble in water and has to be nanonized before being sprayed on to pellets and filled into capsules shell. The objective of the current work is to develop a fast disintegrating thin film dosage form as a better alternative to sublingual tablet. Anticipated patient convenience for thin film shall be significantly better than for sublingual tablets .The types and concentration of polymer and the plasticizer were optimized with respect to physical properties of the films, in vitro disintegration time and in vitro dissolution studies.

MATERIALS AND METHODS

Aprepitant was obtained as a gift sample from EMCO industries, Hyderabad. HPMC E5, HPMC E15, Poly vinyl alcohol (PVA) were obtained from Dow Chemicals, USA. Glycerol, PEG 400, Mannitol (sweetening agent), Isopropyl alcohol (IPA) and Dichloromethane (used as solvents) were obtained from Merck Chemicals, Mumbai.

Drug polymer compatibility studies: The infrared spectra of drug, polymers, physical mixture of drug and polymers were recorded at a scanning range of 400-4000 cm^{-1} using FTIR spectrometer.

Standard curve of Aprepitant: 100mg of Aprepitant was dissolved in 10ml ethanol and volume was made upto 100ml with distilled water. From this standard stock solution – I 10ml was withdrawn and diluted upto 100ml with distilled water (100µg/ml). Then by serial dilution, solutions with concentrations 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml were prepared and analyzed spectrophotometrically at 240 nm and a calibration curve shown in figure 1 was constructed according to the values obtained shown in table 1.

Preparation of Placebo formulations

Placebo formulations were prepared by using solvent casting technique. The film forming polymers HPMC and PVA were accurately weighed and dispersed in 7:3 ratio of IPA and dichloromethane each and then soaked for 4 hours. To these polymer solutions, glycerol and Mannitol were added with continuous stirring on a magnetic stirrer. The resulting bubble free solution was poured on to a glass plate and was dried at 50˚C in hot air oven for 24hr. Like this many blank films were developed by using polymer (HPMC E5, HPMC E15, PVA) and plasticizer (Glycerol, PEG400) in various combination and concentration, which were carefully removed from glass plate and evaluated for drying time, average weight, thickness, tensile strength, folding endurance and in vitro disintegration time[5,6,7] and the best were selected for incorporation of Aprepitant. The placebo film formulations are given in Table 2 and Table 3.

Preparation of Drug loaded formulations

The composition for the drug-loaded films is given in Table 4. The procedure followed was similar to the placebo formulations. Aprepitant was added to the polymer solution and sonicated for 15 minutes until the drug was completely dissolved. The drug-loaded films were evaluated for average weight, thickness, tensile strength, folding endurance, in vitro disintegration time and in vitro dissolution studies.

EVALUATION OF THE ORAL DISSOLVING FILMS

Average weight measurements

The weight of the films was determined by analytical balance. One centimetre sq. was cut at five different places in the casted film. The weight of each film was taken and the average weight was calculated. Uniformity in weight of the films indicates accuracy of dose of the oral films [8].

Thickness

Uniformity in the thickness of the film was related in accuracy of dose of the ODFs. At different locations of the strip the thickness was measured using vernier calliper micrometer [9].

Folding endurance: Folding endurance indicates mechanical strength of the oral films and was

determined by folding the strip repeatedly at the same place till it breaks. The number of times the film was folded without breaking and it was computed as the folding endurance value [9].

Tensile strength

Tensile strength indicates mechanical strength of the oral films. It indicates maximum stress required to break the strip when applied at a point. It was determined using Texture Analyzer Stable Micro system [10].

Percentage elongation: Percentage elongation of the strip was determined using Texture Analyzer Stable Micro system. The strip was taken and force was gradually applied till the film elongates and finally breaks. The readings were taken from the instrument [10].

Assay and Content uniformity

Films of 2×1 cm2 were taken and dissolved in 2.2% SLS in water and made up to 100 ml in a volumetric flask. Then 1mL was withdrawn from the solution and diluted to 10 mL. The absorbance of the solution was measured spectrophotometrically at 240 nm. The assay was calculated by this method. Limit of content uniformity is 85-115% [11].

Disintegration time: The film equivalent to one dose (2×1 cm2) was placed in a glass petridish containing 5 ml of water. The time required for the film to break was noted as disintegration time [12].

In vitro dissolution studies: The *in-vitro* dissolution studies were conducted using 2.2% SLS in water (500 mL). The dissolution studies were carried out using USP dissolution apparatus I (Electrolab, Mumbai, India) at 37± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 1 cm2) was placed on a stainless steel wire mesh. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 0, 2, 5, 10, 15 and 30 min. time intervals and filtered through wattmann filter paper and were analyzed spectrophotometrically at 240 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment [13]

Kinetic modeling: Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles can easily be evaluated depending on the derived model parameters. The model dependent approaches include zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Baker-Lonsdale, Weibull, Hopfenberg, Gompertz, Non-conventional order 1, Non- conventional order 2, Reciprocal powered time and regression models [14]. Among them tried two models to fit the data, with zero order and first order models which are shown in figure 4,5,6,7.

Zero-order model- $Q_{t\,=}\,Q_{o-}\,k_o t$

First order model- $\log C = logC_o - \frac{k_t}{2.303}$

RESULTS AND DISCUSSION

Drug polymer compatibility studies

FTIR studies conducted on pure drug and mixture of drug with excipients given in figure no. 2 showed that there is no marked interaction between drug and excipients used.

Physical characterization of fast dissolving oral films

The physical characterisation of the formulated oral films shown in figure 3 was done by solvent casting method. The results were tabulated in table 5.

The average weight and thickness of the film ranges from 16.5±0.3 to 22±2mg and 0.082±0.01mm to 0.157±0.02 respectively. Percent elongation ranges from 25.44±0.68 to 71.6±0.23

Tensile strength and folding endurance of the films ranges from 1.03±0.05 to 3.02±0.01 N/cm^2 and 119±1 to 140.6±1 folds respectively. Drug Content (mg/ 2cm^2) and content uniformity of films ranges from 19.6 to 20.4mg and 83 to 105% respectively

Distintegration time and in vitro drug release of films ranges from 52±1 to 78±1 secs and 92.9 to 99.98% in 15min in 900ml of 2.2% SLS in water. As the polymer concentration increases the thickness, tensile strength, folding endurance and disintegration time of the film also increases.

The formulation F4 exhibited required Disintegration time of 49±2 seconds, acceptable content uniformity, least thickness of 0.081±0.02 mm, Tensile strength of 1.88±0.02 N/cm^2 and *invitro* dissolution of 99.98% within 15min.

Release kinetics: The regression coefficient R^2 for all the formulations (shown in table 6) in first order kinetics is near to unity than zero order kinetics, hence the films are following first order release kinetics . The highest first order release regression coefficients (R^2) are obtained for formulations F4 and F5 (0.9902 and 0.9013 respectively). Hence, they are the optimized formulations with respect to *in vitro* drug release. Among all the formulations, the formulation

F4 emerged as the overall best formulation based on drug release characteristics and disintegration time which is shown in figure 8.

Table 1. Standard curve of Aprepitant

Concentration (µg/ml)	Absorbance
0	0
2	0.172
4	0.325
6	0.501
8	0.683
10	0.829

Table 2. Composition of Placebo formulations (PF) with Glycerol as Plasticizer

Ingredients (mg)	PF_1	PF_2	PF_3	PF_4	PF_5	PF_6	PF_7	PF_8	PF_9	PF_{10}	PF_{11}
HPMC E5	62.5	125	187.5	250	------	------	------	-----	----	-----	-----
HPMC E15	-----	-----	-----	----	62.5	125	187.5	250	-----	-----	----
PVA	-----	-----	-----	-----	-----	-----	-----	-----	125	187.5	250
Glycerol	9.38	18.7	28.1	37.5	9.38	18.7	28.1	37.5	18.7	28.1	37.5
Mannitol	100	100	100	100	100	100	100	100	100	100	100
IPA: Dichloro methane (ml)	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3

Table 3. Composition of Placebo formulations (PF) with PEG 400 as Plasticizer

Ingredients	PF_{12}	PF_{13}	PF_{14}	PF_{15}	PF_{16}	PF_{17}	PF_{18}	PF_{19}	PF_{20}	PF_{21}	PF_{22}
HPMC E5	62.5	125	187.5	250	-	-	-	-	-	-	-
HPMC E15	-	-	-	-	62.5	125	187.5	250	-	-	-
PVA	-	-	-	-	-	-	-	-	125	187.5	250
PEG 400	9.38	18.7	28.1	37.5	9.38	18.7	28.1	37.5	18.7	28.1	37.5
MANNITOL	100	100	100	100	100	100	100	100	100	100	100
IPA: Dichloro methane(ml)	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3	7:3

Table 4. Composition of drug loaded Aprepitant films

Ingredients (mg)	HPMC E5			HPMC E 15			
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Drug	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Polymer	125	187.5	250	62.5	125	187.5	250
Glycerol	18.7	28.1	37.5	9.38	18.7	28.1	37.5
Mannitol	100	100	100	100	100	100	100
Flavour	5%	5%	5%	5%	5%	5%	5%
IPA: Dichloro methane (ml)	7:3	7:3	7:3	7:3	7:3	7:3	7:3

Formulation code	Average weight (mg)	Thickness (mm)	Folding endurance	*In vitro* disintegration	Tensile strength (N/cm^2)	% Elongation	Drug content (mg)	Content uniformity (%)
F1	16.5±0.3	0.082±0.01	119±1	52±1	1.03±0.05	25.44±0.68	20.2	103-105
F2	18±0.4	0.109±0.02	130.3±9	60±2	1.87±0.01	49.5±0.62	20.0	89-101
F3	19.9±0.8	0.126±0.01	136.3±3	65±2	2.23±0.04	65.5±0.50	19.8	83-91
F4	17.5±0.7	0.081±0.02	112±3	49±2	1.88±0.02	25.62±0.82	20.3	100-104
F5	19±2.6	0.113±0.01	134±2	58±1	2.03±0.07	38.94±0.83	20.4	85-93
F6	21.4±0.4	0.134±0.05	145.3±2	69±2	2.43±0.02	69.2±0.36	20.0	85-87
F7	22±2	0.157±0.02	150.6±1	78±1	3.02±0.01	71.6±0.23	19.6	90-98

Table 4. Composition of drug loaded Aprepitant films

Table 6. Release rate kinetics

Formulation Code	Zero Order		First Order	
	K	R^2	K	R^2
F1	0.8955	0.9294	0.1385	0.9573
F2	1.087	0.8032	0.0818	0.8756
F3	1.3398	0.8341	0.0721	0.8453
F4	0.8192	0.9642	0.2197	0.9902
F5	0.9878	0.8776	0.0968	0.9013
F6	0.9813	0.7413	0.0708	0.8469
F7	1.1827	0.7687	0.0617	0.8014

Figure 1. Standard calibration curve of Aprepitant in 2.2% SLS in water

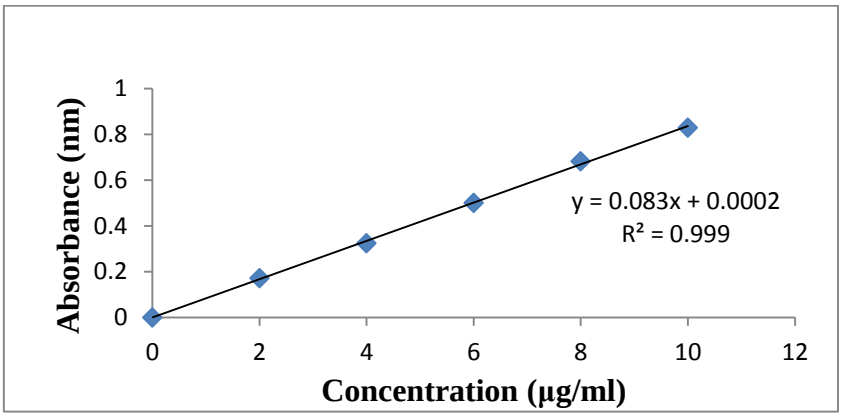


Figure 2. FTIR of Aprepitant+HPMCE15

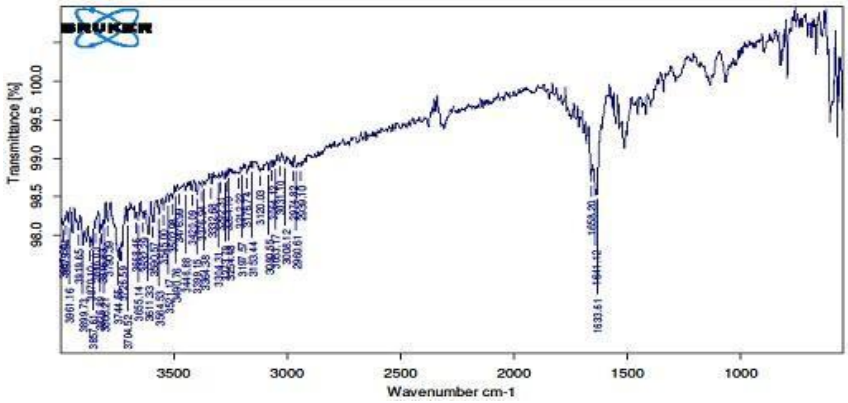


Figure 3. Comparison of Disintegration time and drug release in 2 minutes of ODFs

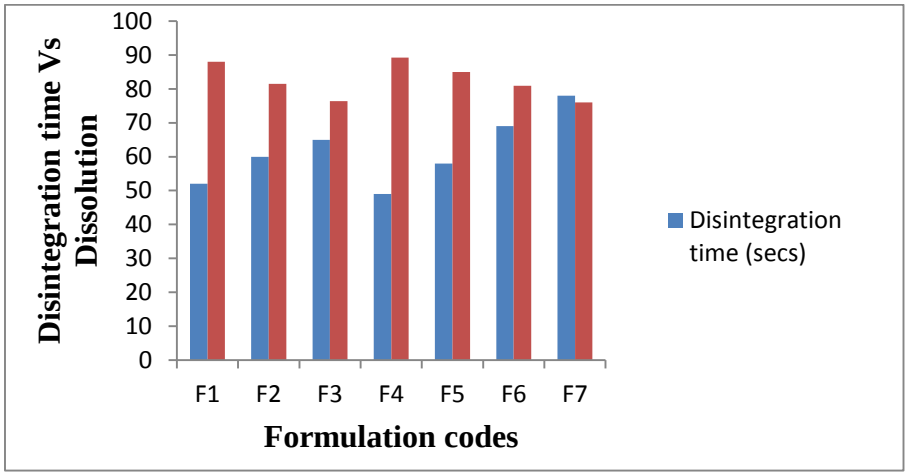


Figure 4. Zero order rate kinetics of F1, F2, F3, F4 formulations

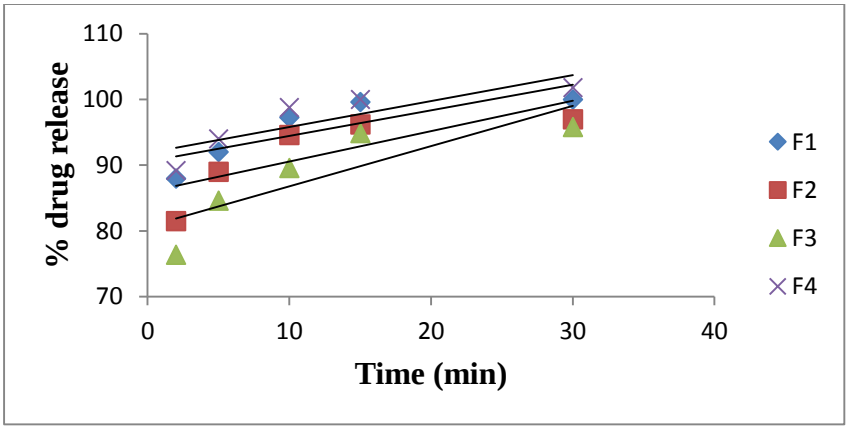


Figure 5. Zero order rate kinetics of F5, F6, F7 formulations

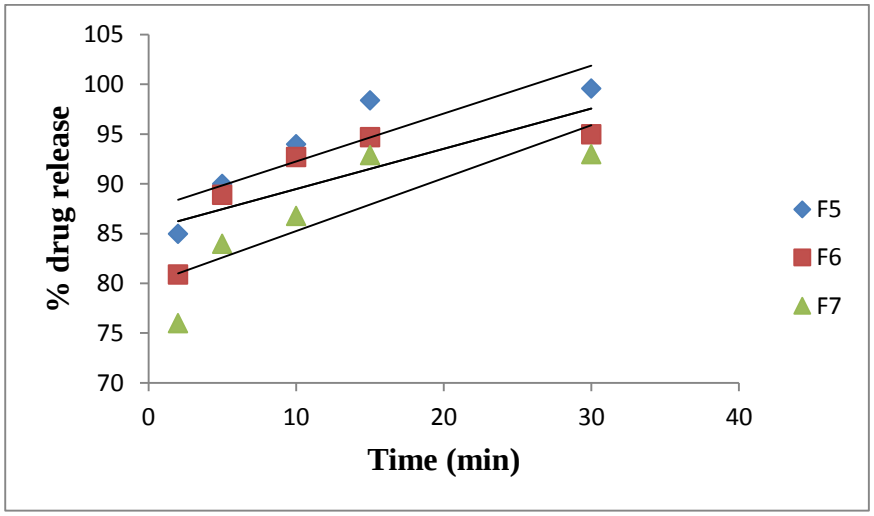


Figure 6. First order rate kinetics of F1, F2, F3, F4 formulations

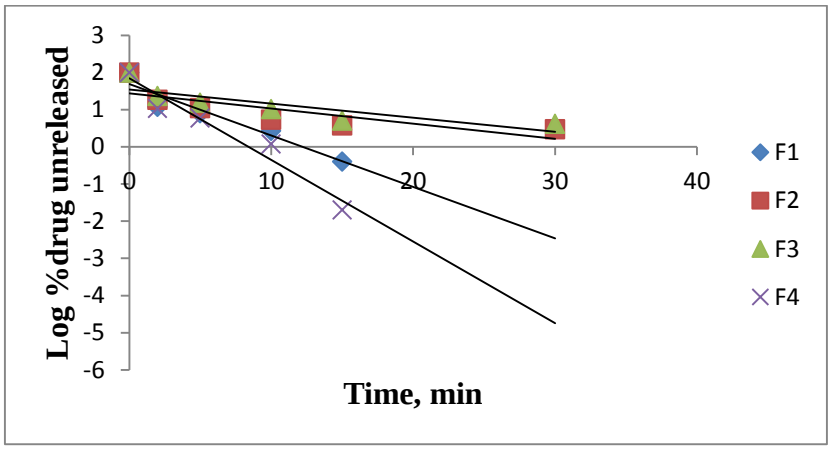


Figure 7. First order rate kinetics of F5, F6, F7 formulations

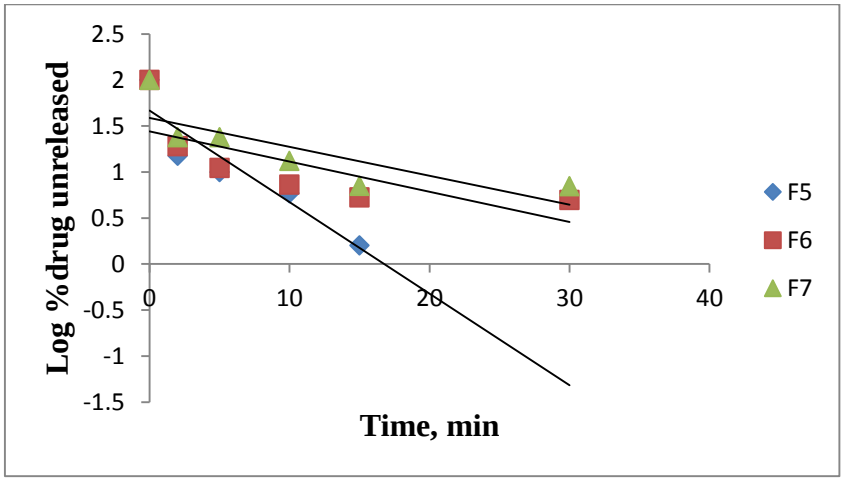
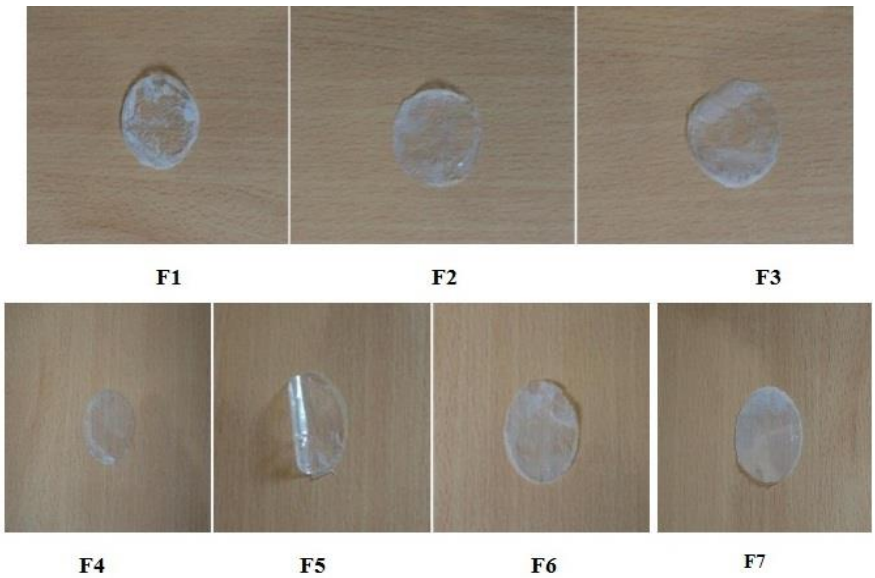


Figure 8. Physical appearance of drug loaded formulations



CONCLUSION:

Fast dissolving oral films have several advantages over the conventional dosage forms. So they are of great importance during the emergency cases such as allergic reactions and asthmatics attacks whenever immediate onset of action is desired. In the present research work, an attempt has been made to prepare films of Aprepitant by solvent casting method with enhanced dissolution rate and taste masking by using suitable combination of polymers, plasticizers, sweeteners and flavours. HPMC polymers can be concluded as the best film forming polymer as they are giving more transparent films. The final composition optimized was drug to HPMC E15 ratio of 1:1 (F4), plasticizer concentration of 15% w/w of polymer. The film had acceptable physical properties, assay and uniformity values and in vitro dissolution within 2 minutes. The prepared strips seem to be an attractive alternative to conventional marketed formulations.

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