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FAST DISSOLVING FILMS OF ITOPRIDE HYDROCHLORIDE

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ABSTRACT

Oral routes are most commonly preferred route for delivering drug. Most common oral dosage forms are tablet and capsules. But many patients such as geriatric, pediatric and dysphasic patients find difficult to swallow conventional tablet and capsule. To overcome various problems related to swallowing, Fast Dissolving Tablets were designed in early 19th century and hence further advancement has led to development of Fast Dissolving Oral Films. These are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or mastication. These thin sized film stripes are designed in such a manner for ease administration of drug when it's placed on or under the tongue. There by the film enables the drug to deliver directly in to the blood stream either buccally or sublingually. Likewise, to improve the onset of action, lower the dosing and enhance the efficacy.

KEYWORDS: Fast Dissolving Film, Film forming polymers, Methods of preparation, Disintegration, *In vitro* Dissolution, Applications of fast dissolving films.

INTRODUCTION

Oral routes are most commonly preferred route for delivering drug. Most common oral dosage forms are tablet and capsules. But many patients such as geriatric, pediatric and dysphasic patients find difficult to swallow conventional tablet and capsule. To overcome various problems related to swallowing, Fast Dissolving Tablets were designed in early 19th century and hence further advancement has led to development of Fast Dissolving Oral Films. These are solid dosage forms, which disintegrate or dissolve within 1 minute when placed in the mouth without drinking water or mastication**. [Gupta, A.K. *et al*., 2015]**

These thin sized film stripes are designed in such a manner for ease administration of drug when it's placed on or under the tongue. There by the film enables the drug to deliver directly in to the blood stream either buccally or sublingually. Likewise, to improve the onset of action, lower the dosing and enhance the efficacy. Fast dissolving films are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of Active Pharmaceutical Ingredients by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin. **[Chaurasiya, Puja *et al*., 2016]**

Fast Dissolving Films are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style. **[Swami, Swati *et al*., 2015]** It is also useful where local action is desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. **[Ravi Kumar K. *et al*., 2014]**

Fast dissolving films come in the form of a thin strip and can be produced by solvent casting method, hot melt extrusion and rolling method. The disintegration time of fast dissolving film is usually short, due to their lower thickness, but the dose of the drug that can be incorporated into the film is strongly limited. **[Alhalbi, F.W. *et al*., 2017]**

Oral film includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, film stabilizing agents, sweeteners, flavors, colors, saliva stimulating agents, preservatives, surfactants etc. but the first and far most a very essential ingredient which helps in film formation is a Polymer. A variety of polymers are available for preparation of fast dissolving film. As the strip forming polymer is the most essential and major component of the fast-dissolving film

at least 45%w/w of polymer should be present based on the total weight of dry film but typically 60 to 65%w/w of polymer is preferred to obtain desired properties. The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation. **[Pathare, Y.S. *et al.*, 2013]**

Overview of oral mucosa

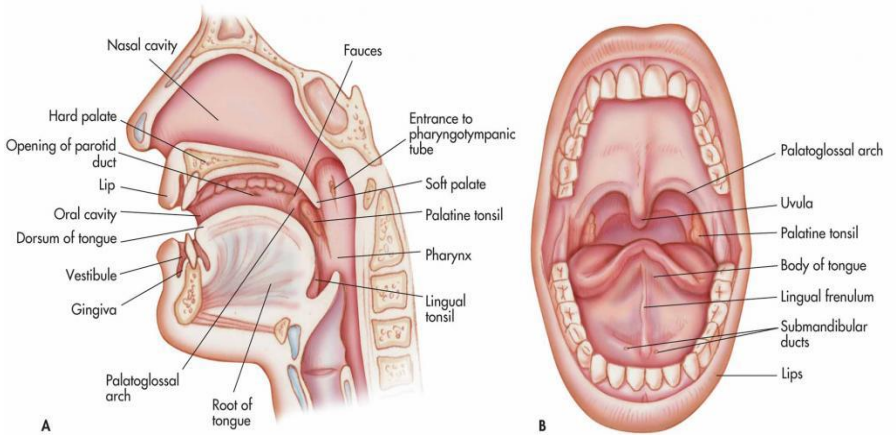

Figure 01: Anatomy of the oral cavity.

Structural features of oral mucosa

Structure: The total area of the oral cavity is about 100 cm^2. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The keratinized and non-keratinized regions of the oral epithelium differ from each other in terms of lipid composition of the cells. The keratinized epithelium has predominantly neutral lipids (e.g., ceramides) while the non-keratinized epithelium has few but polar lipids, particularly cholesterol sulphate and glucosylceramides. Buccal membrane has numerous elastic fibers in the dermis, which is another barrier for diffusion of drug across the buccal membrane. Drug that penetrates this membrane enters the systemic circulation via network of capillaries and arteries. The lymphatic drainage almost runs parallel to the venous vascularization and ends up in the jugular ducts. The oral mucosal surface is constantly washed by the saliva (daily turn out is about 0.5 to 2 liters). The drug absorption across the oral mucosa occurs in the non-keratinized sections for protein/peptide delivery buccal route offers distinct benefits over other mucosal routes like nasal, vaginal, rectal, etc. **[Hooda, Rakesh *et al.*, 2012]**

Composition of oral mucosa

The composition of the epithelium also varies depending on the site in the oral cavity. The mucosa of the gingivae and hard palate are keratinized similar to the epidermis, which contain ceramides and acylceramides (neutral lipids) which have been associated with the barrier function. The mucosa of the soft palate, the sublingual and the buccal regions are not keratinized which are relatively impermeable to water and only have small amounts of ceramides. They also contain small amounts of neutral, but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. **[S. Maheswari *et al.*, 2017]**

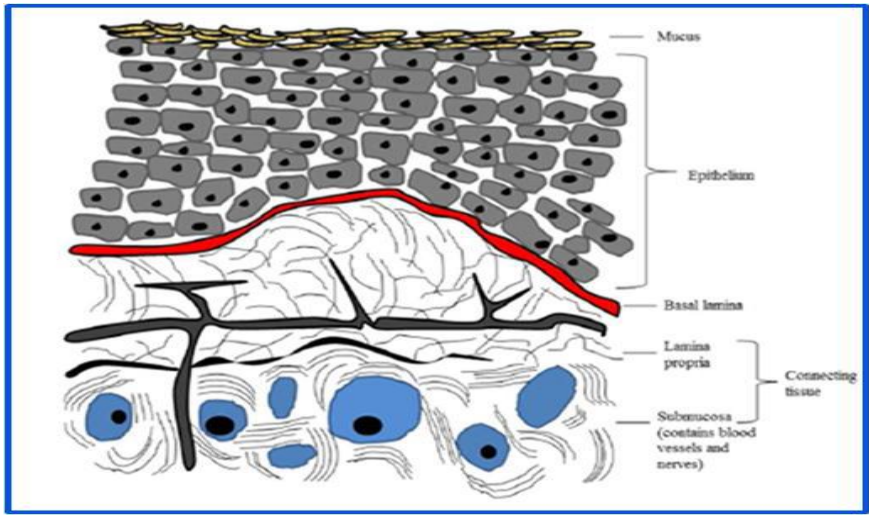

Figure 02: Structure of buccal mucosa.

Permeability: The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. In general, the permeability's of the oral mucosa decrease in the order of sublingual greater than buccal and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and on-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG). When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200μm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxides and lanthanum nitrate. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the sub mucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. **[Hooda, Rakesh *et al.*, 2012]**

Oral mucosa: The oral mucosa contains proteins and carbohydrates. It is adhesive in nature and acts as a lubricant, allowing cells to move relative to one another with less friction. The mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. In another part of body mucus is synthesized and secreted by the goblet cells, however, in the oral mucosa. Mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucus found in saliva is contributed by the minor salivary glands. **[S. Maheswari *et al.*, 2017]**

Absorption Pathways: There are two permeation pathways for passive drug transport across the oral mucosa: Para cellular and Tran cellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage. **[Hooda, Rakesh *et al.*, 2012]**

Saliva: There are three paired extrinsic salivary glands in humans: the parotid, submandibular, and sublingual glands, as well as hundreds of smaller intrinsic salivary glands that are distributed throughout the oral cavity, including the tip of the tongue. The main intrinsic glands consist of blind-ended ducts surrounded by epithelial acinar cells. Salivary flow is under direct and indirect control from both the parasympathetic (PNS) and sympathetic nervous systems (SNS). PNS innervations are via the cranial nerves; specifically, the parotid glands are supplied by the glossopharyngeal nerve (CN IX) via the optic ganglion. The facial nerve (CN VII) supplies PNS innervations to the submandibular and sublingual salivary glands via the submandibular ganglion. PNS input is dramatically increased upon food ingestion, causing enhanced serous (water-rich) saliva to be released from serous/acinar cells. SNS input to the large salivary glands is via fibers in the T1-T3 region and results in an increase in mucin-rich saliva from mucous cells. **[Renshaw, Derek *et al.*, 2010]**

Salient features of fast dissolving films

- Available in various size and shapes.
- Thin elegant film.
- Un-obstructive.
- Fast disintegration or dissolution.
- Rapid release, Mucoadhesive and quick dissolving.
- Criteria for Fast Dissolving Film.
- Oral dissolving film should have a pleasant mouth feel.
- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of second.
- Compatible with taste masking.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions such as temperature and humidity. **[U. Sahul Hameed Niyaz *et al.*, 2018]**

Ideal properties of Fast Dissolving Films

- It should have an acceptable taste with pleasing mouth feel.
- It should be less friable and have good mechanical strength to withstand the post manufacturing handling.
- The drug should have good stability and solubility in water as well as in saliva.
- It should leave least or no residue in mouth.
- It should quickly dissolve to release drug instantaneously in mouth.

- It should be compatible with the other ingredients. **[Chaurasiya, Puja *et al.*, 2016]**

Advantages of Fast Dissolving Films

- No need of water for administration.
- Convenient for pediatric, geriatric and dysphasic patients having difficulty in swallowing.
- Rapid disintegrating and dissolution in the oral cavity due to larger surface area of films.
- Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect.
- Reduce dose, enhances the efficacy and safety profile of the drug with reduced side effects.
- Flexible and portable in nature so they provide ease in handling, transportation and storage.
- Ease of administration to mentally ill, disabled, un-cooperative patients and the patients who are on reduced liquid intake plans or are nauseated.
- Beneficial in cases such as motion sickness, acute pain, sudden allergic attack, asthmatic attack and coughing, where an ultra rapid onset of action is required.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed.
- Accuracy in dose as compared to liquid formulations.
- Pleasant mouth feel, leave negligible or no residue in the mouth after administration. **[Jain, Ashish *et al.*, 2018]**

Disadvantages of Fast Dissolving Films

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which irritate the mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.
- Most drugs have bitter taste, and need taste masking.
- Fast Dissolving Films are fragile and must be protected from water so it needs special packaging.
- Dose uniformity is a technical challenge.
- Expensive packaging of oral film. **[Reddy, S.K. *et al.*, 2018]**

Classification of Fast Dissolving Technology

For ease of description, fast-dissolve technologies can be divided in to three broad groups.

- Lyophilized systems
- Compressed tablet-based systems
- Thin film strips

The lyophilized systems

This system has been by far the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. Dose handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more rapid disintegration than tablet-based systems. **[Patel, A.R. *et al.*, 2010]**

Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. The speed of disintegration for fast dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients, superdisintigrant or effervescent components, to allow rapid penetration of water into the core of the tablet. **[Kaur, Mandeep *et al.*, 2013]**

Thin film strips

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable oral thin films or oral strip evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (API) for transdermal drug delivery capitalized on the opportunity to transition this technology to Oral Thin Films formats. Today, Oral Thin Films are a proven and accepted technology for the systemic delivery of apis for over-the-counter (OTC) medications and are in the early to mid-development stages for prescription drugs. **[Chaurasiya, Puja *et al.*, 2016]**

Classification of Oral Film

There are three different subtypes

- Flash release
- Mucoadhesive melt-away wafer
- Mucoadhesive sustained-release wafers

These three types of oral films are differentiated from each other in following table.

Table 01: Classification of oral film.

Type/Property	Flash Release Wafer	Mucoadhesive melt- away wafer	Mucoadhesive sustained release wafer
Area (cm^2)	2-8	2-7	2-4
Thickness (µm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer systems	Multilayer System
Excipients	Hydrophilic polymers	Hydrophilic polymers	Low/Nonsoluble polymers
Drug phase	Solid solution	Solid solution or suspension	Solid solution or solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival or other region in oral cavity
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Table 02: Comparison between orally fast dissolving films and oral disintegrating tablets.

Orally Fast Dissolving Films	Oral Disintegrating Tablets
It is a film	It is a tablet
Greater dissolution due to larger surface area	Lesser dissolution due to less surface area
Better durable than oral disintegrating tablets	Less durable as compared with oral films
More patient compliance	Less patient compliance than films
Low dose can only be incorporated	High dose can be incorporated
No risk of choking	It has a fear of choking

FORMULATION COMPONENTS OF FAST DISSOLVING FILMS

Formulation of Fast Dissolving Films involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouths feel etc. From the regulatory perspectives, all excipients used in the formulation of fast dissolving films should be Generally Regarded as Safe (i.e. GRAS listed) and should be approved for use in oral pharmaceutical dosage forms.

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizers
- Saliva stimulating agents
- Surfactants
- Sweetening agents
- Cooling agents
- Flavouring agent
- Coloring agents
- Stabilizing and Thickening agents

Active Pharmaceutical Ingredient (5-30%)

The film composition contains 5-30% w/w of the active pharmaceutical ingredient. Always use low dose active pharmaceutical ingredients because high dose of drug is difficult to incorporate in fast dissolving film. A number of drugs can be used as fast dissolving oral film including anti-histamine, antidiarrhoeal, antidepressants, vasodilators, anti-asthmatic, antiemetic, etc. Dimenhydrinate can also be incorporated into Fast Dissolving Film for taste masking. Common examples of drugs incorporated into Fast Dissolving Films are Salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, Rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc. **[Sheoran, Reena *et al.*, 2018]**

The ideal characteristics of a drug to be selected

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue. **[Bhyan, Bhupinder *et al.*, 2011]**

Film Forming Polymers (40-50%)

Fast dissolving Film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Water soluble polymers are used as film formers for fast dissolving films. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water-soluble polymers used as film former are HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxymethylcellulose cekol 30, Polyvinylpyrollidone K-90, Pectin, Gelatin, Sodium Alginate,

Hydroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and Eudragit RD108, Eudragit RL100. Polymerized rosin is a novel film forming polymer. Various polymers can be employed to modulate the disintegration property of the fast-dissolving film. This is especially used in case of slowly disintegrable oral bioadhesive strips or patches that need to be retained in intact form for longer duration in the oral cavity. The bioadhesive polymer used in such formulations imparts the adhesive property to the strip such that it adheres to buccal mucosa to deliver the drug for prolonged period. Bioadhesive polymer should ideally adhere quickly to the buccal mucosa and should have sufficient mechanical strength. **[Pathare, Y.S. *et al*., 2013]**

Ideal properties of the polymers used in the fast-dissolving films

- Polymers should be non-toxic and non- irritant.
- It should be non- bitter.
- Polymers should be tasteless.
- It should be devoid of leachable impurities.
- It should be inexpensive and readily available.
- It should not be an obstacle in the disintegration time.
- It should have good wetting and spreadability property.
- It should exhibit sufficient peel, shear and tensile strength.
- It should have sufficient shelf life.
- It should not cause secondary infection in the oral cavity. **[Saini, Parul *et al*., 2012]**

Plasticizers (0-20%)

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. Most commonly used plasticizers are glycerol, propylene glycol, polyethylene glycol, 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. **[Mahboob, M.B.H. *et al*., 2016]**

Properties of plasticizers

- Plasticizer is a key ingredient for the quick dissolving films. It significantly enhances the film forming properties by diminishing the glass transition temperature of the polymer.
- Plasticizer serves to enhance the flexibility of the strip and reduces the brittleness of the films.
- The chemical structure and concentration of plasticizers play an important role in alleviating the glass transition temperature of the polymers.
- The selection of plasticizer depends on its compatibility with the polymer and also the type of solvent employed in the casting of the film.
- The flow of polymeric solution gets better with the use of plasticizer and improves the strength of the polymer.
- Typically, the plasticizers are used in the concentration of 0–20 percent w/v of dry polymer weight. However, inappropriate use of plasticizer may prompt to film breaking, splitting and peeling of the strip.
- It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug. **[Mishra, Ashwini *et al*., 2017]**

Saliva stimulating agent (2-6%)

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. These agents are used alone or in combination between 2-6% w/w of the strip. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants. **[Prabhu, S.C. *et al*., 2014]**

Surfactants

Surfactants are used as wetting or solublising or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Commonly employed is Poloxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactant is Poloxamer 407. **[Naga, S.J. *et al*., 2013]**

Sweetening agents

Low molecular weight carbohydrates and specially sucrose are most commonly used sweeteners. Sucrose is very soluble in water and being colourless does not impart any undesirable colour to the final formulation. It is stable over the pH range 4-8. It masks the taste of both salty and bitter drugs. Polyhydric alcohols such as sorbitol and mannitol also exhibit sweetening capacity and suitable for diabetic patients. Mannitol is half as sweet as sucrose and sorbitol has 50-60% of sweetness of sucrose. Sorbitol and mannitol have negative heat of solution therefore impart cooling sensation in mouth. Artificial sweeteners also termed as intense sweeteners. They are several hundreds to thousands of times sweeter than sucrose. Therefore, they are hardly required at a concentration more than 0.2%. Only six artificial sweeteners are permitted for oral use within the European Union, the most widely used is sodium or calcium salts of saccharin. Both the salts exhibit high water solubility and are chemically and physically stable over wide pH range. Less widely used artificial sweeteners are aspartame, acesulfame potassium, thaumatin, sodium cyclamate, neohesperidine. Main disadvantage associated with artificial sweeteners is metallic or bitter aftertaste. A quite new sweetening agent in U.S. market is Stevia powder; it is obtained from the extract of the leaves of the plant Stevia rebaudianabertoni. It is natural, non-toxic and safe and

30 times as sweet as sweet as sucrose. It is heat stable. **[Udupa, N. *et al.*, 2015]**

Cooling agents

Cooling agents akin to monomethyl succinate can be added to improve the flavor strength and to enhance the mouth feel effect of the product. Additional cooling agents like WS3, WS23 and Utracoll II can also be used in conjunction with flavors. **[Patel, Dipal *et al.*, 2015]**

Flavoring agents

Flavours are used to mask the bitter taste of selected drug. Amount of flavor depends upon its strength and nature. Any US-FDA approved flavor can be used such as sweet, sour or mint flavor These agents can be selected from the synthetic flavor oils, oleo resins. Extract derived from various parts of the plants like leaves, fruit and flowers. The amount of flavor to be used depends upon the type of flavour used. The age factor has important role in the taste. The young generation like fruit flavours while geriatric population like mint, cinnamon, clove etc. **[Himani *et al.*, 2018]**

Coloring agents

When drug is present in the film in a suspension or insoluble particulate form, coloring agents have to be incorporated in the oral film. Pigments such as titanium dioxide or FD&C approved coloring agents are generally used (not exceeding concentration levels of 1%w/w). **[Udupa, N. *et al.*, 2015]**

Stabilizing and thickening agents

The stabilizing and thickening agents are employed to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Natural gums like xanthan gum, locust bean gum, carrageenan and cellulosic derivatives can be used. **[Ravi Kumar K. *et al.*, 2014]**

METHODS OF PREPARATION OF FAST DISSOLVING FILMS

Generally following methods are used to preparation of fast dissolving films:

- Solvent casting method
- Semisolid casting method
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling method

1. Solvent casting method

The Oral fast dissolving films are prepared by dissolving strip forming agents and plasticizer in the distilled water, then solution is continuously stirred up to 4 hours on magnetic stirrer and kept for 1 hour to remove all the air bubbles entrapped. Meanwhile, in the separate container remaining water-soluble excipients i.e. sweetening agent, saliva-stimulating agent, flavor and drug are dissolved with constant stirring for 45 minutes. When the stirring is over both the solutions are mixed together with stirring for another 1 hour on magnetic stirrer. Then keep the solution stationary for 1 hour to let the foams settle down. The resulting formulation is casted on a suitable platform and is dried to form a film. The film is preferably air-dried or dried under oven then the film is carefully removed. Film is cutted in to desired shape and size. **[Reddy, S.K. *et al.*, 2018]**

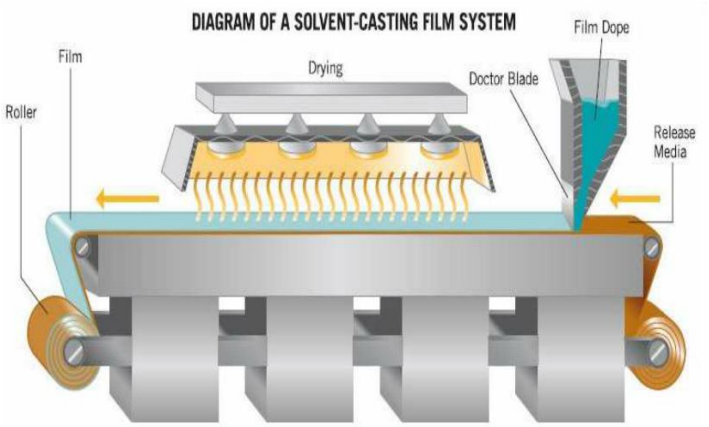

Figure 03: Solvent casting method.

Advantages

- Great uniformity of thickness and great clarity then extrusion.
- A typical relative standard deviation for uniformity testing of an oral thin-film batch prepared by liquid casting is on the order of 1.2% relative standard deviation.
- Films have fine gloss and freedom from defects such as die lines.
- Films have more flexibility and better physical properties. The preferred finished film thickness is typically 12-l00µm.

Disadvantages

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.

- Formation of a homogeneous film and release from the casting support must be possible. **[Reddy, S.K. *et al*., 2018]**

2. Semisolid casting method

In semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally, the gel mass is casted in to the films or ribbons using heat-controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Both mixtures are mixed to form homogenous viscous solution. Degassed under vacuum Bubble free solution is coated on non-treated casting film coated film is sent to aeration drying oven Film is cutted in to desired shape and size. [**Saini, Sandeep *et al*., 2011]**

3. Hot Melt Extrusion

In hot melt extrusion method firstly, the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3– 4 min. The processing temperatures should be 8000C (zone 1), 11500C (zone 2), 10000C (zone 3) and 6500C (zone 4). The extrudate (T = 6500C) then pressed into a cylindrical calendar in order to obtain a film. **[Kumar, R.S. *et al*., 2016]**

Advantages

- Without use of any solvent or water.
- Fewer processing steps.
- Compressibility properties of the Active Pharmaceutical Ingredient may not be of importance.
- Better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.
- Possibility of scale up**. [U. Sahul Hameed Niyaz *et al*., 2018]**

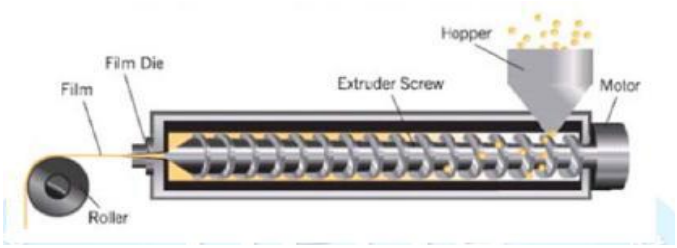

Figure 04: Hot melt extrusion method of preparing fast dissolving films.

Disadvantages

- Thermal degradation due to use of high temperature.
- Flow properties of the polymer are essential to processing.
- Limited number of available polymers.
- All excipients must be devoid of water or any other volatile solvent. **[U. Sahul Hameed Niyaz *et al*., 2018]**

4. Solid dispersion extrusion

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70◦C. Finally the solid dispersions are shaped into the films by means of dies. **[Ketul, Pandya *et al*., 2013]**

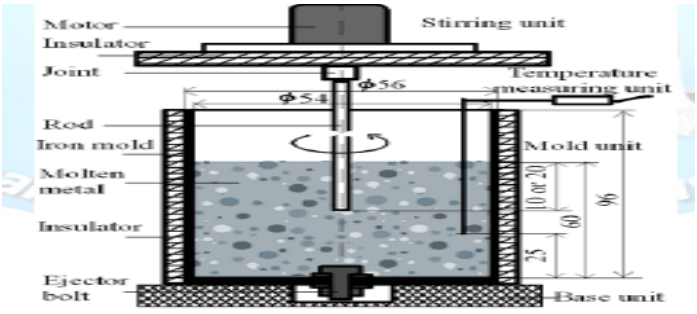

Figure 05: Solid dispersion extrusion method of preparing fast dissolving films.

5. Rolling method

In these methods the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch which includes the film forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank. Then a pre-determined amount of the master batch is controllably fed via a first metering pump and control valve to either or both of the first and second mixers. The required amount of the drug is added to the desired mixer through an opening in each of the mixers. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan through the second metering pumps. The metering roller determines the thickness of the film and applies it to the application roller. The film is finally formed on the substrate and carried away via the support roller. The wet film is then dried using controlled bottom drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film. **[Malke, Sheetal *et al*., 2009].**

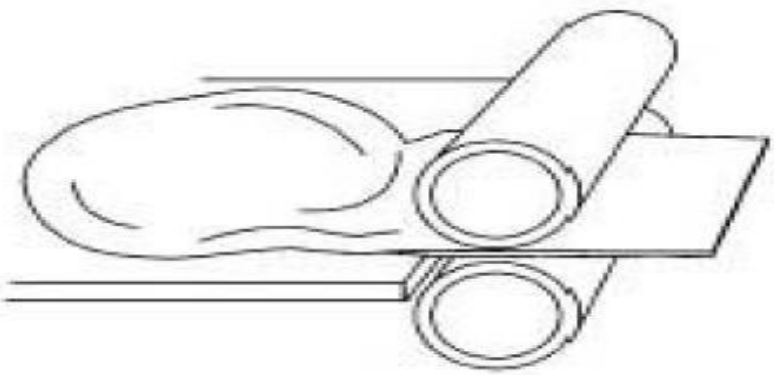

Figure 06: Apparatus used in Rolling Method of preparing fast dissolving.

Patented Technologies

XGel™

XGel™ is at the heart of Meldex international's intellectual properties used in all its film system and its ingestible delivery technologies. XGel™ film Technology developed by Bioprogress is bringing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry. XGel™ film, potentially enhance the product stability. It has also been developed for non-ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare devices. The development and manufacture of XGel™ films uses a means called "solution casting". **[Gupta, A.K. *et al*., 2015]**

Soluleaves™

In this technology, the film is produced in order to release the active ingredients on coming in contact with saliva. This is applied to flavor-release products such as mouth fresheners, confectionery and vitamin products. SOLULEAVES™ technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as nutritional products. SOLULEAVES™ films can also be designed to adhere to mucous membranes and to release the active ingredients slowly over 15 minutes. **[Kaur, Mandeep *et al*., 2013]**

Wafertab™

It 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 pre-manufactured 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 film with different active 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 swallowing. **[S. Maheswari *et al*., 2017]**

Foamburst™

FOAMBURST™ 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. **[U. Sahul Hameed Niyaz *et al*., 2018]**

Micap

Micap signed an option agreement in 2004 to combine its expertise in micro encapsulation technology with the Bio Progress water-soluble films. The developments aimed at providing new delivery mechanisms for the $1.4bn global market for smoking cessation products. **[Reddy, S.K. *et al*., 2018] [Kaur, Mandeep *et al*., 2013]**

Packaging

A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films. Which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. Applied Pharma Research (Switzerland) Labtec GmbH of Germany has developed the Rapid Card, a proprietary and patented packaging system which is specifically designed for the Mouth dissolving Films. The Rapid Card is exactly the same size as a credit card and holds three Mouth dissolving Films on each side. Every dose can be taken out individually, allowing the patient to carry six single, packaged doses of his medication in his purse or wallet and have it readily available. **[Ravi Kumar K. *et al.*, 2014]**

Figure 07: Packaging of film.

Table 03: Marketed formulation of fast dissolving films.

Product	Manufacturer	Active Pharmaceutical Agent	Strength(mg)
Triaminic	Novartis	Dextromethorphan HBr	7.5
Triaminic	Novartis	Diphenhydramine HCL	12.5
Theraflu	Novartis	Dextromethorphan HBr	15
Gas-X	Novartis	Simethicone	62.5
Sudafed	Pfizer	Phenylephrine HCL	10
Benadryl	Pfizer	Diphenhydramine HCL	12.5
Chloraseptic	Prestige	Benzocaine Menthol	3/3
Suppress	InnoZen	Menthol	2.5
Orajel	Del	Menthol/Pectin	2/30
Listerine	Pfizer	Cool mint	-

Functional dyspepsia

Functional (nonulcer) dyspepsia is defined as the presence of postprandial fullness, early satiation, or epigastric pain or burning in the absence of causative structural disease. Dyspepsia is a common clinical condition associated with a complex of upper abdominal symptoms including: upper centered discomfort or pain, feeling of abdominal fullness, early satiety, abdominal distention and bloating, belching, and nausea. Two common causes of dyspepsia are gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). **[Loyd, R.A. *et al.*, 2013]**

Gastroesophageal reflux disease

It is defined as chronic symptoms or mucosal damage produced by the abnormal reflux in the esophagus. GERD is a common health problem in the community. Frequency of GERD in India might be increasing possibly due to modernization, change in lifestyle and diet. Prevalence of GERD (and/or its complications) differs according to gender, pregnancy, race, or geographical regions. Chances of GERD increase during pregnancy: on an average 48-79% of pregnant women complain of heartburn. **[Kumar, Rahul *et al.*, 2014]**

Peptic ulcer disease

PUD is a common cause of dyspepsia and has lifetime prevalence between 8 and 14%.5 while most PUD patients are in their active and productive years; most patients requiring admission for complications are older than 65 years. The risk factors associated with PUD are H. pylori infection which is highly prevalent in South Africa (77.6%) and the widespread use of NSAID. **[M. Torlutter *et al.*, 2018]**

Gastritis

The gastritis is an inflammatory condition of the gastric mucosa characterized by existence of elementary histological alternations. However these structural changes observed by the pioneer of gastric histology were noted more than a century ago, their etiology and proper interpretation for clinical practice required much longer time. Gastritis is the most common illness associated to the stomach, and it is the beginning of different complication that led to ulcers and, in the worst case, gastric cancer. The disease is due to different causes as an imbalanced diet, intake of aggressive agents, or stress process (related to neurological condition) which is very common nowadays due to the population rhythm of life. **[Imre, L.S. *et al.*, 2012]**

Gastroparesis

Gastroparesis is defined as a persistent heterogeneous defect in the gastric motility. Gastroparesis was an unfamiliar disability; it has become an increasingly reported disease in the past two to three decades. It is characterized by the delayed gastric emptying after intake of solid food in the absence of a gastrointestinal obstruction. The symptoms can be mild or severe and they are mostly nausea, vomiting, epigastric pain, early satiety, fullness, anorexia, and/or weight loss. Gastroparesis severely affects the patients' nutrition, health, social interactions and even the duration of hospital stay. The most common aetiologies include diabetes, post-surgical and idiopathic. **[Wen-hao Tang *et al*., 2018]**

MATERIALS AND METHOD

Materials

Table 04: List of chemicals and their suppliers.

Sr. No.	Name of the Ingredient	Name of Manufacturer/ Supplier
1	Itopride Hydrochloride	Swapnroop Drugs and Pharmaceuticals, Aurangabad
2	Pectin	Molychem, Mumbai
3	Xanthan Gum	Oxford Laboratory, Palghar
4	Sodium Alginate	Molychem, Mumbai.
5	Polyethylene glycol	Molychem, Mumbai.
6	Citric acid	Reidel Chemicals Pvt. Ltd. New Delhi
7	Mannitol	Merck Pvt. Ltd. Mumbai
8	Vanillin	Oxford Laboratory, Palghar

Table No.05: List of Ingredients used in formulation and their category.

Sr. No.	Ingredients	Category
1	Itopride Hydrochloride	Active Pharmaceutical Ingredient
2	Pectin	Polymer
3	Xanthan Gum	Polymer
4	Sodium Alginate	Polymer
5	Polyethylene glycol	Plasticizer
6	Citric acid	Saliva stimulating agent
7	Mannitol	Sweetening agent
8	Vanillin	Flavouring agent
9	Purified water	Solvent

OBSERVATION AND RESULTS

Characterization of Itopride Hydrochloride

Description

Itopride Hydrochloride was found to be white, crystalline odourless powder.

Solubility

Itopride hydrochloride is soluble in methanol and very soluble in water.

Melting point

The melting point of Itopride hydrochloride was found to be 194ºC (193-198ºC). Thus it indicates purity of sample.

Results of Preformulation study of Itopride Hydrochloride

Bulk Density

Bulk density (BD) for the Itopride Hydrochloride was performed. The bulk density of the Itopride Hydrochloride was found to be 0.33±0.020 gm/cm^3.

Tapped density

Tapped density (TD) for the Itopride Hydrochloride was performed. The tapped density of the Itopride Hydrochloride was found to be 0.47±0.015 gm/cm^3.

Hausner's ratio

Hausner's ratio for the Itopride Hydrochloride was performed. The Hausner's ratio was found to be 1.40±0.037 gm/cm^3.

Carr's index

The result of Carr's index or compressibility index (%) for the Itopride Hydrochloride was found to be 28.91±0.28 %.

Angle of repose

The angle of repose of Itopride Hydrochloride is 35.98±0.99.

Table 06: Characterization of Itopride Hydrochloride.

Test	Observation
Bulk density (gm/cm^3)	0.33±0.020
Tapped density (gm/cm^3)	0.47±0.015
Carr's index (%)	28.91±0.28
Hausner's ratio (gm/cm^3)	1.40±0.037
Angle of repose (º)	35.98±0.99

Drug-excipients compatibility study

FTIR STUDIES

IR spectra for Itopride Hydrochloride and its mixture with different excipient like Xanthan Gum, Pectin, Sodium alginate, Polyethylene glycol, Mannitol, vanillin were recorded in a Fourier Transform Infrared Spectrophotometer.

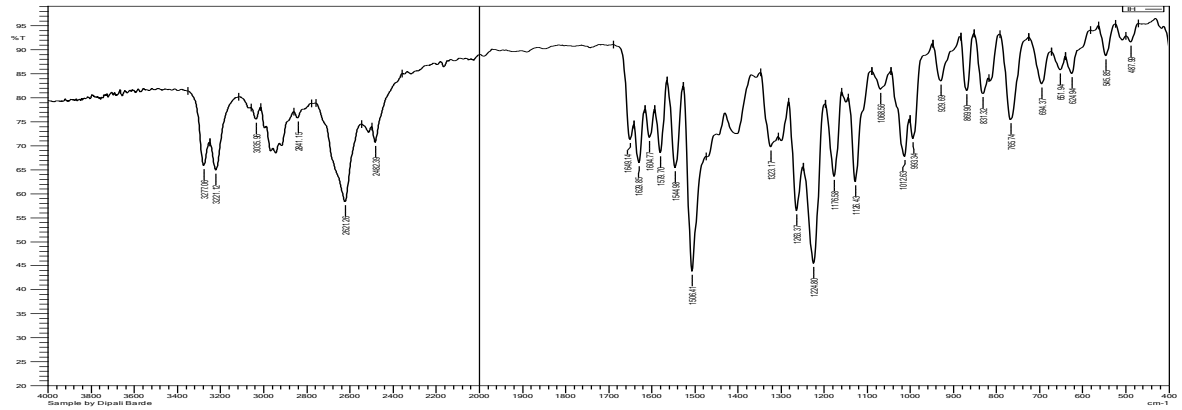

Figure 08: IR spectra of Itopride Hydrochloride.

Table 07: Interpretation of IR spectra of Itopride Hydrochloride.

Sr. No.	Functional group	Characteristics peak (cm^{-1})	Obtained peak (cm^{-1})
1	C-Cl Stretching	600-800	694.37
2	C-O Stretching	1050-1150	1068
3	C=C Stretching	1400-1600	1506
4	N-H Bending	1550-1640	1579.7
5	C=O Stretching	1640-1690	1649.14
6	O-H Stretching	2500-3300	2621.26
7	C-H Stretching	3000-3100	3035.96

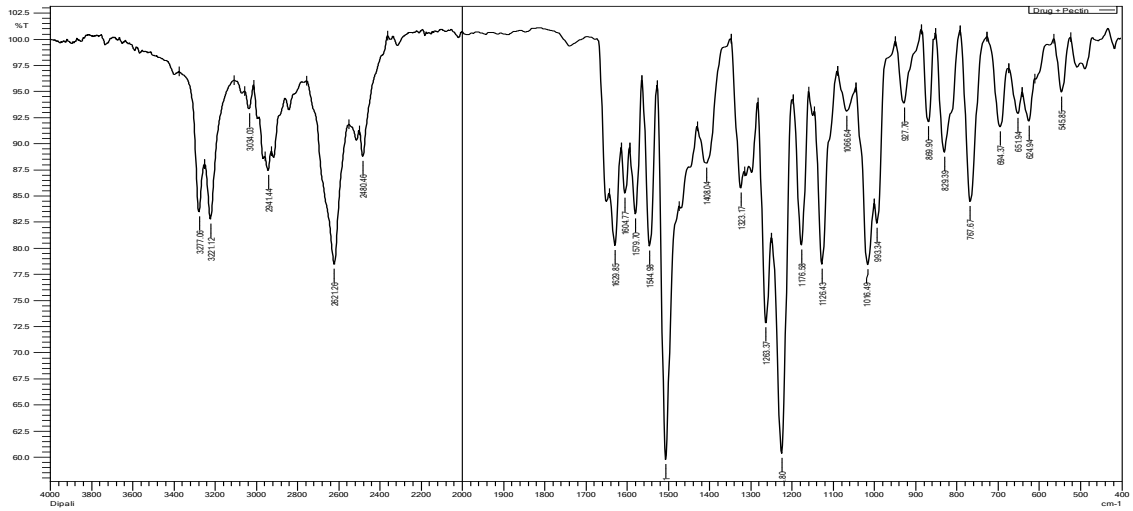

Figure 09: IR spectra of Itopride Hydrochloride with Pectin.

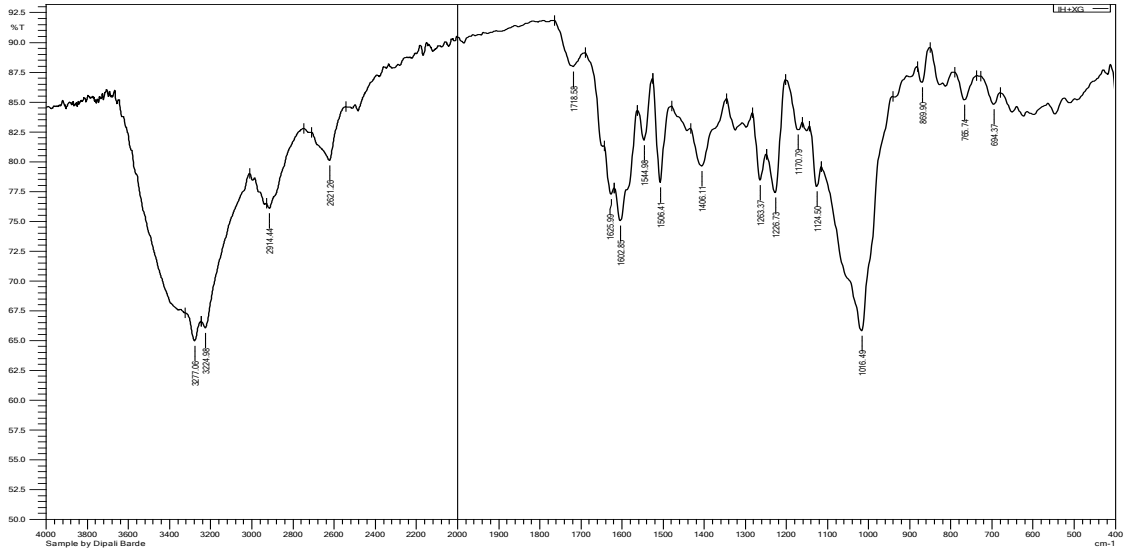

Figure 10: IR spectra of Itopride Hydrochloride with Xanthan Gum.

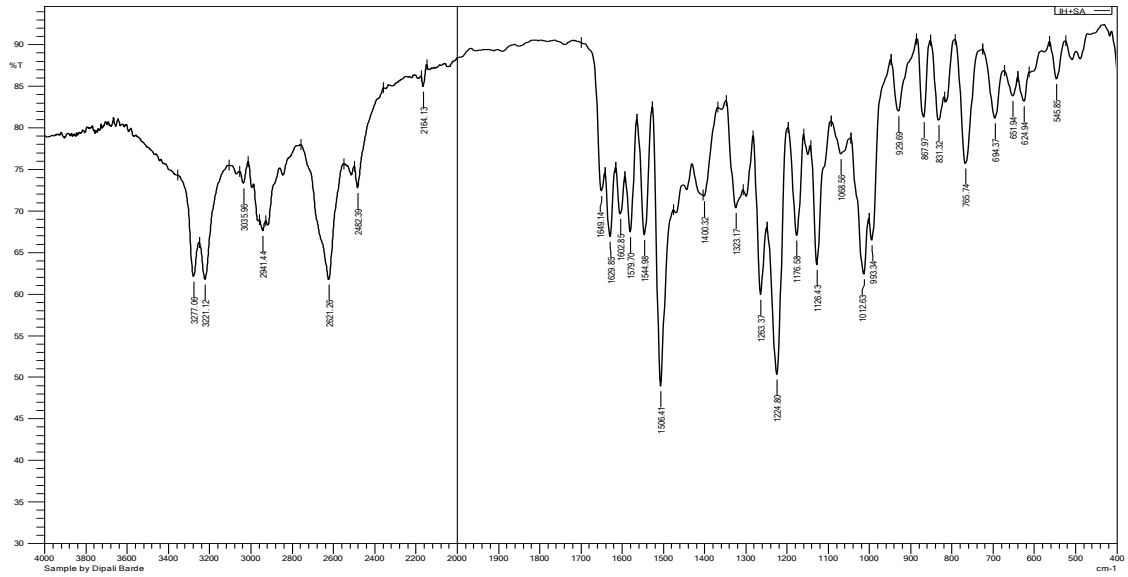

Figure 11: IR spectra of Itopride Hydrochloride with Sodium Alginate.

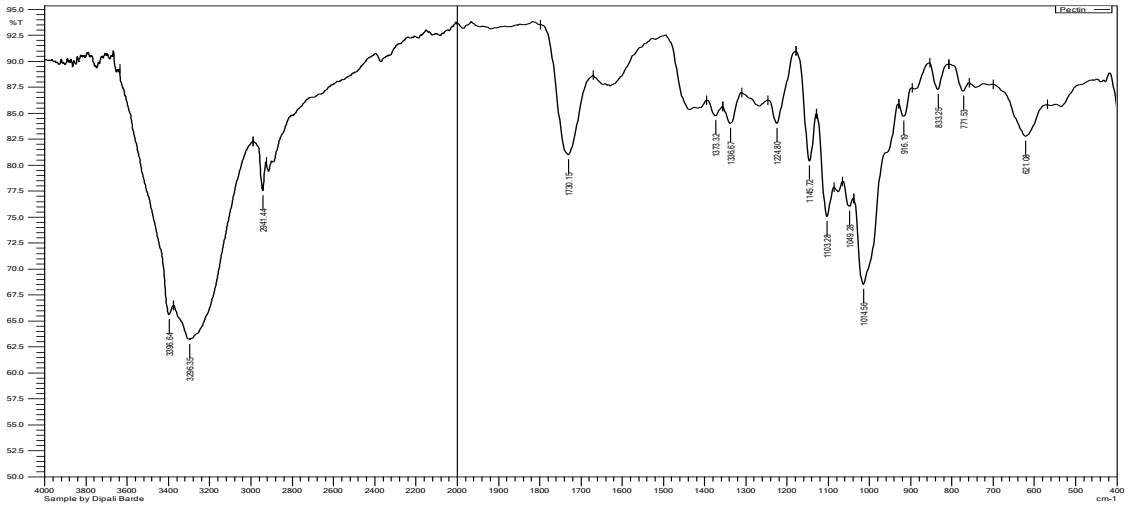

Figure 12: IR spectra of Pectin.

Table 08: Interpretation of IR spectra of Pectin.

Sr. No.	Functional group	Characteristics of peak (cm^{-1})	Obtained peak (cm^{-1})
1	C-O Stretching	1050-1150	1103.28
2	=C-H Bending	675-1000	833.25
3	C-N Stretching	1080-1360	1224.8
4	C=O Stretching	1670-1820	1730.15
5	C-H Stretching	2850-3000	2941.44
6	N-H Stretching	3100-3500	3296.35
7	C-F Stretching	1000-1400	1014.56

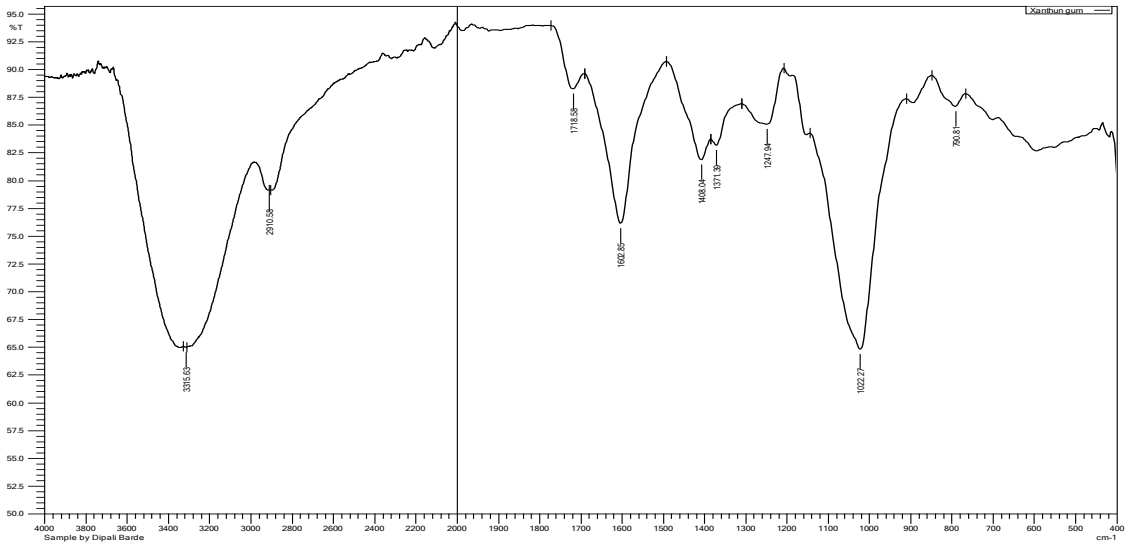

Figure 13: IR spectra of Xanthan Gum.

Table 09: Interpretation of IR spectra of xanthan gum.

Sr. No.	Functional group	Characteristics of peak (cm^{-1})	Obtained peak (cm^{-1})
1	C-O Stretching	1000-1300	1022.27
2	-C-H Bending	1350-1480	1371.39
3	C=C Stretching	1400-1600	1408.04
4	N-H Bending	1550-1640	1602.85
5	C-H Stretching	2850-3000	2910.58
6	O-H Stretching	3200-3600	3315.63

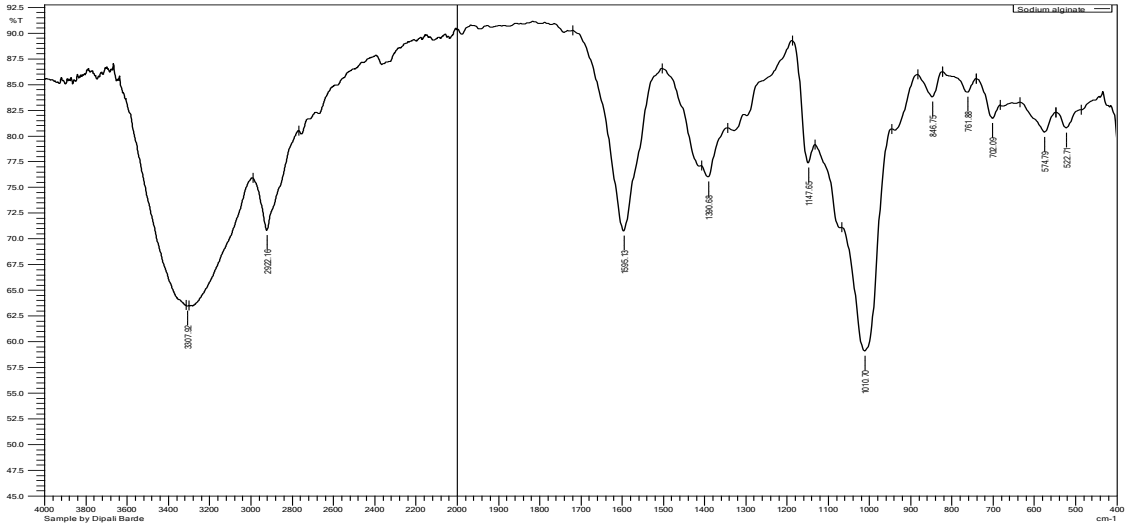

Figure 14: IR spectra of Sodium Alginate.

Table 10: Interpretation of IR spectra of Sodium alginate.

Sr. No.	Functional group	Characteristics of peak (cm^{-1})	Obtained peak (cm^{-1})
1	C-Cl Stretching	600-800	702.09
2	=C-H Bending	675-1000	846.75
3	C-O Stretching	1000-1300	1147.65
4	-C-H Bending	1350-1480	1390.68
5	C=C Stretching	1400-1600	1595.13
6	N-H Bending	1550-1640	1595.13
7	C-Br Stretching	500-600	522.71

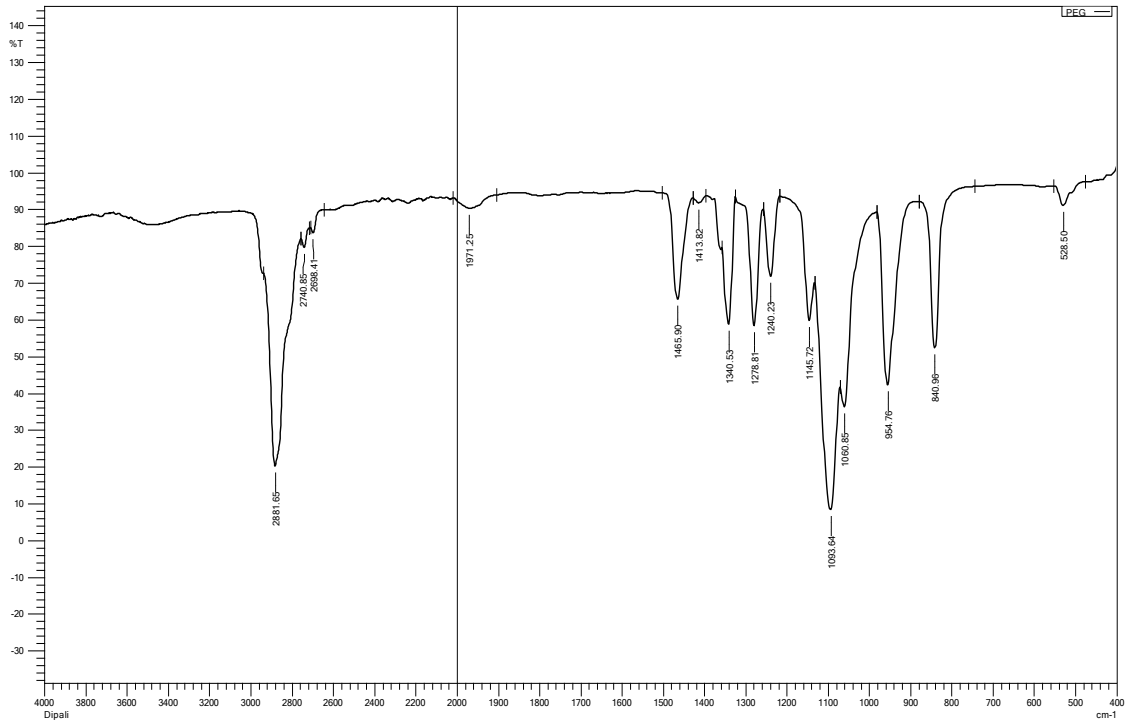

Figure 15: IR spectra of Polyethylene glycol.

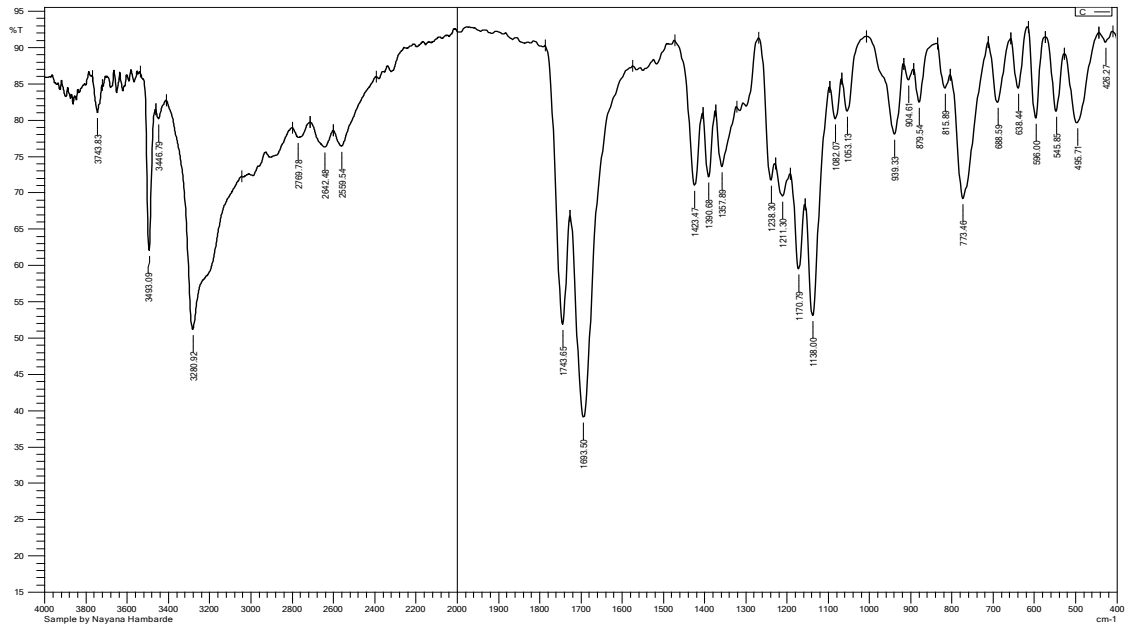

Figure 16: IR spectra of Citric acid.

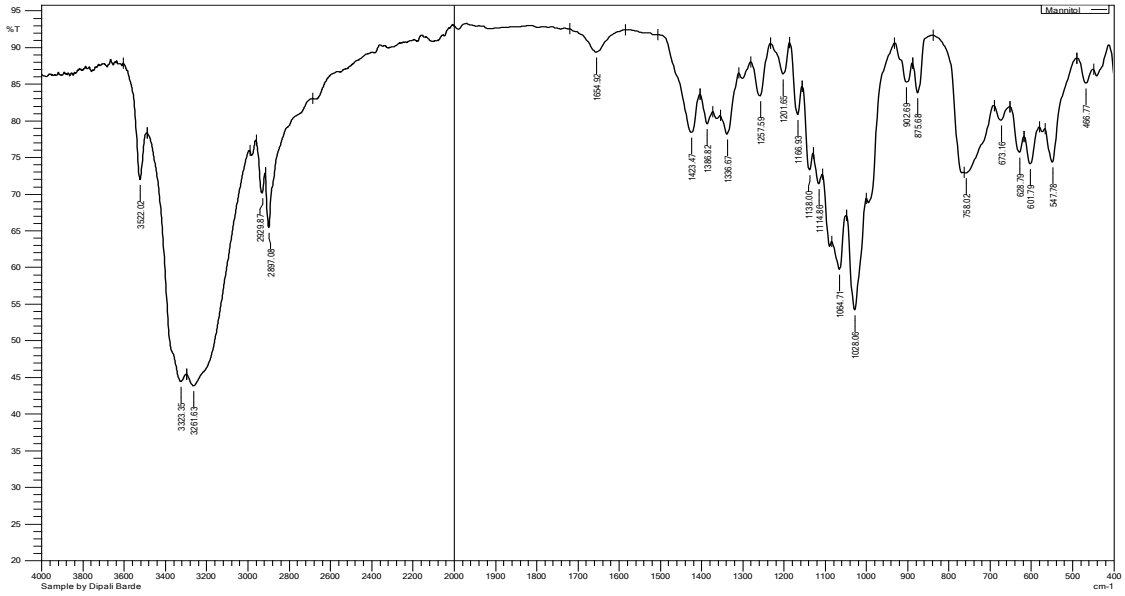

Figure 17: IR spectra of Mannitol.

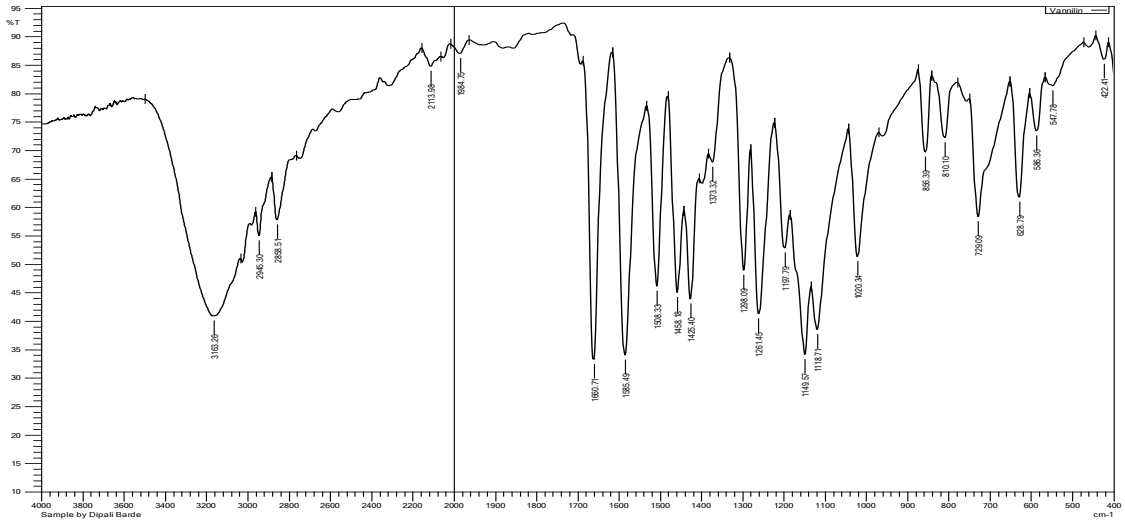

Figure 18: IR spectra of Vanillin.

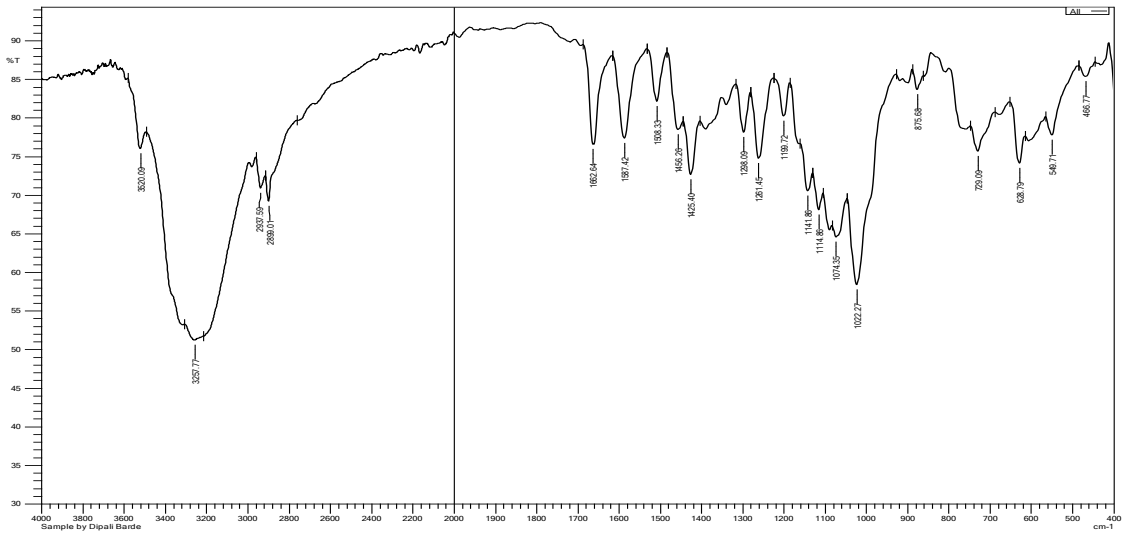

Figure 19: IR spectra of drug + excipients.

Table 11: Interpretation of IR spectra of drug + excipients.

Sr. No.	Functional group	Characteristics of peak (cm^{-1})	Obtained peak (cm^{-1})
1	C-Br Stretching	500-600	549.71
2	=C-H Bending	675-1000	875.68
3	C=C Stretching	1400-1600	1508.33
4	-C-H Bending	1350-1480	1425.4
5	O-H Stretch- Free	3500-3700	3520.09
6	N-H Stretching	3100-3500	325.77

Compatibility study by DSC

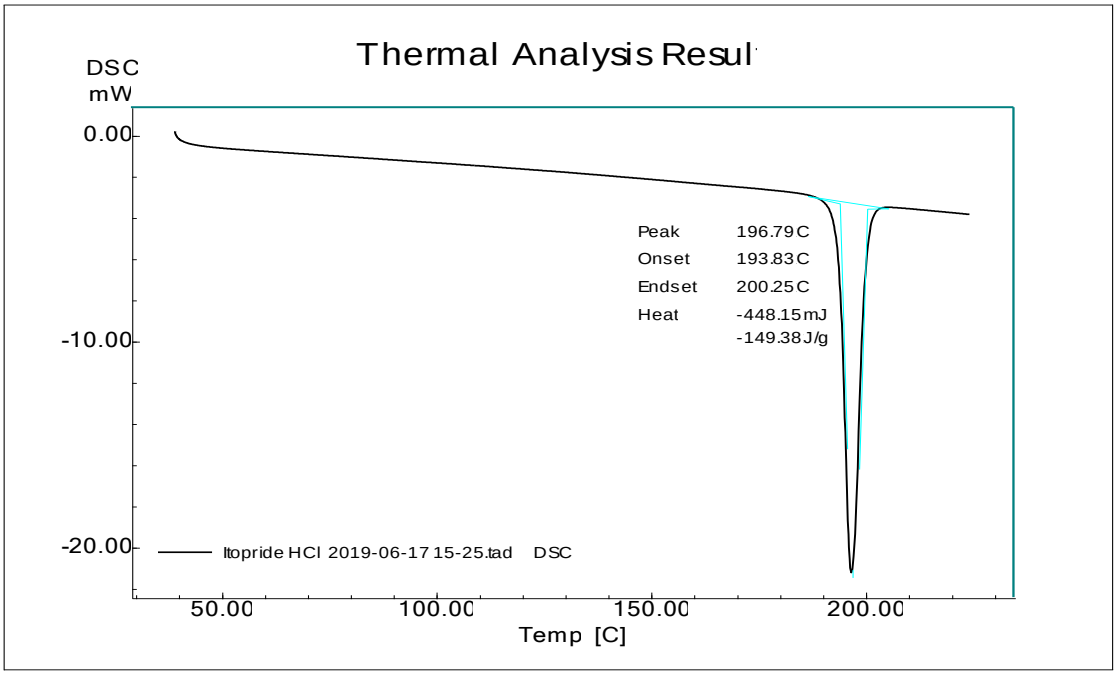

Figure 20: DSC Analysis of Itopride Hydrochloride.

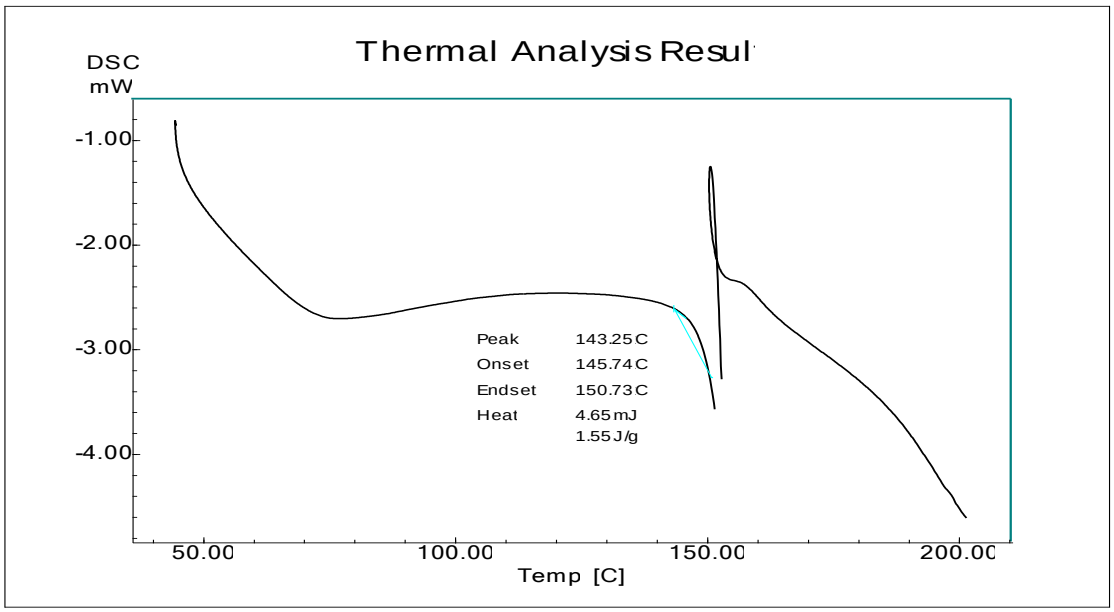

Figure 21: DSC Analysis of Pectin.

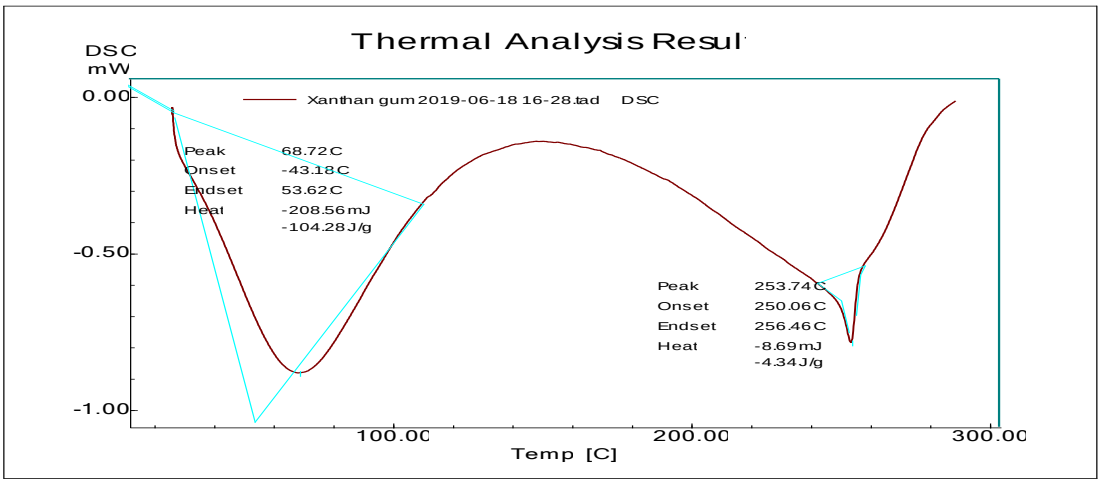

Figure 22: DSC Analysis of Xanthan gum.

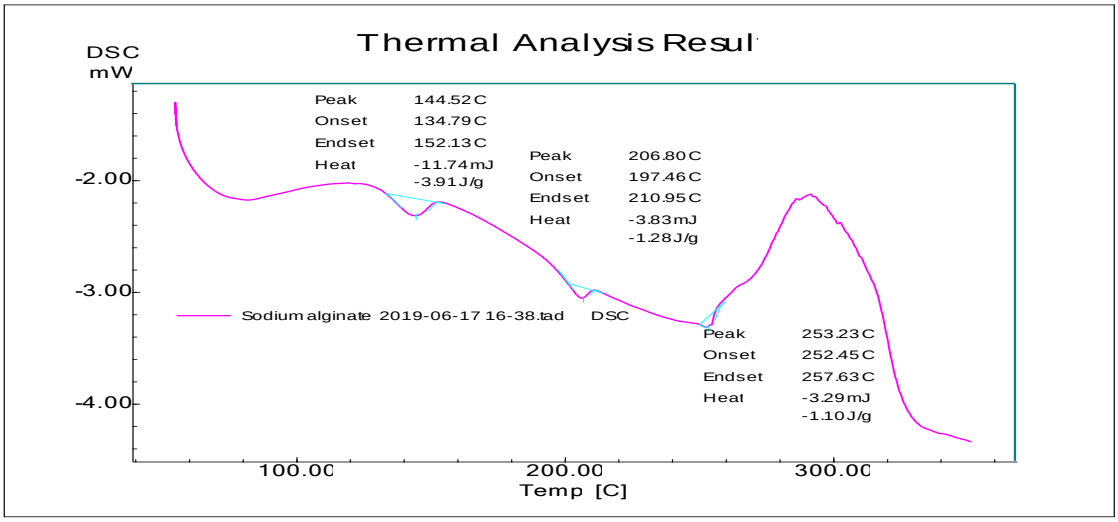

Figure 23: DSC Analysis of Sodium alginate.

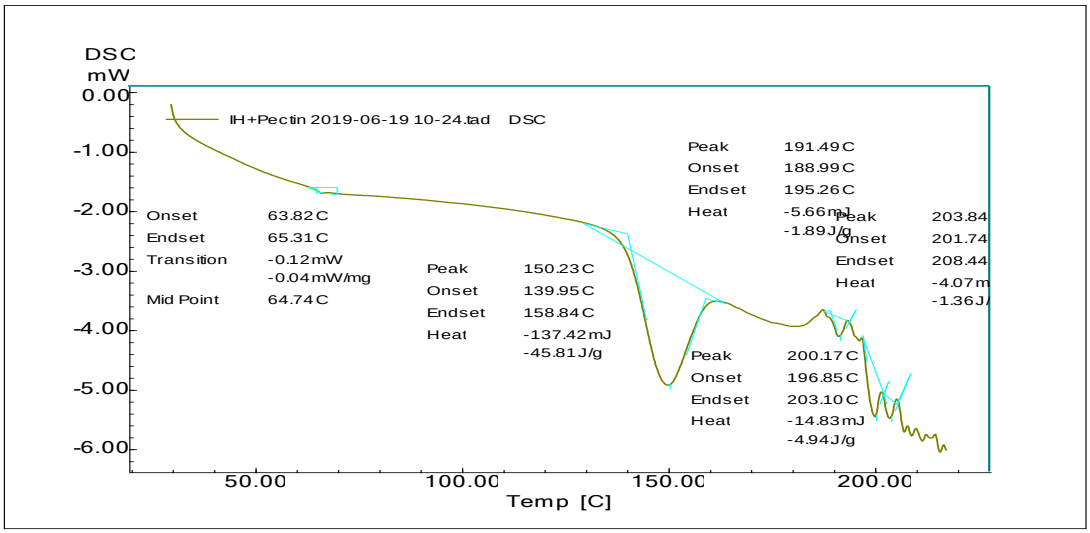

Figure 24: DSC Analysis of Itopride Hydrochloride with Pectin.

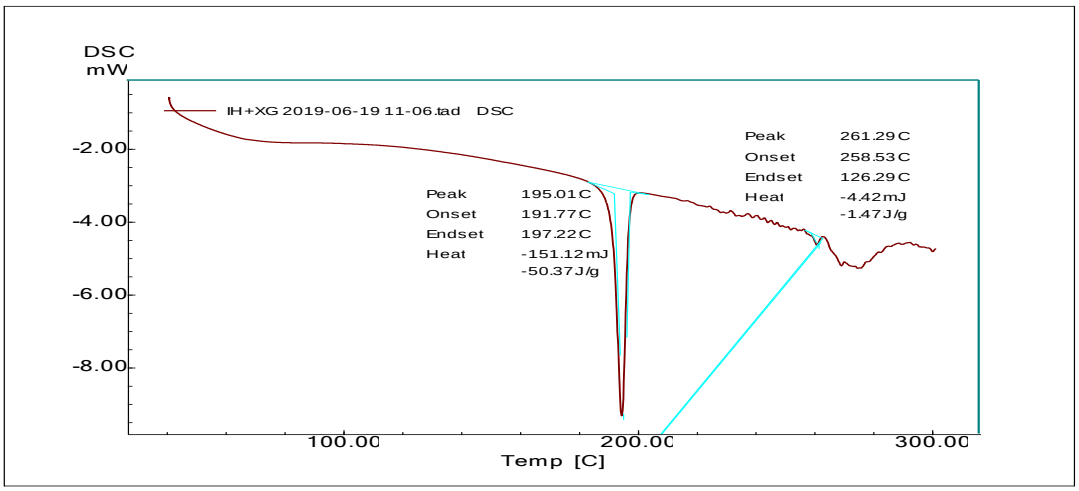

Figure 25: DSC Analysis of Itopride with xanthan gum.

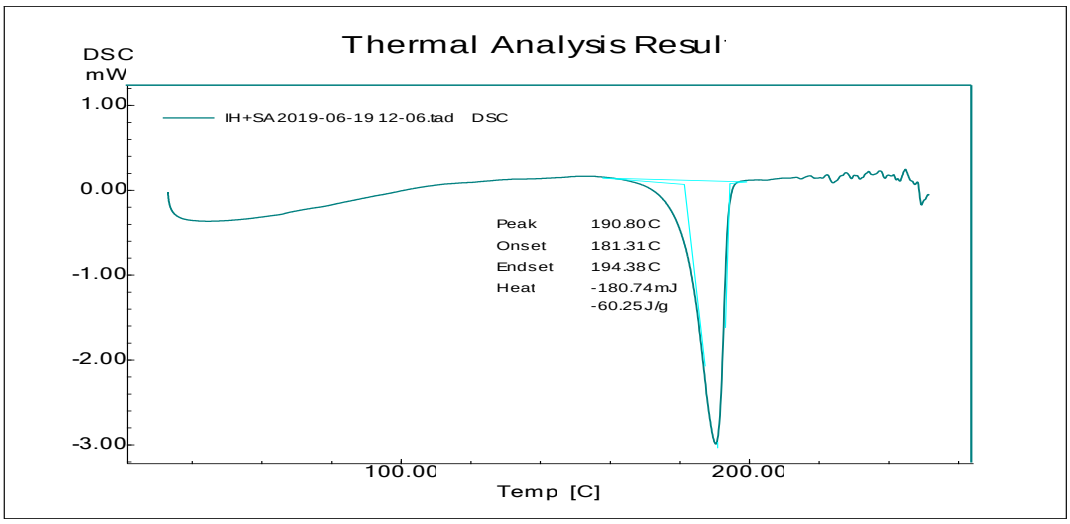

Figure 26: DSC Analysis of Itopride with Sodium alginate.

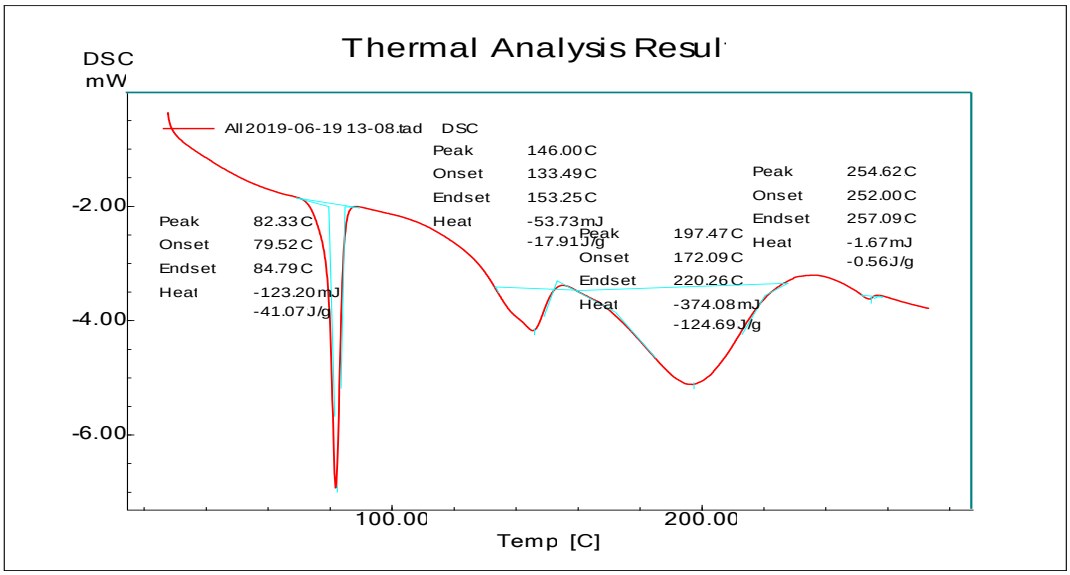

Figure 27: DSC Analysis of Drug + excipients.

Formulation of fast dissolving film

Dose calculation

Diameter of the plate = 9 cm

Area of the plate $= \pi r^2$

= 63.58 cm^2

No. of $4cm^2$ films present in whole plate =63.58/4=15.89

Each film contains 50 mg of drug

The amount of drug to be loaded in each plate was =15.89×50

= 794.5 mg.

Exploration of the polymers for formulation of oral fast dissolving films

Different polymers like Pectin, Xanthan Gum, and Sodium Alginate were used for preparation of fast dissolving film.

Selection of plasticizer for optimization of films

Polyethylene glycol-6000 were used as plasticizer in film formation. PEG-6000 used as plasticizer, films was formed and can be easily removed from Petri plate.

Table 12: Trial batches of fast dissolving films.

Polymer	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pectin	√	√	√							
Xanthan Gum				√	√	√				
Sodium Alginate							√	√	√	
Pectin+Xanthan gum+Sodium Alginate										√
D.W	√	√	√	√	√	√	√	√	√	√

Preparation of trial batches of fast dissolving films

Preparation of film using Pectin as polymer

Fast dissolving films using Pectin and its concentrations were formed. They were evaluated and screened for appearance and dryness. Films formed were transparent, dry; film forming capacity is high as compare to other polymers.

Preparation of film using Xanthan Gum as polymer

Fast dissolving films using Xanthan Gum and its concentrations were formed. Xanthan Gum is largely used as binder, it forms clots in solution. Film forming capacity of Xanthan gum is poor.

Preparation of film using Sodium Alginate as polymer

Fast dissolving films using Sodium and its concentrations were formed. They were evaluated and screened for appearance and dryness.

Formulation design

Fast dissolving films are prepared using Pectin, Xanthan gum, Sodium alginate and combination of pectin, xanthan gum and sodium alginate as polymer.

Table 13: Formulation design.

Ingredients (mg/film)	Formulation code (Quantity: mg/film)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Itopride Hydrochloride	50	50	50	50	50	50	50	50	50	50
Pectin	1	1.5	2	---	---	---	---	---	---	---
Xanthan gum	---	---	---	0.4	0.7	1	---	---	---	---
Sodium alginate	---	---	---	---	---	---	1.5	2	2.5	---
Pectin+ Xanthan Gum+Sodium alginate	---	---	---	---	---	---	---	---	---	1:1:1
Polyethylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Citric acid	1	1	1	1	1	1	1	1	1	1
Mannitol	3	3	3	3	3	3	3	3	3	3
Vanillin	1	1	1	1	1	1	1	1	1	1
D.W	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

*Area of the film- 2×2cm^2

**Dose of drug per film- 50 mg

Evaluation

Evaluation of films prepared in formulation design

In the following table film forming capacity of all formulation batches were checked.

Table 14: Evaluation for film forming capacity of films.

Sr. No.	Formulation batch	Film forming capacity
1	F1	Best
2	F2	Better
3	F3	Better
4	F4	Poor
5	F5	Poor
6	F6	Poor
7	F7	Best
8	F8	Better
9	F9	Average
10	F10	Good

Evaluation parameters of formulation batches

Table 15: Evaluation parameters of formulation batches.

Batch	Weight variation (mg)	Folding endurance	Surface pH	Disintegration time (sec)
F1	29.55±0.88	41.66±1.52	6.76±0.05	23.66±0.57
F2	28.6±0.68	37.33±1.15	6.56±0.05	27.66±0.57
F3	38.2±0.69	34.66±0.57	6.5±0.1	31.33±1.15
F4	39.95±0.68	24.66±0.57	6.66±0.05	41.66±0.57
F5	29.7±0.73	24±1	6.66±0.11	44.66±1.52
F6	49.9±0.64	22.66±1.52	6.56±0.11	38.33±0.57
F7	34.95±0.68	41.33±1.52	6.76±0.05	26.66±1.15
F8	45.05±0.75	37.66±0.57	6.56±0.15	35±1
F9	51.9±0.78	28.66±0.57	6.63±0.15	39±1
F10	29.9±0.78	19±1	6.53±0.15	31±1

*All values are expressed as mean± S.D. (n=3)

Table 16: Evaluation parameters of formulation batches.

Batch	Thickness (mm)	Tensile strength (gm/cm^2)	% Drug content
F1	0.86±0.05	57.64±0.44	98.53±1.09
F2	1±0.1	44.58±0.38	93.13±1.2
F3	1.1±0.1	41.36±0.68	92.33±0.27
F4	0.96±0.20	46.17±0.54	90.03±1.7
F5	0.93±0.15	45.84±1.01	91.41±0.13
F6	1.3±0.1	37.6±0.21	90.36±1.55
F7	0.93±0.15	52.86±0.41	93.5±0.82
F8	1.2±0.1	35.20±0.54	92.87±0.76
F9	1.43±0.15	29.89±0.30	91.44±0.98
F10	0.93±0.15	43.74±0.64	92.7±0.27

Evaluation parameters

In the present research work, films were prepared using Itopride Hydrochloride as drug and polymers like Pectin, Xanthan gum and Sodium alginate in different concentrations by solvent casting method. The prepared fast dissolving films were evaluated for various parameters and the results of these parameters were given in table no.14- 16.

Appearance of fast dissolving films

These parameters were checked simply with visual inspection of fast dissolving film and by feel or touch. The observation suggests that the fast-dissolving film were having smooth surface and elegant enough to see.

Weight variation of fast dissolving films

The weight of fast dissolving film was determined using digital balance and the average weight of fast dissolving film was given in table no.22. It was found to be in the range of 28.6±0.68 to 51.9±0.78 mg.

Thickness of fast dissolving films

The average thickness of all fast-dissolving film was given in table no.23. The thickness of the fast-dissolving films was found in between 0.86±0.05 to 1.43±0.15mm (n=3).

Folding endurance of fast dissolving films

The average folding endurance of all fast-dissolving film was given in table no.22. Folding endurance ranges from 19±1 to 41.66±1.52 as shown in following figure no.28.

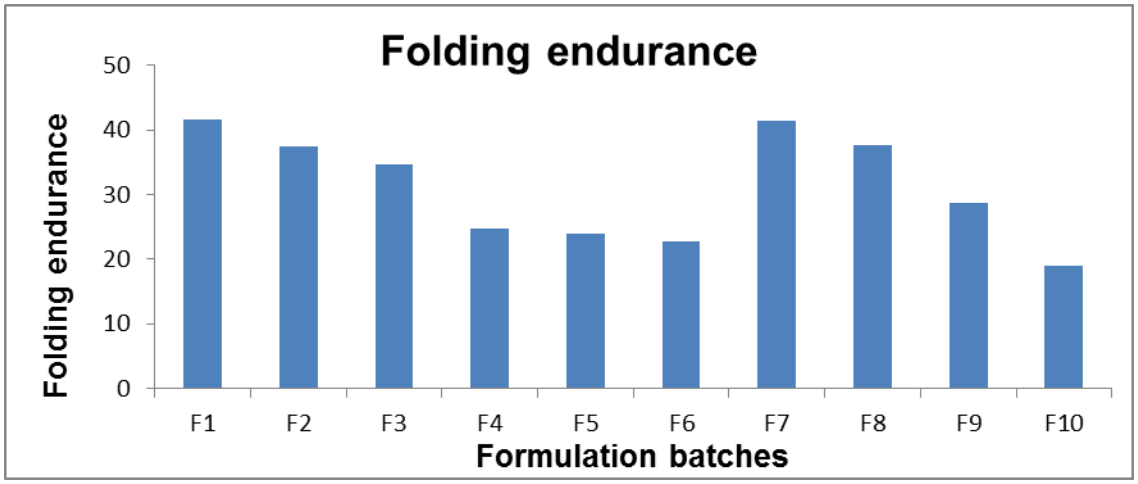

Figure 28: Folding endurance of F1-F10 batches.

Surface pH of fast dissolving films

The surface pH was noted by pH meter near the surface of fast dissolving film and allowing equilibrating for 1 minute and the surface pH of the fast dissolving film was given in table no.15. The surface pH of fast dissolving film was found to in between 6.5±0.1 to 6.76±0.05 pH (n=3).

Disintegration time of fast dissolving films

Film of 2×2 cm^2 size taken and disintegration time checked visually. In each case three fast dissolving films were used and the results were shown in table no.15. Disintegration time ranges from 23.66±0.57 to 44.66±1.52 seconds, which indicates disintegration time of film ranges within a minute.

Tensile strength of fast dissolving films

The Tensile strength of fast dissolving film was given in table no. 16. Tensile strength found to in between 29.89±0.30 to 57.64±0.44.

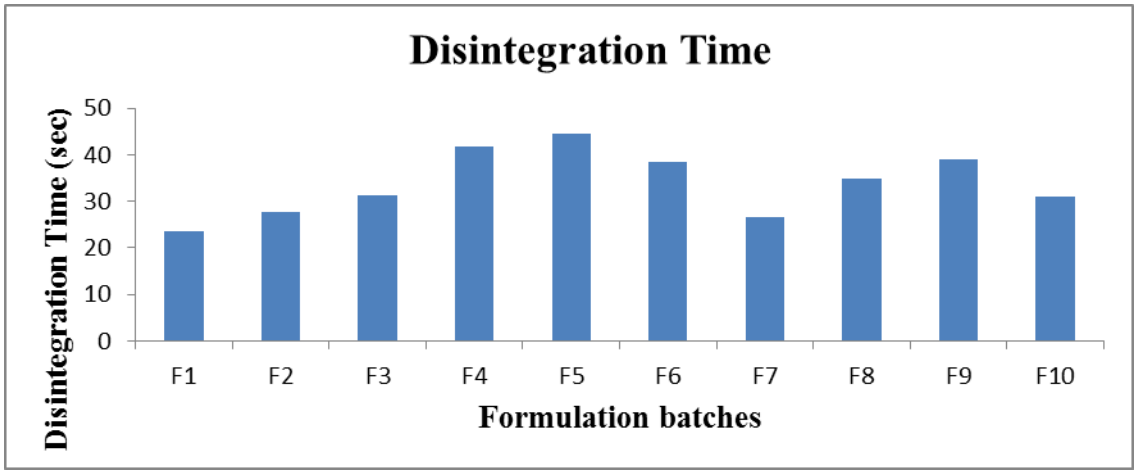

Figure 29: Disintegration time of F1-F10 batches.

% Drug content of fast dissolving films

In each case three fast dissolving films were used and the average drug content was calculated, the results were shown in table no.16. The drug was dispersed in the range of 90.03±1.7 to 98.53±1.09 (n=3), suggesting that drug was uniformly dispersed in all fast dissolving films. The standard deviation value calculated for such formulation was very less which suggest that the results were reproducible and accuracy in the method used to prepare the fast-dissolving film. The F1 batch showed 98.53±1.09 and drug content uniformity.

***In vitro* dissolution study**

Results of *In vitro* dissolution study was given in the following figures. In figure no.30 % cumulative drug release of batches F1-F5 and in figure no. 31 % cumulative drug release of F1-F10 batches were given. F1 batch show 99.81±0.09% drug release in 10 minutes while F2 showed 95.47±0.08%, F3 showed 94.59±0.33%, F4 showed 92.45±0.29% and F5 showed 88.33±0.18 % drug release. In figure no.26 % cumulative drug release of batches F6-F10 were given. F7 batch showed 96.55±0.39 % of drug release in 10 minutes while F6 showed 90.58±0.32%, F8 showed

90.64±0.77%, F9 showed 91.4±0.3% and F10 showed 91.26±0.40% drug release.

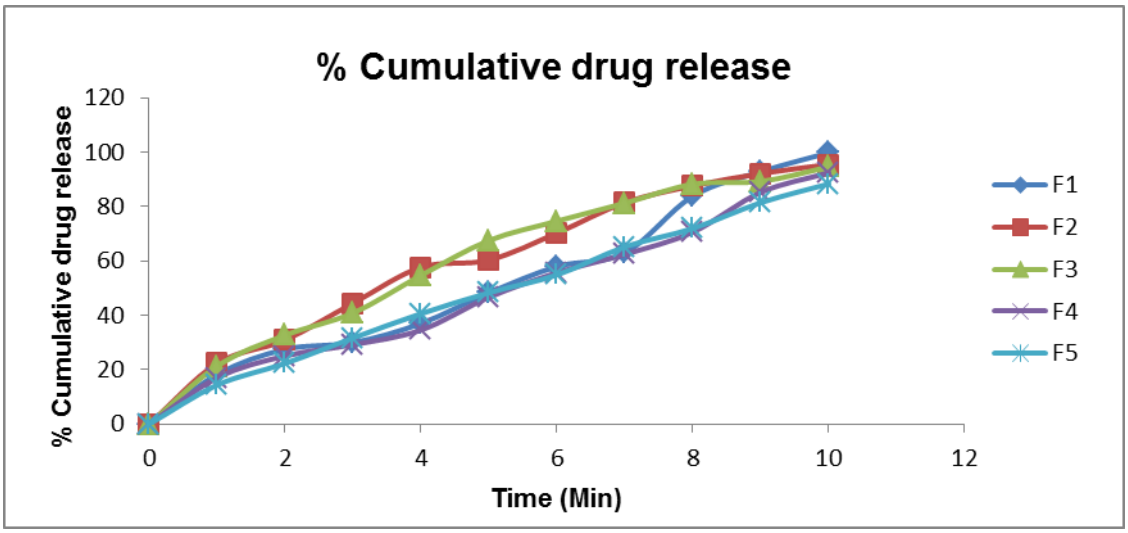

Figure 30: % Cumulative drug release from F1-F5 batch.

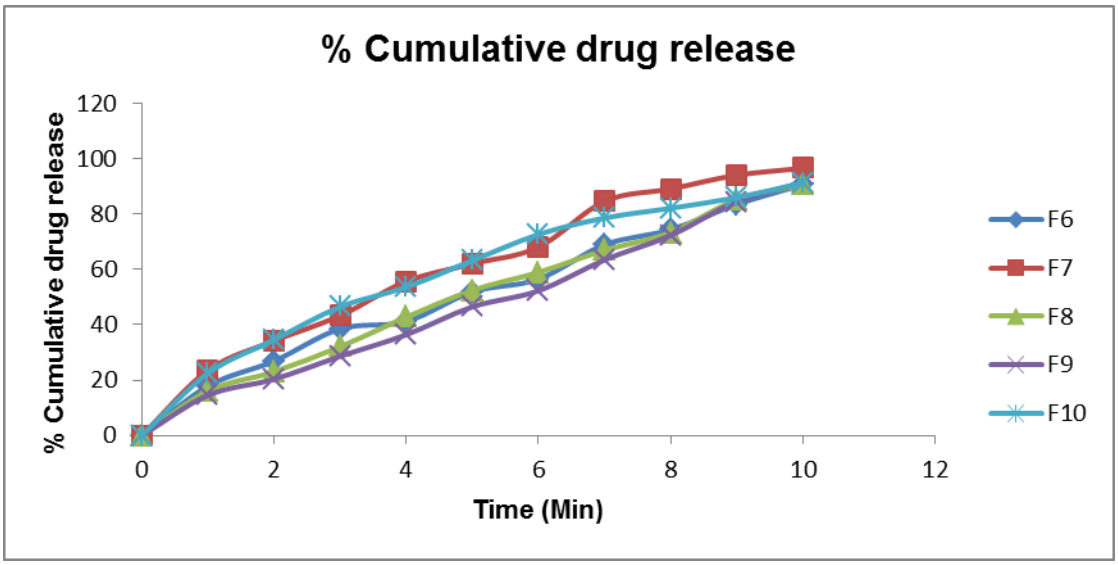

Figure 31: % Cumulative drug release from F6-F10 batch.

Table 17: *In vitro* drug release from F1-F5 batch.

Time (min)	% Cumulative drug release				
	F1	F2	F3	F4	F5
1	18.27±0.39	22.32±0.55	21.35±0.29	17.05±0.21	14.37±0.41
2	27.52±0.37	30.94±0.49	32.7±0.22	25.07±0.46	22.33±0.08
3	29.98±0.41	44.46±0.98	40.88±0.24	29.22±0.41	31.67±0.44
4	37.02±0.49	57.65±0.12	54.7±0.03	34.59±0.31	40.61±0.66
5	48.29±0.54	60.32±0.36	67.52±0.32	46.65±0.47	48.33±0.33
6	57.98±0.12	70.27±0.49	74.65±0.32	55.69±0.19	54.89±0.07
7	62.98±0.45	81.50±0.86	81.29±0.43	62.46±0.14	65.21±0.71
8	83.88±0.76	87.63±0.35	88.21±0.28	78.63±0.36	71.96±0.61
9	92.83±0.39	92.15±0.73	89.24±0.34	85.27±0.34	81.45±0.37
10	99.81±0.09	95.47±0.08	94.59±0.33	92.45±0.29	88.33±0.18

All values expressed as mean ± SD (n=3), F= formulation batch

Table 18: *In vitro* drug release from F6-F10 batch.

Time (min)	% Cumulative drug release				
	F6	F7	F8	F9	F10
1	17.84±0.64	23.53±0.23	16.08±0.79	14.53±0.28	22.45±0.12
2	26.91±0.32	34.18±0.56	23.04±0.22	20.35±0.43	34.54±0.13
3	38.53±0.41	43.27±0.04	32.08±0.46	28.62±0.16	46.47±0.15
4	41.18±0.62	55.65±0.79	42.75±0.89	36.42±0.35	53.61±0.14
5	51.88±0.77	62.02±0.67	52.43±0.07	46.47±0.28	63.22±0.31
6	56.49±0.86	68.02±0.34	58.95±0.71	52.3±0.45	72.62±0.29
7	68.93±0.43	84.58±0.92	66.92±0.38	63.45±0.39	78.56±0.31
8	74.36±0.11	89.08±0.88	73.34±0.96	72.26±0.40	82.1±0.47
9	83.47±0.18	94.02±0.07	85.20±0.21	84.48±0.36	85.96±0.22
10	90.58±0.32	96.55±0.39	90.64±0.77	91.4±0.3	91.26±0.40

*All value expressed as mean± SD (n=3), F= formulation batch

Selection of best batch

All films prepared were smooth and elegant in appearance, were uniform in thickness, weight variation, drug content and folding endurance was precise. From all formulated batches F1-F10, it was observed that the batch F1 which contain 98.53±1.09 % of drug content. % cumulative drug release was 99.81±0.09 in 10 minutes. It was the best regarding other batches. Disintegration time of this batch was found to be 23.66±0.57 seconds, so the formulation was selected as best batch.

Fast dissolving films were prepared by using Itopride Hydrochloride drug which is used in the treatment of gastrointestinal reflux disease, nonfunctional dyspepsia, and gastroparesis and in gastritis. The drug has site of absorption in mouth and having short half-life (6 hours) are intended for the application in the oral cavity and they are an innovative and promising dosage form.

Preformulation study: The Preformulation study of selected drug was done. The scanning of pure drug shows maximum absorbance 257nm, calibration curve of Itopride Hydrochloride in pH 6.8 phosphate buffer were carried out at 257nm. The melting point was found to be 194ºC (193ºC-198ºC).

Drug- excipients compatibility study

By IR Spectroscopy

The FTIR imaging produced important information about the physical and chemical interactions between drug and excipients. FTIR spectra of Itopride Hydrochloride and formulation show characteristic peak at same wave number indicating no interaction between drug and polymer. FTIR spectroscopy was used as means of studying drug- excipients compatibility study.

By Differential Scanning Colorimetry

DSC analysis was performed. Sample was analyzed by heating at a scanning rate 193ºC to 198ºC under nitrogen environment. Thermal characterizations of film were performed using DSC studies and were represented in figure. On the basis of spectral and thermal characterization studies on films, no interaction between drug and excipients in fast dissolving films had been observed.

MATERIAL AND METHOD

Fast dissolving films were prepared by solvent casting method in ten formulation batches with three different film forming polymers such as Xanthan gum, Pectin and Sodium alginate and Polyethylene glycol as a plasticizer and excipients with purpose of fast disintegration and dissolution characteristics.

Evaluation parameters

Evaluations of all ten batches were carried out. The parameters evaluated were weight of film, thickness, folding endurance, surface pH, content uniformity, disintegration time etc. they were in the range of weight variation 28.6±0.68 to 51.9±0.78 mg, thickness 0.86±0.05 to 1.43±0.15 mm (n=3), folding endurance 19±1 to 41.66±1.52, surface pH 6.5±0.1 to 6.76±0.05 pH (n=3), content uniformity 90.03±1.7 to 98.53±1.09 (n=3) and disintegration time 23.66±0.57 to 44.66±1.52 seconds (n=3), Tensile strength 29.89±0.30 to 57.64±0.44 Respectively.

***In vitro* drug release:** *In vitro* drug release of films occur in 10 minutes for all batches. F1 batch show 99.81±0.09% drug release in 10 minutes while F2 showed 95.47±0.08%, F3 showed 94.59±0.33%, F4 showed 92.45±0.29% and F5 showed 88.33±0.18 % drug release. F7 batch showed 96.55±0.39 % of drug release in 10 minutes while F6 showed 90.58±0.32%, F8 showed 90.64±0.77%, F9 showed 91.4±0.3% and F10 showed 91.26±0.40% drug release. Among these F1 batch shows better drug release than other batches.

CONCLUSION

Fast Dissolving Oral Films are intended for the application in the oral cavity and they are an innovative and promising dosage form especially for use in pediatrics and geriatrics. On the Indian market no licensed fast dissolving film drug product is available yet. Itopride Hydrochloride was selected as the active drug as it has very high solubility and it is indicated into GI motility disorders where an immediate relief is always needed. Moreover, fast dissolving dosage form is very convenient for geriatric patient and those who have difficulty in swallowing tablets or in situations where

access to water is not possible. Drug free films were prepared according to the literature starting with a pre-evaluation of different film formers such as pectin, xanthan gum, sodium alginate. The characterization of drug and drug polymer interaction were carried. The oral films prepared using pectin, xanthan gum, sodium alginate are evaluated regard to their film forming capacity, disintegration time, mechanical properties and % drug release. These polymers have better film forming capacity but pectin has faster disintegration other than xanthan gum and sodium alginate. Pectin and sodium alginate are evaluated gives good mechanical properties with better drug release.

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