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Formulation and in-vitro evaluation of mucolytic fast dissolving oral film Containing ambroxol hcl using various polymers

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ABSTRACT

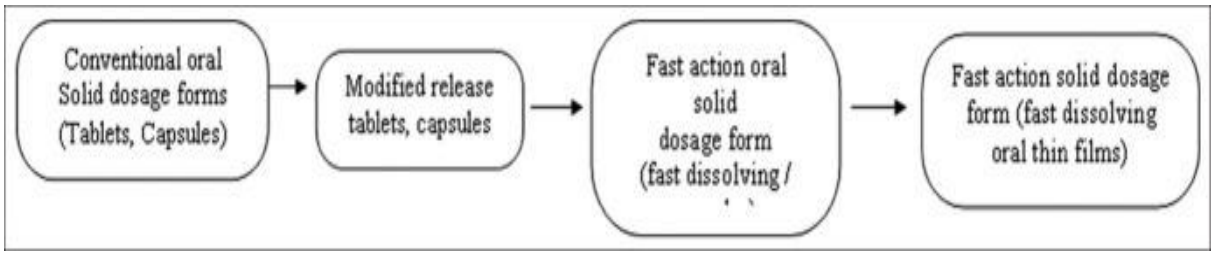
AmbroxolHCl is a drug that breaks up phlegm, used in the treatment of respiratory diseases associated with viscid or excessive mucus. Ambroxol is often administered as an active ingredient in cough syrup. Present work aimed at preparing quick onset of action which is beneficial in respiratory diseases, aiding in the enhancement of bioavailabity and is very convenient for administration without the problem of swallowing and using water. The film was prepared by using polymers such asHPMC,HPMC K100 and HPMC K1500by a solvent casting method. They wereevaluated for physical characteristics such as Thickness, Weight Variation, Disintegration time, Drug content, Tensile strength, % Elongation, Folding Endurance and *Invitro* Dissolution Studies give satisfactory results. The *in vitro* dissolution time of the optimized batch F4 was found to be 98.97 %. The optimized batch*in vitro* disintegration time was found to 14 to 22 sec.

Keywords: AmbroxolHCl, HPMC,HPMC K100 and HPMC K1500 and solvent casting method.

INTRODUCTION

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear of choking. Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing. Fast dissolving drug delivery systems were first invented in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane.[1,2] It is interesting to note that the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin, but less than that of the intestine.[3] Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration.[4] The primary barrier to permeability in otiral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 μm layer.[5] These dosage forms have a shelf life of 2-3 years, depending on the active pharmaceutical ingredient but

are extremely sensitive to environmental moisture.[6] An ideal fast dissolving delivery system should have the following properties: High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for application, and a pleasant taste. Therefore, they are very suitable for pediatric and geriatric patients; bedridden patients; or patients suffering from dysphagia, Parkinson's disease, mucositis, or vomiting. This novel drug delivery system can also be beneficial for meeting current needs of the industry. Rapidly dissolving films (RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms are introduced in the United States and European pharmaceutical markets for therapeutic benefits. The first of the kind of oral strips (OS) were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening. Chloraseptic relief strips were the first therapeutic oral thin films (OTF) which contained[7] benzocaine and were used for the treatment of sore throat. Formulation of fast dissolving buccal film involves material such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents, permeation enhancers, and super disintegrants. All the excipients used in the formulation of fast dissolving film should be approved for use in oral pharmaceutical dosage forms as per regulatory perspectives.



Advantages

- Oral films have some special advantages over other oral dosage forms given as follows:
- Rapidly dissolved and disintegrated in the oral cavity because of large surface area which lowers dosage interval, improves onset of action, efficacy and safety profile of therapy.
- Oral films are more flexible, compliant and are not brittle as ODTS.
- Easily handled, storage and transportation.
- Accuracy in the administered dose is assured from every strip or film.
- Pharmaceutical companies and customers practically accepted OTFs as an alternative of conventional OTC dosage forms such tablets and capsules etc. (Frey, 2006).
- Oral film is desirable for patient suffering from motion sickness, dysphagia, repeated emesis and mental disorders.
- From commercial point of view, oral films provide new business opportunity like product differentiation, promotion etc.[8,9]

Disadvantages

The main disadvantage of this delivery system is we cannotincorporate high dose into strip or film. Novartis consumerhealth's Gas-x thin strip has loaded 62.5mg of simethiconeper strip but there remain number oflimitations with the use of film strips.[10]

Ideal Characteristics of a Suitable Drug Candidate [11]

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drug should have smaller and moderate molecular weight.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have ability to permeate the oral mucosal tissue.

Classification of oral films

There are three types of oral films:

1. Flash release
2. Mucoadhesive melt away wafer
3. Mucoadhesive sustained release wafers

Applications of oral films in drug delivery

- Oral drug delivery by sublingual, mucosal and buccal become preferable for therapies in which immediate absorption is required including those used to manage pain, allergies, sleep problems and CNS disorders.
- **Topical applications,** the oral films are ideal in the delivery of active agents like analgesic or antimicrobial ingredients for the care of wound and other applications.
- **Gastroretentive dosage systems**, poorly soluble and water soluble molecules
- of different molecular weights are found in film format [12]. Dissolution of oral films could be initiated by the pH or enzymatic secretion of GIT and are used to treat gastrointestinal disorders.
- **Diagnostic devices**, Oral films loaded with sensitive reagent to allow controlled release faced to biological fluid for separating multiple reagents to allow a timed reaction within diagnostic device.[13]

MATERIALS

Ambroxol HydrochlorideProvided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC Fisher Scientific, India, HPMC K100Morepen labs ltd,Parwanoo(HP), India, HPMC K1500Praavar Chemtech, Mumbai, Poly propylene glycol (mL) Millipore system, D.W Rankem, Citric AcidSignet Chemical Corporation, Mumbai.

METHODOLOGY

Drug –Polymer compatibility studies by FT-IR

Drug polymer compatibility studies were performed by FT-IR (Fourier transform infrared spectroscopy). In order to confirm that the entrapment of drug within the polymeric systems involve only the physical process and no interaction between drug and polymer. FTIR absorption Spectra's were shows no significant interaction between drug and polymers.

Selection of the drug

- The Ambroxol Hydrochloride which has significantly different pharmacokinetic profiles.
- AmbroxolHydrochlorideis a drug that breaks up phlegm, used in the treatment of respiratory diseases associated with viscid or excessive mucus. Ambroxol is often administered as an active ingredient in cough syrup.

Construction of calibration curve for Ambroxol Hydrochloride

Determination of λmax

Ambroxol Hydrochloride λmax was determined by spectrophotometer using pH 6.8 buffer medium. First dissolve 10mg of pure drug in 10ml of 6.8 buffer medium. From this 10µg/ml solution was prepared by using pH 6.8 buffer. 10µg/ml solution absorbance was measured at 200-400 nm range by spectrophotometrically using pH 6.8 buffer as reference solution.

Preparation of calibration curve

1. **Primary stock solution:** Standard calibration curve of Ambroxol Hydrochloride in 6.8 buffer were prepared. First dissolve 10mg of pure drug in 10ml of 6.8 buffers this is primary stock solution.
2. **Second stock solution:** From the above primary stock solution pipette out 1ml of solution and again make up to 10ml this is secondary stock solution. From this secondary stock solution different concentrations of Ambroxol Hydrochloride (2, 4, 6, 8, and 10µg/ml) in 6.8 buffers were prepared and absorbance of these solutions measured at 240 nm by spectrophotometrically using pH 6.8 buffer as reference solution.

Preparation of mouth dissolving films

General method of formulation of oral dissolving films

Following processes are generally used to manufacture the mouth dissolving film.

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

The current preferred manufacturing process for making this film is solvent casting method. In this method water soluble polymer is dissolved in suitable solvent to make homogenous viscous solution. In this other excipients (plasticizer and sweetner) including drug resinate complex were dissolved under stirring. Then the solution is degassed by keeping it in the sonicator. The resulting bubble free solution poured into petriplate and was kept in oven. Dried film is then cut into the desired shape and size for the intended application.

Preparation of blank films using different polymers

- Accurately weighed quantity of polymer was dissolved in specific quantity of water.
- The dissolved polymer was made to a uniform dispersion using a homogenizer.
- During stirring other excipients (plasticizer and sweetner) were added.
- Then the solution is degassed by keeping it in the Sonicator.
- The bubble free solution poured into petriplate and was kept in oven.
- Then the dried films were used to select the best film forming polymers.

Selection of best film forming polymer

The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spreadability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. Film obtained should be tough enough to avoid the damage while handling or during transportation.

Different Polymers Used For Trails

- Hydroxy propyl methyl cellulose
- HPMC K100
- HPMC K1500

Preparation of oral fast dissolving film

The fast dissolving films of Ambroxol Hydrochloride were prepared by solvent casting technique. The fast dissolving films were prepared using different polymers like Hydroxy propyl methyl cellulose, HPMC K100 and HPMC K1500. Propylene Glycol (PG) was used as plasticizer.

Formulation of Ambroxol Hydrochloride oral fast dissolving films

Table 1: Composition of Ambroxol Hydrochloride oral dissolving films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ambroxol Hydrochloride	30	30	30	30	30	30	30	30	30
HPMC	30	60	90	-	-	-	-	--	-
HPMC K100	-	-	-	30	60	90	-	-	-
HPMC K1500	-	-	-	-	-	-	30	60	90
Poly propylene glycol (mL)	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
D.W	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Citric Acid	10	10	10	10	10	10	10	10	10
Cross Povidone	20	30	40	50	-	-	-	-	-
Kyron-T314	-	-	-	-	20	30	40	50	60
Mannitol	8	8	8	8	8	8	8	8	8
Total weight	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION

Analytical Method Development forAmbroxol Hydrochloride

Construction of CalibrationCurve

Ambroxol Hydrochloride λ_{max} was determined by spectrophotometer using pH 6.8 buffer medium. First dissolve 10 mg of pure drug in 10 ml of 6.8 buffer medium. From this 10 µg/ml solution was prepared by using 6.8 buffer. 10µg/ml solution absorbance was scanned at 200 to 400nm range by spectrophotometrically using 6.8 buffer as reference solution and λ_{max} was observed at 240 nm. A standard graph of pure drug in suitable medium was prepared by plotting the concentration (µg/ml) on X-Axis and absorbance on Y-Axis. An excellent correlationco-efficient (R^2=0.999) was observed.

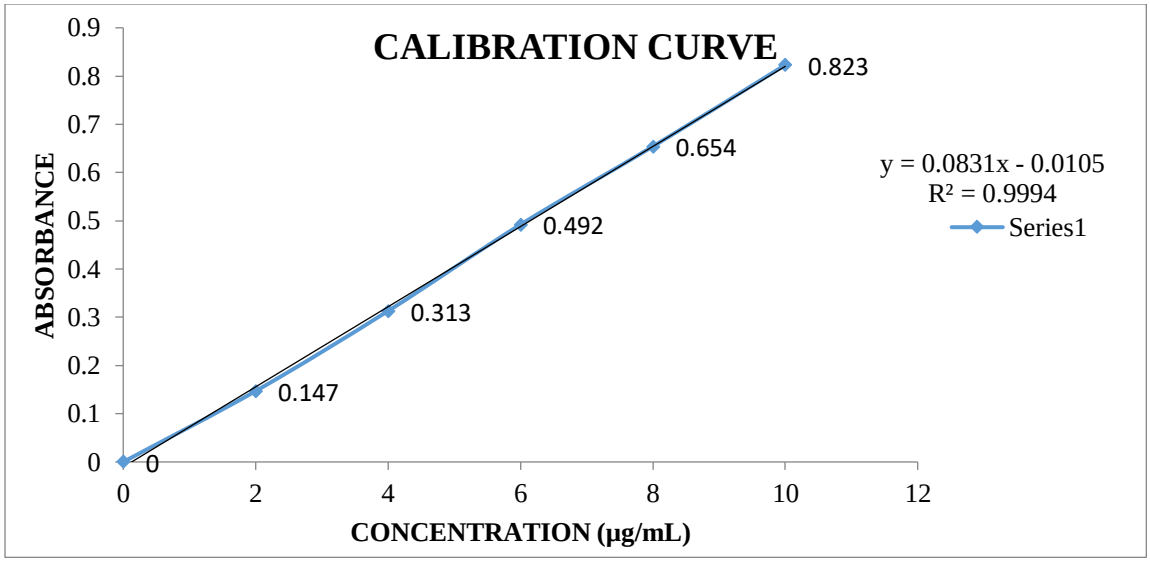


Fig 1: Calibration curve of Ambroxol Hydrochloride in pH 6.8 phosphate buffer at λ_{max} =240 nm

Drug-Excipient Compatibility (FTIR studies)

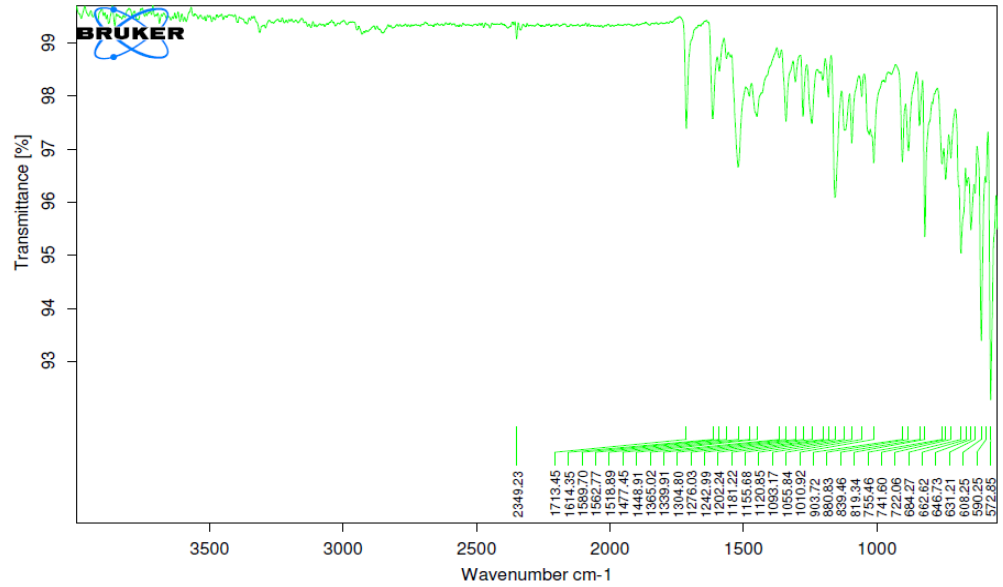


Fig2: Ambroxol Hydrochloride Pure Drug FTIR

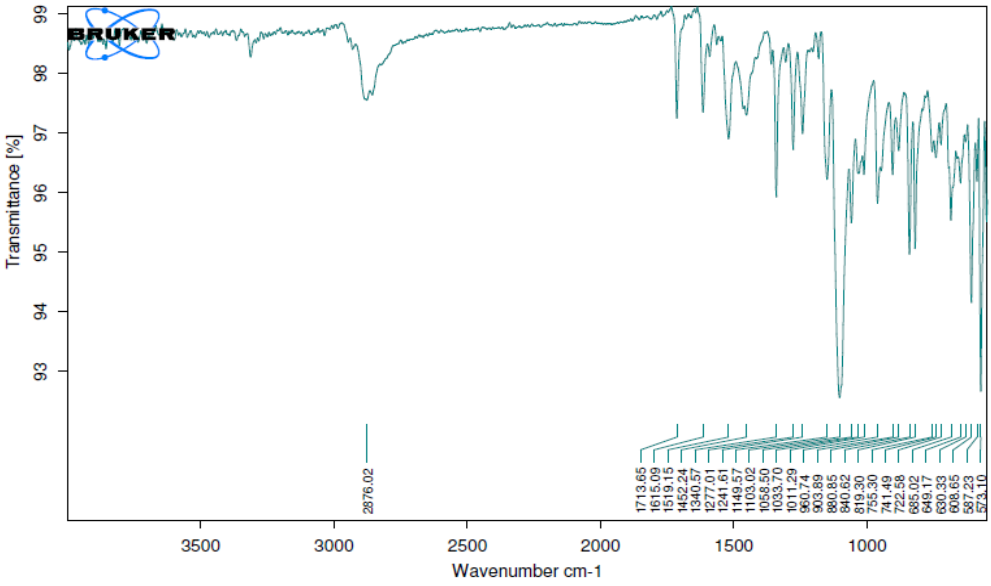


Fig3: Ambroxol Hydrochloride Optimised Formulation FTIR

Table 2: Physical evaluation parameters of all formulations

Formulation Code	Thickness (mm)	Weight Variation (mg)	Disintegration time (sec)	Drug content (%)
F1	1.14	99.12	15	98.32
F2	1.26	98.60	20	99.14
F3	1.28	97.51	18	98.96
F4	1.33	100.05	14	99.61
F5	1.19	98.41	22	99.22
F6	1.19	99.72	19	99.31
F7	1.24	99.14	17	98.07

F8	1.12	97.09	21	98.13
F9	1.25	100.14	19	99.10

Table 3: Evaluation of transdermal films

Formulation Code	Folding endurance	Flatness (%)	Appearance
F1	61± 2.06	97	Transparent
F2	68± 1.01	96	Transparent
F3	71± 3.19	97	Transparent
F4	75± 2.01	99	Transparent
F5	52± 3.51	95	Transparent
F6	57± 2.28	98	Transparent
F7	65± 2.49	94	Transparent
F8	67± 2.27	93	Transparent
F9	72± 2.61	97	Transparent

Table 4: *In vitro*drug releases for F1 to F9 formulations

TIME (MINS)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	39.22	41.33	43.88	49.22	47.55	43.55	38.22	42.66	47.52
10	48.59	52.71	55.38	63.58	61.9	57.40	46.33	54.33	58.61
15	61.17	65.31	69.44	73.75	66.27	64.06	59.72	71.27	68.77
20	72.31	76.46	78.05	86.52	82.89	75.34	71.11	83.61	79.16
30	86.33	89.60	91.75	98.97	96.33	94.35	89.88	93.57	88.61

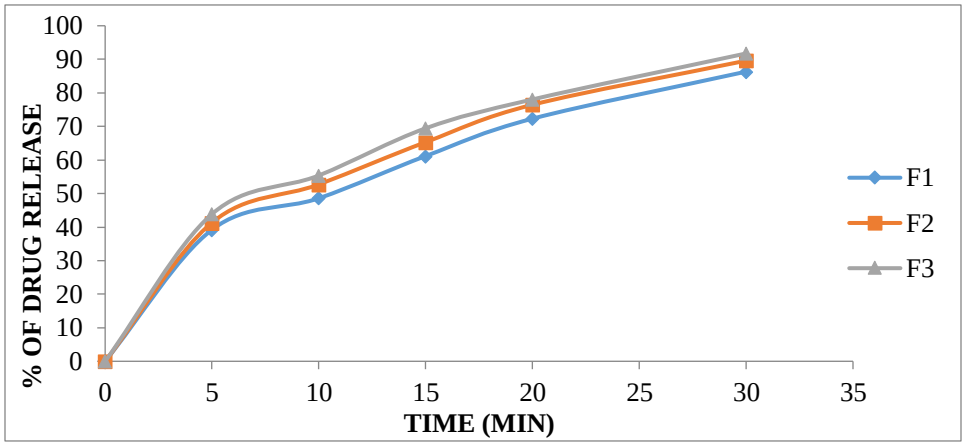


Fig4: Comparison curve of *Invitro* drug release for F1- F3 formulations

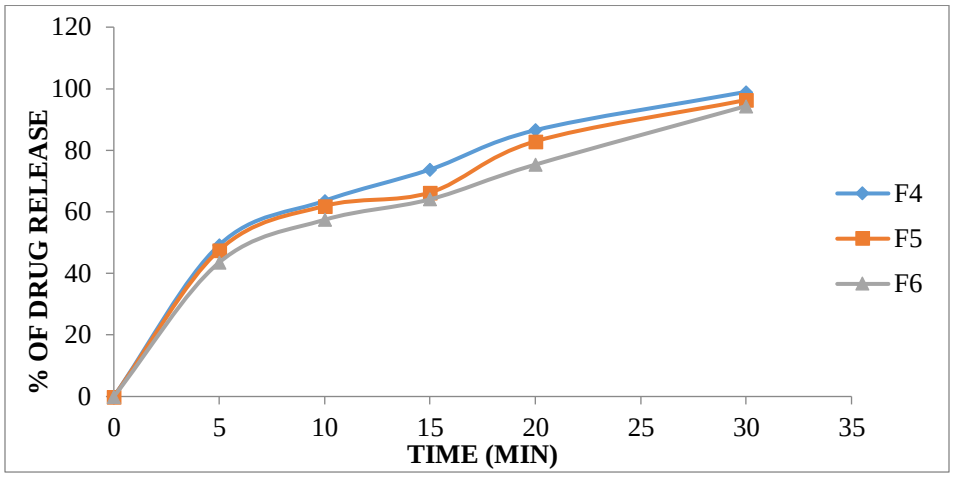


Fig5: Comparison curve of *Invitro* drug release for F4- F6 formulations

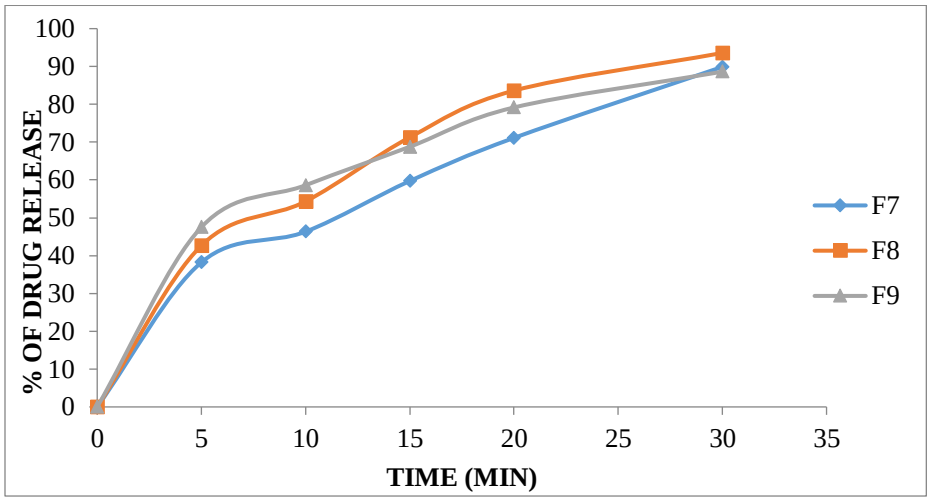


Fig6: Comparison curve of *Invitro* drug release for F7- F9 formulations

DISCUSSION

Analytical method development for Ambroxol Hydrochloride λ max determination

λ max determination of Ambroxol Hydrochloride pH 6.8 phosphate buffer was determined by using UV Spectrophotometer at 240 nm.

Development of standard graph

Standard plot of Ambroxol Hydrochloride pH 6.8 phosphate bufferwere plotted to concentration vs absorbance at 240nm and the slope value and R^2 value were found to be 0.999.

Evaluation properties

The different Ambroxol Hydrochloride film formulations were evaluated for mechanical properties like thickness, drug content uniformity, folding endurance, tensile strength, weight uniformity, disintegration time, *in vitro* dissolution studies.

Thickness

The thickness of the films from F1-F9 formulations were ranged from 1.33. F4formulation had the maximum thickness values in all the formulations. From the thickness values it is concluded that as the polymer concentration increases, thickness also increased.

Tensile strength & Percentage elongation

The tensile strength of the films from F1-F9 formulations were ranged from 1.182 to 1.469 kg. F4 formulation had the maximum tensile strength and. From the tensile strengthvalues it is concluded that as the polymer concentration increases, tensile strength and percentage elongation also increased.

Drug content uniformity

The drug content uniformity of the films from F1-F9 formulations were ranged from97.54 % to 99.61 %. F4 formulation had the maximum drug content uniformity.

Folding endurance

The folding endurance value of the films from F1-F9 formulations were ranged from 52± 3.51 to 75± 2.01. In HPMC K100containing formulations as polymer concentration increases folding endurance values were also decreases.

Weight uniformity

Weight uniformity of films was carried out for all the formulations and weight variation varies from 97.09to 100.14mg.

Disintegration time

The disintegration time is the time when a film starts to break or disintegrate. The *in vitro*disintegration time was calculated for all the formulations and it ranges from 14 sec to22 sec Disintegration time of the films was increased with low concentration of the polymer, as more fluid is required to wet the film in the mouth. F4 formulation was quickly disintegrated that is in 14sec.

Finally selection of the best formulation from all the formulations was carried by using *In Vitro* dissolution studies.

In vitro dissolution studies

In vitro dissolution study of F1-F9 formulations were showed different drug release of 91.75 %, 98.97 %, 93.57 %,respectively within 30min. Among the formulations F4showed good dissolution property hence it is optimized and it contains30 mg of HPMC K100as film forming polymer. Small differences were observed in dissolution of drug from the different formulations of the film. Present study reveals that maximum all formulated films showed satisfactory film parameters. Among the optimized formulations F4formulation showed better drug release of 98.97 %within 30 min. F4 formulation contains 30mg of HPMC K100polymer as film forming agent.

So, it is assumed that 30 mg HPMC K100containing oral fast dissolving film was optimized in which it showed a drug release of 98.97%compared with other batch formulations.

CONCLUSION

The Ambroxol Hydrochloride oral films could be promising one as they, increase bioavailability, minimize the dose, reduces the side effects and improve patient compliance and also Ambroxol Hydrochloride might be a right and suitable candidate for oral delivery.Low dose of drug can be suitable for oral films with low density of polymers. ODF are the thin film with more surface area they get wet quickly and disintegrate then dissolve faster than other formulations.From the present investigation it can be concluded that Oral Disintegrating Films formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population. The prepared Ambroxol Hydrochloride oral films were characterized based upon their physiochemical characteristics like tensile strength, Disintegration time, thickness, weight uniformity, folding endurance, drug content uniformity, dissolution studies. All the results were found to be were found to be within the pharmacopeia limits.

Based on the results F4 was the best one when compared to other. Based on disintegration and drug releases faster of the ODF formulation F4 has less disintegration time and compared to other formulations.So ODF formulated with HPMC K100Polymer F4 is best formulation.

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