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Research

Formulation And *In Vitro* Evaluation Of Ambroxol Hcl Fast Dissolving Films Using Various Polymers

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Abstract

Ambroxol HCl 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: Ambroxol HCl, 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 superdisintegrants. 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 cannot in corporate high dose into strip or film. Novartis consumer health's Gas-x thin strip has loaded 62.5mg of simethicone per strip but there remain number of limitations 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]

Film Forming Polymers[14]

A variety of polymers are available for preparation of fast dissolving oral films. The use of film forming polymers in oral films has attracted considerable attention in medical and nutraceutical applications. The selection of film forming polymers, is one of the most important and critical parameter for the successful development of film formulation. The polymers can be used alone or in combination to provide desired film properties. The polymers used in oral film formulation should be:

- ✓ Nontoxic and nonirritant.
- ✓ Devoid of leachable impurities.
- ✓ Should not retard disintegration time of film.
- ✓ Tasteless.
- ✓ Should have good wetting and spread ability property.
- ✓ Should have sufficient peel, shear, and tensile strength.
- ✓ Readily available.
- ✓ Inexpensive.
- ✓ Sufficient shelf life.
- ✓ Should not aid in causing secondary infections in oral mucosa.

Presently, both natural and synthetic polymers are used for the preparation of orally dissolving films. represent various natural and synthetic polymers used for preparation of fast dissolving films. represent the quality parameters of natural and synthetic polymers, respectively.

ORAL STRIP FORMULATION COMPONENTS

- ✓ Active pharmaceutical ingredients
- ✓ Strip forming polymers
- ✓ Plasticizers
- ✓ Sweetening agents
- ✓ Saliva stimulating agents
- ✓ Flavoring agents
- ✓ Coloring agents
- ✓ Stabilizing and thickening agents

Active pharmaceutical ingredients

The main disadvantage of oral strip/ film is the size of the dosage form due to which high dose could not be loaded. We incorporate 5% w/w to 30% w/w of active pharmaceutical ingredients [15]. For multivitamins, up to 10% w/w of dry film weight was loaded. APIs can be milled, micronized or loaded in the form of nanocrystals or particles depending upon the ultimate release profile desired [16]. For bitter drugs taste required to be masked before incorporating APIs in the OS [17]. To enhance the taste different techniques are used but the simplest method includes mixing and co-processing of bitter testing API with excipient with good pleasant taste called as obscuration technique. Regiospecific delivery of the drugs would also be required in allergy, cough, sore throat and other local oral manifestations.

Strip forming polymers

Polymers can be used alone or in contrast to get the required film properties for the preparation of oral film to prevent damage during handling and transportation. At least 45% w/w of polymers should present because strip forming polymer is the important constituent of the OS[18]. Generally, 60-65% of water soluble polymer is suitable for OS preparation with desired properties[19].Ability of polymers about formulation of desired strip (film forming capacity), visual appearance, disintegration time values are given in the table. Visual appearance of the film is transparent and free of bubbles necessary for aesthetic appeal of the films

Plasticizers

Plasticizer can be used to improve the elasticity and decrease the fragility of film by decreasing the glass transition temperature of polymer. The choice of plasticizer depends on its compatibility with polymer and the solvent type[20]. Most commonly used plasticizers are glycerol, propylene glycol, PEG, phthalate derivatives such as dimethyl, diethyl and dibutyl phthalate, citrate derivatives. like tributyl, triethyl, acetyl citrate, triacetin and castor oil.0-20% w/w plaster concentration is used by preventing cracking, splitting and peeling of strip [21].

Sweetening agents

Sweeteners are the essential constituent of pharmaceutical product for pediatric patients. Generally, two types of sweeteners are most commonly used which are natural sweeteners and artificial sweeteners. Sucrose is the major source of sweeteners; dextrose, fructose glucose and maltose are also source of sweeteners. The use of natural sugar is limited in diabetic patients, that’s why artificial sweeteners are most commonly used in pharmaceutical preparations. First generation artificial sweeteners include cyclamate and aspartame while second generation include acesulfame-K, sucralose, alitame and neotame [22].

Saliva stimulating agent

To enhance the rate of production of saliva, saliva stimulating agents are added. Generally, acids such as citric acid, malic acid, lactic acid, ascorbic acid and tartaric acids are salivary stimulants. These agents are used in 2-6% w/w of weight of strip. Sweeteners also used as salivary stimulants [23].

Flavoring agents

The choice of flavors depends on age, taste and liking of the people. Younger people like fruit punch, raspberry etc. while the geriatric patient prefer orange, lemon and mint flavor. The selection of flavor is done on the type of drug candidate. Almost 10%w/w flavors are added in oral film preparations. Cooling agents can also be added to enhance the flavor strength [24].

Coloring agents

When formulation ingredients or drug candidates are present in insoluble or suspension form pigments like titanium dioxide or FD&C approved coloring agents which are incorporated up to 1% w/w [25].

Stabilizing and thickening agents

To improve the viscosity and consistency of formulation, the stabilizing and thickening agents are incorporated. Natural gum, like xanthan gum, carragenan, locust beangum and cellulose derivative are loaded up to 5% w/w[25].

Methods for the preparation of oral films

- ✓ Various methods for producing oral films are classified as follows:
- ✓ Casting and drying: (a) solvent casting (b) semi-solid casting.
- ✓ Extrusion: (a) hot melt extrusion (b) solid dispersion extrusion
- ✓ Rolling method:

Casting and Drying

a) Solvent- Casting Method

The oral film is mostly prepared by using the solvent-extraction method, in which water soluble ingredients are dissolved to form a clear viscous solution. The active pharmaceutical ingredient and other agents are dissolved in small amount of solution and combine with bulk. This mixture is then added into aqueous solution. Remove entrapped air and resulting solution is casted as film and then dried which is then cut into pieces of the desired sizes[26].

b) Semi-solid Casting

First of all, a solution of water soluble film forming polymer is prepared in semi solid casting method. Then resulting solution is added to insoluble polymer like cellulose acetate butyrate, cellulose acetate phthalate etc., prepared in sodium or ammonium hydroxide. Then add accurate amount of plasticizer to get gel mass. Finally cast gel mass into films by using heat controlled drums. The thick ness of the film is about 0.015-0.05.

Extrusion

a) Hot-Melt Extrusion

Hot melt extrusion is widely employed method to formulate granules, sustained release tablets; transdermal and transmucosal drug delivery system. Processing film involves shaping a polymer into a film by using the heating process. Filled the hopper with drug carrier mix and is conveyed, mixed and melted by the extruder. Then die shaped melt in the desired film form. prepared chlorpheniramine maleate films by hot melt extrusion method[27].

b) Solid-Dispersion Extrusion

In this method, drug is firstly dissolved in a suitable liquid solvent and then this solution is incorporated in melt of PEG below 70C. The selected solvent or drug could not be miscible with melt of PEG and polymorphic form of drug precipitated in solid dispersion may affected by solvent[28].

Rolling method

In rolling method, film is formulated by preparation of premix, by adding active and subsequent formation of film. The pre-mix batch include film forming polymer, polar solvent and other ingredients except API added to the master batch feed tank. Then a predetermined amount of the master batch is fed by first metering pump and control valve. The desired amount of drug is add edinto mixer, and then blended for a sufficient time to form ahomogenized matrix. A specific amount of matrix is fedinto pan through second metering pump. The metering roller determined thickness of film. The film is finally formed on substrate and carrier away by the support roller. The wet is dried by using controlled bottom drying.[29]

Patented approaches[30]

XGel

XGel™ film provides unique product benefits for healthcare and pharmaceutical products: It is nonanimal derived, approved on religious grounds, and is suitable for vegetarians; the film is genetically modified organism (GMO) free and continuous production processing provides an economic and competitive manufacturing platform. XGel™ film can be taste masked, colored, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGel™ film systems can be made to encapsulate any oral dosage form and can be soluble in either cold or hot water. XGel™ film is comprised of a range of different water soluble polymers, specifically optimized for the intended use.

Soluleaves

This technology is used to produce a range of oral delivery films that can incorporate active ingredients, colors, and flavors. Soluleaves™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients, and flavors. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses, this method of administration is especially useful for pediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal, and pain therapeutic areas as well as delivering nutritional products. Soluleaves™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 min.

Wafertab

Wafertab™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The Wafertab™ filmstrip can be flavored for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a premanufactured XGel™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The Wafertab™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. Wafertab™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release or for use by patients who have difficulty in swallowing.

Foamburst

It is a special variant of the Soluleaves™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. Foamburst™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavors.

Micap

Micap plc signed an option agreement in 2004 to combine its expertise in microencapsulation technology with the Bio Progress water soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4 billion global market for smoking cessation products (SCPs).

MATERIALS

Ambroxol Hydrochloride-Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC -Fisher Scientific, India, HPMC K100-Morepen labs ltd ,Parwanoo (HP), India, HPMC K1500, Praavar Chemtech, Mumbai, Poly propylene glycol (mL)-Millipore system, D.W-Rankem, Citric Acid-Signet Chemical Corporation, Mumbai, Cross Povidone-S.d.fine chem. Ltd, Mumbai, India, Kyron-T314-Purchased from SD Fine- Chem Limited, Mumbai, Mannitol-Purchased from SD Fine- Chem Limited, Mumbai.

METHODOLOGY

I Drug Polymer Compatibility Studies Using FTIR
II Construction of Calibration Curve
III Preparation of Oral Disintegrating Films
IV Evaluation of Oral Disintegrating Filmsformulation

- Thickness
- Weight of films
- Percentage elongation
- Tensile strength
- Folding endurance
- Drug content estimation
- Disintegration test
- In vitro dissolution test

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.
- ✓ AmbroxolHydrochloridewas soluble in water and in solvents.
- ✓ AmbroxolHydrochloridewas stable at salivary pH.

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.

III. 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
Procedure

- ❖ 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. The calculated amount of polymer was dispersed in the solvent with continuous stirring using magnetic stirrer and the homogenous solution is formed. Then add 4 ml of plasticizer. Then the sweetner and flavor was added to drug mixed polymeric solution. Then the solution was kept in sonicator for degassing. Then the bubble free solution was casted on to petriplate and was kept in hot air oven. Dried film is then cut into the desired shape and size (1cm x 1cm) for the intended application. By carrying out the trial and error method different quantity of film forming polymers were used for optimizing the formulation.

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 DISCUSSIONS

Analytical Method Development for Ambroxol Hydrochloride

Construction of Calibration Curve

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 correlation co-efficient (R^2=0.999) was observed.

Table 2: Calibration Curve values of Ambroxol Hydrochloride in phosphate buffer pH 6.8 at λ_{max} =240nm

Concentration (µg/ml)	Absorbance λ_{max}=240 nm
0	0
2	0.147
4	0.313
6	0.492
8	0.654
10	0.823

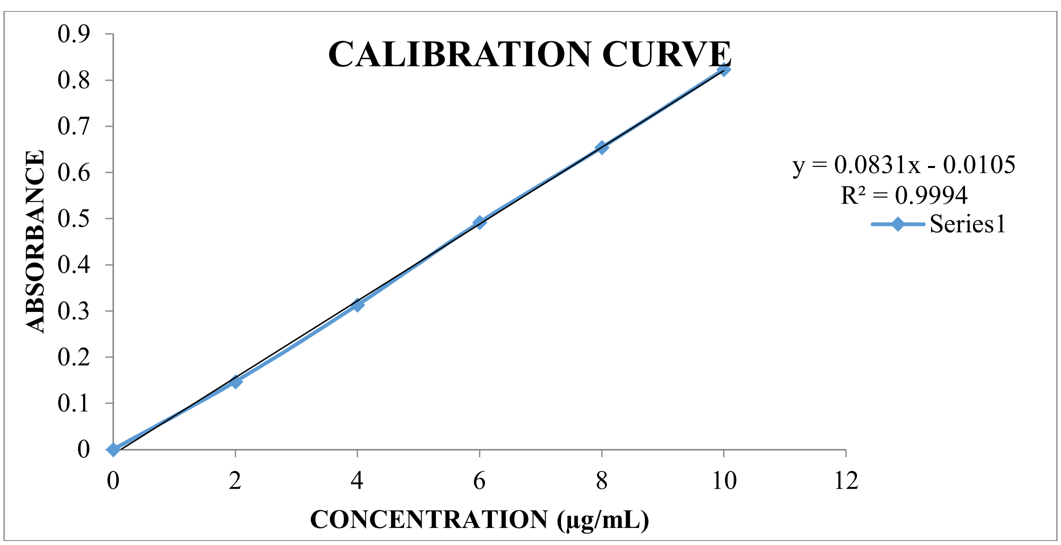

Fig 1 : Calibration curve of Ambroxol Hydrochloride in pH 6.8 phosphate buffer at λ_{max} =240 nm

Drug-Excipient Compatibility (FTIR studies)

IR spectral analysis was carried out using FT-IR and the results showed that there were no interactions between drug and Excipients.

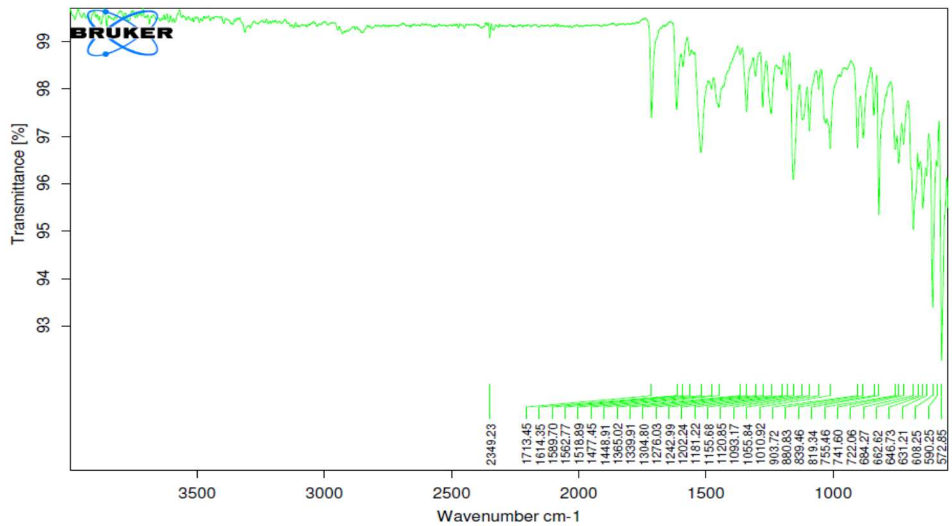

Fig 2: Ambroxol Hydrochloride Pure Drug FTIR

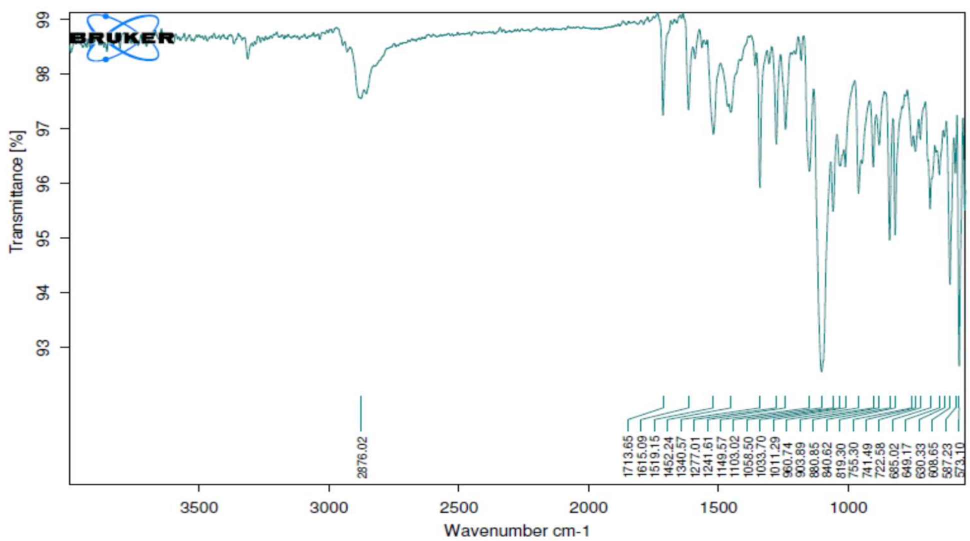

Fig 3: Ambroxol Hydrochloride Optimised Formulation FTIR

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Ambroxol Hydrochloride is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

IV) EVALUATION OF ORAL DISINTEGRATING FILMS

Oral Disintegrating Films were evaluated for the following parameters.

Ambroxol Hydrochloride Oral Disintegrating Films were evaluated for

1) Weight Variation
2) Thickness
3) Tensile strength
4) Folding endurance
5) Disintegration time
6) Content uniformity
7) *InVitro*dissolution studies

Weight Variation

Nine films of Ambroxol Hydrochloride each of 2x2 cm^2 size were cut at five different places from casted films and weight variation was measured. Weight variation varies according to official limits.The results of weight variation are shown in the table.

Thickness

The thickness of the drug loaded films was measured with screwguage. The results of thickness are shown in the table.

Tensile strength& Percent elongation

Tensile strength of the film was determined with digital tensile tester. The film of specific size 3 inch x 10 mm was taken for the test. From the results it is clear that as the concentration of polymer increases the tensile strength of the film also increases. The formulation F4showsthe maximum tensile strength, percent elongation and folding endurance. This might be formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture. The results of Tensile strength & Percent elongation of the film was mentioned in the table.

Folding endurance

Folding endurance was measured manually. A strip of 2 cm^2 was cut and subjected for this study. As the concentration of polymer increases folding endurance of the film also increases. The result of folding endurance of the film was mentioned in the table.

Disintegration Time

Disintegration test was performed in the USP disintegration testing apparatus. Phosphate buffer of pH 6.8 was used as medium. The films were placed in the tubes of the container and the disks were placed over it. Disintegration time of the films was found to be increased with increase in the concentration of the polymer. The results are reported in the table.

Drug Content Uniformity

The prepared formulations were analyzed for drug content and it was observed that all the formulations found to contain almost uniform quantity of drug. The results are reported in the table.

***In- Vitro*-dissolution studies**

Dissolution profiles from films of Ambroxol Hydrochloride were carried out in USP dissolution apparatus-II. The results are reported in the table.

Table 3: 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 4: 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

***Invitro* Dissolution Studies**

*Invitro*dissolution of Ambroxol Hydrochloride Oral Disintegrating Films wasstudied in paddle type dissolution test apparatus. Bowl volume 900ml of 6.8 phosphate buffer solution was used asdissolution medium. The stirrer was adjusted to rotate at 50rpm. The temperature ofdissolution medium was maintained at 37±0.5ºC throughout the experimentSamples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre filter at known intervals of time and analyzed for drug release by measuring the absorbance at 240 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.Cumulative percent ofAmbroxol Hydrochloride release was calculated and plotted against time.

Table 5: *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

*Invitro*dissolution study of formulations F1-F9 shown Good drug release respectively within 30min. Among the all formulations F4 showed good dissolution property. F4 batch contain HPMC K100 as film forming polymer.

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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