

FORMULATION AND EVALUATION OF FAST DISSOLVING FILMS OF ISOSORBIDE MONONITRATE

Dissertation

Submitted to

The Tamil Nadu Dr.M.G.R Medical University, Chennai

In partial fulfillment for the award of degree of

MASTER OF PHARMACY

in

PHARMACEUTICS

by

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DEPARTMENT OF PHARMACEUTICS

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OCTOBER-2013

ABBREVIATIONS

°C	:	Degree Centigrade
Abs	:	Absorbance
µl	:	Micro litre
µg/ml	:	micro gram per millilitre
λ_{max}	:	Lambda maximum
mg	:	Milligrams
g	:	Grams
SD	:	Standard deviation
Kg/cm²	:	kilogram per centimetre square
min	:	Minute
ml	:	Milli litre
N	:	Normal
Nm	:	Nanometre
RPM	:	rotation per minute
Hr	:	Hour
Sec	:	Second
V_d	:	Volume of distribution
Cm	:	Centimetre
nm	:	Nanometre
Cps	:	Centi poise
HPMC	:	Hydroxy Propyl Methyl cellulose
PVA	:	Poly Vinyl Alcohol
%w/w	:	Percentage weight by weight

Q.S : **quantity sufficient**

ISMN : **Isosorbide mononitrate**

FTIR : **Fourier transfer infrared spectroscopy**

Kg/mm² : **Kilogram per millimetre square**

1. INTRODUCTION

The oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility⁽¹⁾ and are administered in the form of both solid dosage forms (powders, pills, spansules, moulded tablets) and liquid dosage forms (elixirs, syrups, emulsions, mixtures). A pill can be designed for swallowing or chewing to deliver a precise dose of medication to the patients. Under moderate pressure, the pills including tablets and capsules are able to retain their shapes. Major disadvantage of this route is the difficulty in swallowing or chewing solid dosage forms particularly in pediatric and geriatric patients⁽²⁾. Due to fear of throat choking many pediatric and geriatric patients are unwilling to take these solid preparations⁽⁴⁾. In order to overcome the difficulties associated with this system of administration, several fast dissolving drug delivery systems have been developed. By using variety of technologies, including direct compression, wet granulation and freeze drying Fast dissolving drug delivery systems can be manufactured. In order to dissolve the dosage form rapidly in the mouth, some make use of different disintegrating mechanisms, such as high level of disintegrating or effervescent agents. Because of its easy administration and better compliance, recently fast dissolving drug delivery system have started gaining popularity and acceptance as new drug delivery systems. Without the need of water or chew to aid in swallowing, these fast dissolving drug delivery systems can be dissolve or disintegrate in the patient's mouth within a few seconds or minutes⁽³⁾. Oral film drug delivery is a better alternative against oral solid tablets because of its fear of taking and the risk of choking for certain patient populations even it has short disintegration/dissolution times and also the oral availability of many drugs are very poor because of the pH stomach, the presence of enzymes,

extensive first-pass metabolism these can also be solved by making oral films. These drugs have been administered as parenteral drug delivery systems, but because of poor patient compliance the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery. Intraoral fast-dissolving drug delivery system is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also have an advantage for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs.^{(5),(6)}

1.1 Overview of oral cavity: ^{(7),(8)}

1.1.1 Structural Features of Oral Mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium .The turnover time for the buccal epithelium has been estimated at 5-6 days and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm , while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 μm . The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of the gingivae and hard palate are keratinized similar to the epidermis which containe 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, however, are not keratinized which are relatively impermeable to water and only have small amounts of

ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. The nonkeratinized epithelia have been found to be considerably more permeable to water than keratinized epithelia.

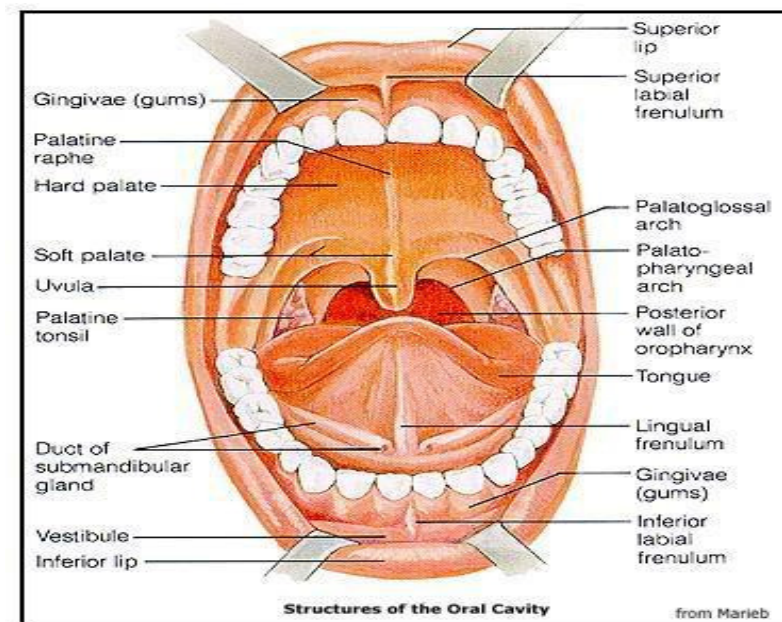


Figure No.1 Structure of Oral cavity

1.2 Classification Of Fast Dissolve Technology:

Fast-dissolve technologies can be divided in to three broad groups:

1. Lyophilized systems,
2. Compressed tablet-based systems,
- 3 Thin film strips.

1.2.1 The lyophilized systems:

This system is the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. Through the use of a mould or blister pack, suspension or solution of drug with other structural excipients will convert into tablet-shaped units. The units or

tablets are then frozen and lyophilized in the pack or mould. The resulting units having high porosity are responsible for 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.

1.2.2 Compressed tablet-based systems:

This system is produced using standard tablet technology by direct compression of excipients. The tablet technologies have different levels of hardness and friability depending on the method of manufacture..The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or superdisintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail.s Fuisz technology. It uses the proprietary Shear form system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast-dissolve dosage forms.⁽⁹⁾

1.2.3 Oral Thin Films (OTF):

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 (OTFs) or oral strip (OS) 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 (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to middevelopment stages for prescription drugs⁽¹⁰⁾. This is largely as a result of the success of the consumer breath freshener products such as Listerine PocketPaks in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. This film can reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats⁽⁹⁾.

Property / Sub Type	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	Multilayer
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic polymers	Low, non-soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspended and/or solid solution
Application	Tongue (upper plate)	Gingival or Buccal region	Gingival or buccal Region Gingival, (other region in the 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 No.1 , Types of wafers and their properties

1.2.3.1 Classification of Oral Film:

There are three different subtypes

- (1) Flash release,
- (2) Mucoadhesive melt-away wafer,
- (3) Mucoadhesive sustained-release wafers.

1.2.3.2 Advantages of Oral Thin Film:

This dosage form enjoys some distinct advantages over other oral formulations such as-

- Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.

- The disadvantage of most ODT is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.
- As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
- Pharmaceutical companies and consumers alike have embraced OTFs as a practical and accepted alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices⁽¹¹⁾
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect⁽¹²⁾.
- Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
- Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
- OTFs are typically the size of a postage stamp and disintegrate on a patients tongue in a matter of seconds for the rapid release of one or more APIs. The formulation of dissolvable films is customarily facilitated through aqueous polymer matrices that span a wide molecular weight (MW) range, thereby providing flexibility to achieve certain physical properties.

1.2.3.3 Disadvantage of Oral Thin films:

The disadvantage of Oral thin film is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active can be improved up to 50% per dose weight⁽¹¹⁾. There remain a number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose products. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose of up to 30 mg. This clearly limits the range of compatible drug products. The other technical challenge with these dosage forms is achieving Dose Uniformity⁽⁹⁾.

1.2.3.4 Application of Oral Films in Drug Delivery:

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of OTFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders.

1.2.3.5 Advantages of oral fast dissolving films.

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of OTFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders.

•**Topical applications:** The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial

ingredients for wound care and other applications.

- **Gastro retentive dosage systems:** Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format⁽¹³⁾ Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could potentially be used to treat gastrointestinal disorders.
- **Diagnostic devices:** Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device⁽¹⁴⁾

1.3 Oral films Formulation consideration

Oral dissolving film is a thin film with an area of 1-20 cm² (depend on dose and drug loading) containing drug. Drugs can be loaded up to a single dose of 30mg. The important factors affecting mechanical properties of the films are the formulation considerations (plasticizers etc).

A typical composition contains the following components:

➤ Drug	5% to 30% w/w
➤ Water soluble polymer	45% w/w
➤ Plasticizers	0-20% w/w
➤ Surfactants	q.s
➤ Sweetening agent	3 to 6 % w/w
➤ Saliva stimulating agent	2 to 6% w/w

Fillers, colors, flavors etc. q.s⁽¹⁵⁾

1.3.1 Film Forming Polymers

INTRODUCTION

For the preparation of fast dissolving films, a variety of polymers are available. In order to obtain the desired strip properties, the polymers can be used alone or in combination. To avoid damage while handling or during transportation, the film obtained should be tough. Type of polymer and the amount in the formulation are the factors which help in the robustness of the strip. On the other hand, fast dissolving strip dosage form should have the property to disintegrate in seconds when placed in mouth a deliver the drug to the oral cavity instantaneously. Lists of polymers which are used in oral strip are given in table

Pullulan	Sodium carboxy methyl cellulose
Gelatin	Hydroxyl ethyl cellulose
Hydroxyl propyl methyl cellulose (hypromellose)	xanthan gum
Polyvinyl Pyrrolidone (PVP)	Iocust bean gum
Modified starches	Guar gum
Polyvinyl alcohol	Carrageenan
Polpolyethylene oxide	Low viscosity grade HPC

Table No.2 ,List of polymers used in oral film formulation

At least 45%w/w of polymer should generally be present based on the total weight of dry, because the strip forming polymer is the most essential and major component of the fast dissolving film. For the preparation of fast dissolving film, most commonly used polymers are pullulan, gelatin and hypromellose⁽¹⁶⁾

1.3.2 Plasticizers

The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer in the range of 40–60 °C for non aqueous solvent system and below 75 °C for aqueous systems. Typically the plasticizers are used in the concentration of 0–20%w/w of dry polymer weight.^(16, 17)

1.3.3 Active pharmaceutical ingredient

The Oral thin film technology has the potential for delivery of variety of APIs. A number of molecules can be incorporated into this delivery system. They may include cough/cold remedies (antitussives, expectorants), antianxiety drugs, cardiovascular agents, sore throat, erectile dysfunction drugs, antihistamines, antiasthmatics, gastrointestinal disorders, nausea, pain and CNS (e.g. anti-Parkinson's disease). Other applications comprise caffeine strips, snoring aid, multivitamins, sleeping aid etc. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in Oral thin films. It is always useful to have micronized API which will improve the texture of

the film and also for better dissolution and uniformity .Many APIs, which are potential candidates for OTF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OTF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Certain pathologies require instantaneous release of the medicament for prompt relief. For instance, in the case of migraine a rapid clinical effect is desired by the individual. Regiospecific delivery of the medicament would be required in the cases of sore throat, cough, allergy and other local oral manifestations. ^(15,16,18) .

1.3.4 Surfactants:

Surfactants can act as solubilizing or wetting or dispersing agent. In formulation, the film is getting dissolved within seconds and release active agent quickly. Some of the commonly used surfactants are sodium lauryl sulfate, benzalkonium chloride, tweens, polyethylene glycol, etc. is Polaxamer 407 is one of the most important surfactant that is used as solubilizing, wetting and dispersing agent⁽¹⁵⁾

1.3.5 Sweetening Agents

1.3.5.1 Natural Sweeteners:

Sweeteners have become the important component for those nutraceuticals as well as pharmaceutical products. Sweetners will dissolve in the oral cavity. The sources of sweetener are sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. Fructose is used widely as sweetner because it is sweeter than sorbitol and mannitol. They additionally provide Because of good mouth-feel and cooling sensation. Polyhydric alcohols such as sorbitol, mannitol and isomalt can be used in combination. Main advantages of Polyhydric alcohols are less

carcinogenic and do not have after taste which is a vital aspect in formulating oral preparations.

1.3.5.2 Artificial Sweeteners:

The artificial sweeteners have gained more popularity in food and pharmaceutical preparations. The artificial sweeteners can be classified in I generation and II generation sweeteners which are Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant *Stevia rebaudiana* (South American plant) has more than 200 - 300 time sweetness ^(15, 18)

1.3.6 Saliva Stimulating Agent:

For the faster disintegration of the fast dissolving film formulations, more saliva production is needed. So the formulations may contain acids which are used in the preparation of food as salivary stimulants. Examples of salivary stimulants are Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. In this Citric acid being the most preferred amongst them⁽¹⁵⁾.

1.3.7 Flavor:

Any flavor (US-FDA approved) can be added in the formulation. For example, intense mints, sour fruit flavors or sweet confectionery flavors¹⁵. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

1.3.8 Coloring Agents:

Coloring agents are used mainly to impart a distinctive appearance to a pharmaceutical dosage form. Pigments such as titanium dioxide or a full range of colors are available, including FD and C colors, EU Colors, Natural Colors like curcumin, chlorophylls, carotenoids and custom Pantone-matched color.⁽¹⁵⁾

1.4 Manufacturing Methods:

One or combination of the following process can be used to manufacture the mouth dissolving films ⁽¹⁹⁾

- i) Solvent casting
- ii) Semisolid casting
- iii) Hot melt extrusion
- iv) Solid dispersion extrusion
- v) Rolling

1.4.1 Solvent casting method:

The Oral fast dissolving film is preferably formulated using the solvent-casting method. In solvent casting method water soluble polymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried. solution. The API and other agents are dissolved in smaller amounts of the solution, and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

Water-soluble hydrocolloids used to prepare RDFs include: hydroxyl

propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), pullulan, sodium alginate, pectin, carboxy methyl cellulose (CMC), polyvinyl alcohol (PVA). The selection of solvent essentially depends on the API to be incorporated into the strip. The physicochemical properties of the API like heat sensitivity, shear sensitivity, the polymorphic form of the API employed, compatibility of the API with solvent and other strip excipients are to be critically studied. The significant elements in this are liquid rheology, desired mass to be cast and content or dosage uniformity. Solvents used for the preparation of solution or suspension should ideally be selected from ICH Class 3 solvent list.

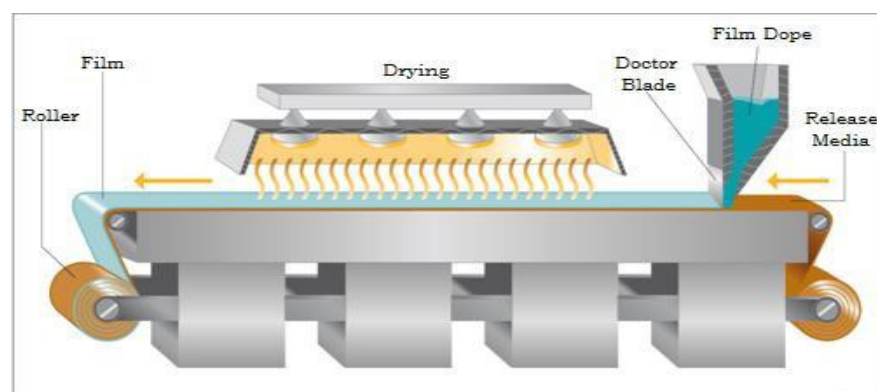


Figure No.2, Solvent casting system

Advantages

- Great uniformity of thickness and great clarity than extrusion
- Film have fine gloss and freedom from defects such as die lines
- Film have more flexibility and better physical properties

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. ⁽¹⁵⁾

1.4.2 Semisolid casting:

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. ⁽²⁰⁾

1.4.3 Hot melt extrusion:

In present method the mass is prepared first under the control of temperature and steering speed. Afterwards, the film is coated and dried in a drying tunnel, once again the temperature, air circulation and line speed are controlled. Then follows a slitting and in the last step the films are punched and sealed. In hot melt extrusion method firstly the drug is

mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. ^(16,21)

Advantages:

Without use of any solvent or water

Fewer processing steps

Compressibility properties of the API 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.

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 ⁽¹⁶⁾.

1.4.4 Solid dispersion extrusion:

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies ^(16, 20).

1.4.5 Rolling Method:

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutter in to desired shapes and sizes.

⁽¹¹⁾ Other ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor Water soluble hydrocolloids dissolved in water to form homogenous viscous solution. ⁽²⁰⁾

1.5 TECHNOLOGIES

1.5.1 SOLULEAVES™

This is applied to flavour-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.. SOLULEAVES™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients and flavours. 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 pediatrics 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 minutes.

1.5. 2 WAFERTAB™

It is a patented delivery system that uses a unique process to prepare drug-loaded thin films which can be used in topical or oral application. Active ingredients are incorporated into the film after casting 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 flavoured 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 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 swallowing.

1.5.3 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 flavours.

1.5.4 XGEL™

This film is at the heart of Meldex International's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. 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 GMO free and continuous production processing provides an economic and competitive manufacturing platform. XGEL™ film can be taste masked, coloured, 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. All of the XGEL ingredients are well known and generally regarded as safe (GRAS). XGel film Technology developed by BioProgress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.

(16)

2 Literature Review

2.1 Literature Review

Aditya Dingu et al., (2008) Triclosan containing fast dissolving films are developed for local delivery to oral cavity. For the preparation of fast dissolving films Different types of film forming agents, film modifiers and polyhydric alcohols were evaluated for optimizing the composition . The potential of poloxamer 407 and hydroxypropyl- β -cyclodextrin to improve solubility of Triclosan was investigated. Fast dissolving films containing hydroxypropyl methylcellulose, xanthan gum, and xylitol were formulated. Use of poloxamer 407 and hydroxypropyl- β - cyclodextrin resulted in significant improvement in the solubility of Triclosan. Fast dissolving films containing Triclosan hydroxypropyl- β - cyclodextrin complex and Triclosan-Poloxamer 407 were formulated and were evaluated for the in vitro dissolution profile and in vitro microbiological assay. Films containing Triclosan-Poloxamer 407 shows better in vitro dissolution profile and in vitro antimicrobial activity as compared to the films containing Triclosan hydroxypropyl- β - cyclodextrin complex. ⁽³⁴⁾

Mohammed Gulzar Ahmed et al.,(2009) This study was designed to develop and evaluate chitosan films containing ciprofloxacin and diclofenac sodium for the topical treatment of periodontitis. Chitosan films containing ciprofloxacin alone and in combination with diclofenac sodium were prepared by solvent casting method. Some of the drug-loaded films were crosslinked with 2%gluteraldehyde for 2 and 4 h, respectively. The films were then evaluated for their physicochemical properties including weight variation, thickness, tensile strength, in vitro release, stability and antibacterial activity.. The study suggests that cross linked chitosan film containing ciprofloxacin and diclofenac is a potential drug delivery device for the topical treatment of periodontitis ⁽³⁵⁾.

Yoshinori Itoh et al., (2009) Formulated fast dissolving oral thin film that contains dexamethasone and microcrystalline cellulose, polyethylene glycol, hydroxypropylmethyl cellulose, polysorbate 80 , low-substituted hydroxypropyl cellulose etc. used as base materials.. This preparation showed excellent uniformity and stability, at

temperature at 40°C and 75% in humidity for up to 24 weeks. The film was disintegrated within 15 s after immersion into distilled water. The In vitro dissolution test showed that approximately 90% of dexamethasone was dissolved within 5 min.. The fast dissolving oral thin film containing dexamethasone is likely to become one of choices of dexamethasone preparations for antiemesis during cancer chemotherapy⁽³⁶⁾.

Sandeep Saini et al., (2009) development and evaluation of Fast dissolving film of levocetirizine dihydrochloride were prepared by solvent casting method . Maltodextrin & Hydroxy propyl methyl cellulose as the main film forming polymers.To reduce the disintegration time,concentration of maltodextrin & were optimized be using Hydroxy propyl methyl cellulose . Disintegration time, drug release pattern, mouth dissolving time and content uniformity were also evaluated. Compatibility between drug and recipients were studied by means of Differential scanning calorimetry analysis. Batch F1 was found to be the optimized batch as its disintegration was completed within the minimum time as compared to all other batches. The formulation (F1) was also showing sufficient drug release after 5 min. All the 6 formulation was showing approximately 90% drug release after 5min⁽³⁷⁾.

Francesco Cilurzo et al., (2010) develop a fast-dissolving film made of low dextrose equivalent maltodextrins containing nicotine hydrogen tartrate salt. maltodextrins with two different dextrose dextrose 6 , dextrose12 were selected in order to evaluate the effect of polymer molecular weight on film tensile properties. The bitterness and astringency intensity of hydrogen tartrate salt and the suppression effect of several taste-masking agent were evaluated by a Taste-Sensing System. The films were characterised in term of hydrogen tartrate salt content, tensile properties, and disintegration time and drug dissolution test. As expected, placebo films made of maltodextrins DE 6 appeared stiffer and less ductile than film prepared using maltodextrins DE 12. The films disintegrated within 10 s. Among the tested taste-masking agent, the milk and mint flavours resulted particularly suitable to mask the taste of hydrogen tartrate salt. The addition of and taste-masking agents affected film tensile properties; however, the effect of the addition of hydrogen tartrate salt these components can be counterweighted by

modulating the glycerine content and/or the maltodextrins molecular weight. The feasibility of hydrogen tartrate salt loaded fast-dissolving films was demonstrated ⁽³⁸⁾

Doaa Ahmed El-Setouhy. , (2010) the present investigation was undertaken with the objective of formulating orodispersible film(s) of the antidepressant drug tianeptine sodium to elderly and pediatric patients. The novel film former, lycoat NG73 (granular hydroxypropyl starch), along with different film-forming agents (hydroxypropyl methyl cellulose, hydroxyethyl cellulose, and polyvinyl alcohol), in addition to three film modifiers; namely, maltodextrin, polyvinyl pyrrolidone K90 and lycoat RS780 (pregelatinized hydroxypropyl starch) were evaluated. Eight formulae were prepared by the solvent-casting method; and were evaluated for their in vitro dissolution characteristics, in vitro disintegration time, and their physico-mechanical properties. The promising orodispersible film based on lycoat ; showing the greatest drug dissolution, satisfactory in vitro disintegration time and physico-mechanical properties that are suitable for orodispersible films (26)

Renuka Mishra et al., (2010) in the present study, rapidly dissolving films of cetirizine hydrochloride were formulated using pullulan as film forming polymer. Solvent casting was the method used for formation of rapidly dissolving films. The rapidly dissolving films were evaluated for the effect of type of casting surface and plasticizer on film separation and taste masking properties.. Cetirizine hydrochloride being slightly bitter, taste masking was achieved by use of sweeteners, flavours and citric acid. The in vitro and in vivo disintegration time of the optimized batch was found to be 30 seconds and 20 seconds respectively. The films exhibited satisfactory thickness, mechanical properties like tensile strength, % elongation and elastic modulus ⁽³⁷⁾

Nidhi P. Sapkal et al., (2011) developed oral thin films of Ambroxol hydrochloride, a mucolytic agent and to investigate the effect of the formulation variables like concentration of film forming polymer, emulsifying agent and plasticizer on the physico chemical properties and in vitro dissolution studies. Hydroxypropyl methylcellulose was used as a film former, Tween 80 as an emulsifying agent and polyethylene glycol 4000 as

a plasticizer. The role of Hydroxylpropyl methylcellulose in deciding the film properties was significant. It affected folding endurance, tensile strength, percent moisture absorption, disintegration time and in vitro dissolution rate significantly. polyethylene glycol 4000 also found to play a role in deciding the properties of films. The film that contained Hydroxylpropyl methylcellulose (15 mg /film i.e. 2x3 cm²) in low levels and Tween 80 (5 mg/film i.e. 2x3 cm²) and polyethylene glycol 4000 (8 mg/film i.e. 2x3 cm²) in high levels was found to be suitable for film formation with desirable physicochemical properties, faster disintegration and optimum in vitro release ⁽³⁸⁾

Sumitha et al., (2011) developed oral films of Sildenafil citrate using Hydroxy propyl methyl cellulose. Films were prepared by solvent casting method. Polacriline potassium, an ion exchange resin was used to mask the bitter taste of the drug by forming a complex with the drug, although the exact mechanism is yet to be determined. Glycerol, menthol and sucralose were incorporated in the drug containing films as plasticizer, cooling agent and sweetener, respectively. The films were evaluated for hydration study, folding endurance and in-vitro drug dissolution in the distilled water. The films showed neutral surface pH when prepared using 0.1 N Hydrochloric acid as a solvent. The bitter taste of the drug was masked by using Polacriline potassium and menthol accompanied by the synergistic effect of glycerol. The films containing the higher proportion of glycerol showed higher water uptake and faster drug release at all the sampling time in the in-vitro dissolution test. Optimum plasticity was obtained using the required concentration of Hydroxypropylmethylcellulose and glycerol. The study revealed that taste masked Sildenafil citrate films can be developed by the selection of appropriate film former and by the use of auxiliary excipients ⁽³⁹⁾.

Samta et al., (2011) this aim of the present study was to optimize the formulation of fast dissolving films made of pullulan polymer. The films formed from solvent casting method and subsequent evaporation of solvent resulted in pullulan forming a circular film. Pullulan was used as film forming agent due to excellent film forming property. Propylene glycol, glycerine were used as plasticizers. Increasing pullulan concentration in formulation resulted in thick films as compared to lower concentration of same.

Thickness of the film was controlled by adjusting the concentration of polymer. Higher concentration of polymer and plasticizer results in increase in-vitro disintegration time and in-vitro dissolution time of films. Propylene glycol forms white colored films i.e. translucent films. Films containing glycerin takes longer time to dry than films containing propylene glycol. Lower concentration of pullulan and propylene glycol showed optimum performances ⁽⁴⁰⁾.

Yellanki et al., (2011) an attempt to develop and evaluate mouth-dissolving film of phenobarbital for quick effect in treatment of epilepsy occurring in pediatric population has been made in the present study. Suitable film formers and plasticizers are selected based on optimization studies. Effect of superdisintegrants in formulation of mouth dissolving films at different concentrations has been investigated. Films were prepared by solvent casting method. The prepared films were evaluated for physicochemical parameters, in vitro disintegration and dissolution time, in vitro release rate study, stability study, and in vivo animal safety study. The best formulation was found to be F3 showing 96.57% drug release in 14 min, following first-order kinetics. In vivo studies in hamster reports effective and safe use of formulation in animals ⁽⁴¹⁾

Raju et al., (2011) Formulate and evaluate fast dissolving oral films of metoclopramide which is an excellent antiemetic drug. Which is used in the treatment of emesis in paediatrics. Two metoclopramide film were prepared by solvent casting technique using two water soluble polymers, hydroxypropyl methyl cellulose, and carboxy methyl cellulose. Infrared analysis revealed no interaction between Metoclopramide and polymers. The prepared films were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, surface pH and In-vitro release. Formulation F1 released 99.40% of drug within 30 sec and was considered as best formulation. This case study showed that hydroxypropyl methyl cellulose was the most suitable film-forming material for metoclopramide -loaded films, providing fast dissolution films that were not sticky and were easy to handle ⁽⁴²⁾.

Ajaykumar Patil et al.,(2011) Fast dissolving films of Montelukast sodium were prepared by solvent casting method using Hydroxy propyl methyl cellulose as film polymer with different concentrations of superdisintegrants like microcrystalline cellulose and crospovidone. Poly ethylene glycol 400 is used as plasticizer. The physicochemical parameters of the fast dissolving films were evaluated. Infrared spectroscopy is done for compatibility study. In vitro dissolution studies and mechanism of drug release was identified. The formulation F2 and F5 with 4% of crospovidone and 10% microcrystalline cellulose respectively shows a maximum cumulative percentage drug release of 97.42% and 94.64% at the end of 30 min respectively. ⁽⁴³⁾.

Gupta et al., (2011) the aim of work to rapidly release the drug when it is placed in the mouth. These dosage forms are mostly preferred for pediatric and geriatric patients because these are not associated with fear of choking. The fast dissolving films prepared by solvent casting method with suitable appearance, mechanical strength, peel ability and disintegration time were obtained using Methocel E-5 as a primary film former. Meclizine Hydrochloride, a poorly water soluble and bitter drug could be successfully incorporated in the fast dissolving films with the help of solubilizers such as β -Cyclodextrine and Polyethylene glycol-400⁽⁴⁴⁾.

Prasanthi et al., (2011) Formulate a novel fast dissolving drug delivery system of Salbutamol sulphate. The fast dissolving films were prepared by solvent evaporation technique using different water-soluble polymers (hydroxy propyl methylcellulose, hydroxy propyl cellulose and Sodium Alginate). In this study Tween 80 and Aspartame used as solubilizing agent and sweetener respectively. The prepared films were evaluated for thickness, uniformity in drug content, folding endurance, and disintegration time, swelling index, moisture loss, in-vitro drug release studies and drug-polymer compatibility studies. The prepared films were clear, transparent and smooth surface. Film containing hydroxy propyl methylcellulose (2%w/w), Tween 80 (0.5%w/w) and Aspartame (0.5% w/w) showed optimum performance against all other prepared formulations ⁽⁴⁵⁾.

Narasimharao et al., (2011) formulate and evaluate the rapidly dissolving Etophylline films, which is a bronchodilator used in treatment of asthma. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. In order to assist these patients, several fast-dissolving drug delivery systems have been developed. Some of the drugs even take a very long time to dissolve, therefore the drug even takes much longer time to show its activity, hence our work is aimed at fast dissolution of the drug and maximum bioavailability of bronchodilator Etophylline drug by forming thin films which are administered orally⁽⁴⁶⁾.

Dhagla Ram Choudhary et al., (2011) Fast dissolving films of Ondansetron Hydrochloride were prepared by solvent casting technique using carboxy methyl cellulose, hydroxy propyl cellulose, and hydroxy propyl methyl cellulose as film forming polymers. β – Cyclodextrin, neotame and citric acid were employed to mask the bitter taste of Ondansetron hydrochloride. The prepared films were subjected to characterization for mechanical properties. Disintegration time, drug release pattern, mouth dissolving time and content uniformity were also evaluated. Films with 3% hydroxyl propyl methyl cellulose and 10% w/w propylene glycol showed better results as compared to hydroxyl propyl cellulose and carboxy methyl cellulose. Films showed good mechanical properties like, tensile strength, folding endurance and percentage elongation in comparison to other films prepared by using hydroxyl propyl cellulose and carboxy methyl cellulose. Films were disintegrated in time of 23 sec and dissolved in time of 55 sec. These results suggest that hydroxyl propyl methyl cellulose is an excellent film former, that has shown rapid drug release (80% in 120 sec) amongst different cellulose derivatives used to prepare films⁽⁴⁷⁾.

Sapkal NP et.al,(2011) have developed fast dissolving oral thin films of Ambroxol Hydrochloride and effect of formulation variables like concentration of film forming polymer was investigated. Also the effect of emulsifying agent and plasticizer on physicochemical properties and in vitro dissolution studies were identified. HPMC was used as a film former, tween 80 as emulsifying agent and PEG 400 as plasticizer⁴⁹

Ghorwade et al,(2011) have formulated and evaluated fast dissolving films of Montelukast sodium by solvent casting method using HPMC as film base with different concentrations of superdisintegrants like microcrystalline cellulose and crospovidone using PEG 400 as plasticizer. The physicochemical parameters of the fast dissolving films were evaluated. In vitro dissolution studies and mechanism of drug release were identified.²⁴

Joshi et.al,(2012) have formulated and evaluated mouth dissolving films of Domperidone. The solid dispersions of domperidone were prepared with the use of β -cyclodextrins in various ratios (1:1,1:2,1:3) and solubility study was performed to determine in which domperidone solubility was highest. The film was prepared by solvent casting technique utilizing HPMC E15 as film forming agent and PEG 400 as plasticizer. The formulations were evaluated for their thickness, folding endurance, drug content, in vitro disintegration time and in vitro dissolution studies.²⁵

Shelke et al,(2012) have formulated and evaluated rapidly disintegrating films of amlodipine besylate. Fast dissolving film of Amlodipine Besylate was prepared using sodium alginate as film forming polymer. To decrease the disintegration time of formulations, sodium starch glycolate was used as disintegrating agent. The formulations were evaluated for their thickness, folding endurance, drug content, in vitro disintegration time and in vitro dissolution studies.⁴⁸

Bhanushali et al (2011),have formulated and evaluated mouth dissolving tablet of isosorbide mononitrate. The superdisintegrant used was crospovidone. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study.tablets were prepared by direct compression method. Here the disintegration and dissolution rate of isosorbide mononitrate was enhanced to great extent by addition of superdisintegrants.²⁷

Pahade et al,(2010) have formulated and developed bilayer sustained release tablets of isosorbide mononitrate. The tablets were prepared by wet granulation method. Hydrophilic and hydrophobic matrix materials such as hydroxypropyl methylcellulose, and polyox were used, which can release the drug up to 24hrs in predetermined rate.

Binder used was pvp k-30. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied.²³

Margret et al,(2012) have formulated and evaluated sustained release tablet of isosorbide-5-mononitrate by porous osmotic technology.wet granulation technique was used. The coating solutions were prepared by using various polymers and pore formers. The drug release was found to be more with PVP than with HPMC, Ethyl Cellulose and PEG4000. Compatibility evaluation was performed by FT-IR spectroscopy analysis. The study implies that the drug and polymers were compatible with each other.²⁸

Panchal et al,(2012)have formulated and evaluated mouth dissolving films of Ropinirole Hydrochloride by using pullulan polymers for a very quick onset of action. The films were prepared by using polymers such as pullulan and PEG 400 as plasticizer, by a solvent casting method. A marked increase in the % drug release was exhibited by mouth dissolving films of Ropinirole Hydrochloride containing pullulan as a polymer at 60 sec, when compared to other polymers films. Mouth dissolving films of Ropinirole Hydrochloride containing pullulan showed better tensile strength.²⁹

3. SCOPE, OBJECTIVE AND PLAN OF THE WORK

3.1 SCOPE

Isosorbide mononitrate relaxes vascular smooth muscles by stimulating cyclic-GMP. It decreases left ventricular pressure (preload) and arterial resistance (after load).⁽²²⁾

Isosorbide mononitrate is a nitrate-class drug used for the prophylactic treatment of angina pectoris; that is, it is taken in order to prevent or at least reduce the occurrence of angina. Research on isosorbide mononitrate as a cervical ripener to reduce time at hospital to birth is supportive.

It is available in the USA by Kremers Urban under the trade name Monoket, and marketed in the UK under the trade names: Monosorb, Chemydur. In India, this drug is available under the brand names of Ismo, Isonorm, Monotrate, Solotrate, and Monit. Isosorbide mononitrate is available as 10 mg and 20 mg of immediate release tablets. But it is not available as an orally disintegration dosage form.

Isosorbide mononitrate film formulation is useful for bedridden and geriatric patient with Angina pectoris who are unwilling to take solid dosage form. Hence an effort was taken to formulate Isosorbide mononitrate as a mouth dissolving film.

3.2 Objectives

The main objective of present work is to formulate and evaluate fast dissolving oral thin film of Isosorbide mononitrate with the use of polymers like HPMC and PVA for the treatment of angina pectoris.

3.3 Plan of Work

- 1) Literature studies
- 2) Analytical method development
 - Construction of standard curve for Isosorbide mononitrate
- 3) Preformulation studies
 - Drug polymer compatibility by FTIR studies.
- 4) Formulation of Fast dissolving oral films.
 - Selection of polymer
 - Optimization of polymer concentration
 - Preparation of film by solvent casting method.

- 5) Evaluation of fast dissolving films
- Physical appearance and surface texture of film
 - Weight variation.
 - Thickness of film.
 - Tensile strength.
 - Percentage elongation
 - Folding endurance.
 - Surface pH.
 - Dispersion time
 - Disintegrating time
 - Invitro drug release study

4. MATERIALS AND INSTRUMENTS

4.1 LIST OF MATERIALS

S.No	Chemicals and reagents	Supplier
1	Isosorbide mononitrate	RA CHEM Pharma, Hyderabad
2	Hydroxy propyl methyl cellulose 5cps (Hyperomellose)	S.D.Fine chem Ltd. Mumbai
3	Poly vinyl alcohol(Medium viscosity; Molecular weight: 1,25000)	S.D.Finechem Ltd. Mumbai
4	Sucralose	S.D Finechem Ltd. Mumbai
5	Pineapple Flavour	
6	Glycerine	Vama pharma. Nagpur

Table No.3, List of Materials

4.2 List of Instrument Used

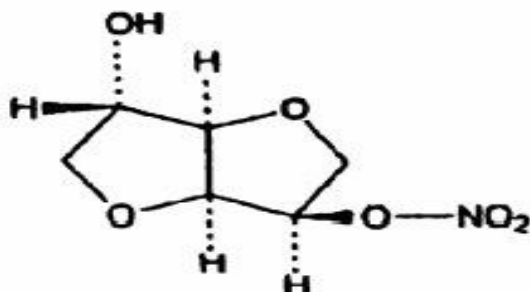
Sr.no.	Name of instrument/ Equipments	Manufacture
1	Electronic balance(BL-2200H)	Shimadzu corporation
2	pH-meter	Universal biochemals
3	Dissolution apparatus	Lab India Disso-2000
4	UV-Visible double beam spectrophotometer	Systronic 118
5	Bath Ultrasonicator	Life care
6	FTIR spectrophotometer	Perkin Elmer
7	Desiccator	Qualigens Fine Chem. Mumbai
8	Dial gauge	Baker Precision measuring instruments
9	Magnetic stirrer (2MLH)	Remi equipment Pvt. Ltd. Mumbai
11	Heating mantle	Guna enterprises, Chennai
12	Vacuum oven	Shavani scientific Pvt. Ltd. Bombay
13	TA.XT plus Texture analyser	Stable Microsystems, U.K
14	Microwave oven	Magic cook, Whirlpool

4.3
DRUG

PROFILE

ISOSORBIDE MONONITRATE

Structure: -


 $C_6H_9NO_6$

M. W. · 191.14

Formula	: $C_6H_9NO_6$
IUPAC Name	: 8-nitrooxy-2,6-dioxabicyclo[3.3.0]octan-4-ol
BCS Class	: Class 1
Molecular Weight	: 191.14 g/mol
pka (dissociation constant)	: -3.9
Category	: Anti Anginal, Vasodilator Agents
Description	: Colourless prismatic crystals
Solubility	: Soluble in water, methanol, ethanol and chloroform
Melting Point	: 89°C
Partition coefficient (logP)	: -0.2
Volume of distribution	: 0.6 to 0.7 L/kg.
Protein binding	: Plasma protein binding is <5%
Mechanism of Action	

Isosorbide Mononitrate is converted to nitric oxide (NO), an active intermediate compound which activates the enzyme guanylate cyclase (Atrial natriuretic peptide receptor A). This stimulates the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP) which then activates a series of protein kinase-dependent phosphorylations in the smooth muscle cells, eventually resulting in the dephosphorylation of the myosin light chain of the smooth muscle fiber. The subsequent release of calcium ions results in the relaxation of the smooth muscle cells and vasodilation.

Pharmacodynamics

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

Pharmacokinetics:-

Absorption/ Distribution

Isosorbide-5-mononitrate is rapidly and completely absorbed from the conventional dosage forms. Unlike isosorbide dinitrate, isosorbide mononitrate is free from first-pass metabolism in the liver, and its bioavailability therefore shows lower inter-individual variability. AUC values assessed by reference to the plasma levels increase linearly with the dose. With Corangin, the peak concentrations attained are approximately 60% lower than after administration of the same dose in conventional dosage forms. Peak concentrations are reached 4-8 hours after ingestion of Corangin and in less than 1 hour after administration of conventional formulations. The amount absorbed from sustained-release formulations such as Corangin is slightly reduced (by 10-20%) in comparison with conventional formulations. No accumulation of isosorbide-5-mononitrate was seen

after repeated once-daily administration in normal volunteers or in patients. The results of pharmacokinetic studies suggest that no alterations of the dosage should be necessary in patients with coronary heart disease, renal failure, or hepatic cirrhosis. Ingestion of food has been reported to have only a negligible effect on the absorption of isosorbide-5-mononitrate. The volume of distribution of isosorbide mononitrate is approximately 0.6 L/kg, which is close to the total body water. The plasma protein binding of isosorbide mononitrate is negligible.

Metabolism

Isosorbide mononitrate is almost completely metabolized in the liver. The resulting metabolites are inactive.

Elimination

Isosorbide mononitrate is excreted via the kidneys almost exclusively in the form of metabolites. Approximately 2% is excreted via the kidneys in unchanged form. Mean half lives of isosorbide-5-mononitrate calculated after administration of conventional formulations range between 4.0 and 4.8 hours.

Contraindications

Isosorbide Mononitrate Extended-Release Tablets are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrites

Drug interactions

The vasodilating effects of Isosorbide Mononitrate may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Therapeutic uses

Isosorbide mononitrate is a nitrate class drug used for the prophylactic treatment of angina pectoris; that is, it is taken in order to prevent or at least reduce the occurrence of angina.

Adverse Reactions

Autonomic Nervous System Disorders: Dry mouth, hot flushes.

Body as a Whole: Asthenia, back pain, chest pain, edema, fatigue, fever, flu-like symptoms, malaise, rigors.

Cardiovascular Disorders, General: Cardiac failure, hypertension, hypotension.

Central and Peripheral Nervous System Disorders: Dizziness, headache, hypoesthesia, migraine, neuritis, paresis, paresthesia, ptosis, tremor, vertigo.

Gastrointestinal System Disorders: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gastric ulcer, gastritis, glossitis, hemorrhagic gastric ulcer, hemorrhoids, loose stools, melena, nausea, vomiting.

Hearing and Vestibular Disorders: Earache, tinnitus, tympanic membrane perforation.

Heart Rate and Rhythm Disorders: Arrhythmia, arrhythmia atrial, atrial fibrillation, bradycardia, bundle branch block, extrasystole, palpitation, tachycardia, ventricular tachycardia.

Liver and Biliary System Disorders: SGOT increase, SGPT increase.

Metabolic and Nutritional Disorders: Hyperuricemia, hypokalemia.

Musculoskeletal System Disorders: Arthralgia, frozen shoulder, muscle weakness, musculoskeletal pain, myalgia, myositis, tendon disorder, torticollis.

Myo-, Endo-, Pericardial and Valve Disorders: Angina pectoris aggravated, heart murmur, heart sound abnormal, myocardial infarction, Q wave abnormality.

Platelet, Bleeding and Clotting Disorders: Purpura, thrombocytopenia.

Psychiatric Disorders: Anxiety, concentration impaired, confusion, decreased libido, depression, impotence, insomnia, nervousness, paroniria, somnolence.

Red Blood Cell Disorder: Hypochromic anemia.

Reproductive Disorders, Female: Atrophic vaginitis, breast pain.

Resistance Mechanism Disorders: Bacterial infection, moniliasis, viral infection.

Respiratory System Disorders: Bronchitis, bronchospasm, coughing, dyspnea, increased sputum, nasal congestion, pharyngitis, pneumonia, pulmonary infiltration, rales, rhinitis, sinusitis.

Skin and Appendages Disorders: Acne, hair texture abnormal, increased sweating, pruritus, rash, skin nodule.

Urinary System Disorders: Polyuria, renal calculus, urinary tract infection.

Vascular (Extracardiac) Disorders: Flushing, intermittent claudication, leg ulcer, varicose vein.

Vision Disorders: Conjunctivitis, photophobia, vision abnormal.

Overdosage

Hemodynamic Effects

The ill effects of Isosorbide Mononitrate overdose are generally the result of Isosorbide Mononitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo, palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Methemoglobinemia

Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of Isosorbide Mononitrate. Certainly nitrate ions liberated during metabolism of Isosorbide Mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moiety of Isosorbide Mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of Isosorbide Mononitrate should be required before any of these patients manifest clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of Isosorbide Mononitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8-11.1 mg of Isosorbide Mononitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Dosage

The recommended starting dose of Isosorbide Mononitrate is 30 mg once daily. After several days, the dosage may be increased to 120 mg once daily. Rarely, 240 mg may be required. The daily dose of Isosorbide Mononitrate should be taken in the morning on arising. (21)

4.4 POLYVINYL ALCOHOL⁽²²⁾

Nonproprietary Names

PhEur: Poly (vinylis acetat)

USP: Polyvinyl alcohol

Synonyms: Airvol; Alcotex; Elvanol; Gelvatol; Gohsenol; Lemol; Mowiol; Polyvinol; PVA, vinyl alcohol polymer.

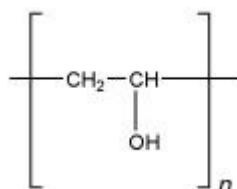
Chemical Name: Ethenol, homopolymer

Empirical Formula: (C₂H₄O)_n

Molecular Weight: 20 000–200 000

Polyvinyl alcohol is a water-soluble synthetic polymer represented by the formula (C₂H₄O)_n. The value of *n* for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately (20 000–200 000)

Structural Formula:



Description: Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

Melting point: 228°C for fully hydrolyzed grades;

180–190°C for partially hydrolyzed grades.

Functional Category: Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

Solubility

Soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 90°C for approximately 5 minutes. Mixing should be continued while the heated solution is cooled to room temperature.

Specific gravity:

1.19–1.31 for solid at 25°C;

1.02 for 10% w/v aqueous solution at 25°C.

Specific heat: 1.67 J/g (0.4 cal/g)

Grade	Dynamic viscosity of 4% w/v aqueous solution at 20°C (mPa s)
High viscosity	40.0–65.0
Medium viscosity	21.0–33.0
Low viscosity	4.0–7.0

Table No.5 Viscosity of commercial grades of polyvinyl alcohol.

Applications in Pharmaceutical Formulation or Technology:

Polyvinyl alcohol is primarily used in topical pharmaceutical and ophthalmic formulations; it is a stabilizing agent for emulsions (0.25–3.0% w/v). For viscous formulations such as ophthalmic products Polyvinyl alcohol is also used as a viscosity-increasing agent. It is used in contact lens and artificial tears solutions for lubrication purposes. Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution. It is also used in transdermal patches.

Stability and Storage Conditions:

Polyvinyl alcohol is stable in cool, dry place when it is stored in tightly sealed container. Aqueous solutions are stable in corrosion-resistant sealed containers. Preservatives needed to the solution if extended storage is required. Polyvinyl alcohol slow degradation undergoes at temperature 100°C and rapid degradation at 200°C; it is stable on exposure to light.

Incompatibilities:

Polyvinyl alcohol undergoes reactions typical of a compound with secondary hydroxy groups, such as esterification. It decomposes in strong acids, and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulfates and phosphates; precipitation of polyvinyl alcohol 5% w/v can be caused by phosphates. Gelling of polyvinyl alcohol solution may occur if borax is present.

Safety

Polyvinyl alcohol is a nontoxic material. It is nonirritant to the skin and eyes at

concentrations up to 10%; concentrations up to 7% are used in cosmetics.

Studies in rats have shown that polyvinyl alcohol 5% w/v aqueous solution injected subcutaneously can cause anemia and infiltrate various organs and tissues.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Polyvinyl alcohol dust may be an irritant on inhalation. Handle in a well-ventilated environment.

4.5 HYDROXYPROPYL METHYLCELLULOSE⁽²²⁾

Non-proprietary Names : BP: Hypromellose

JP: Hydroxypropylmethylcellulose

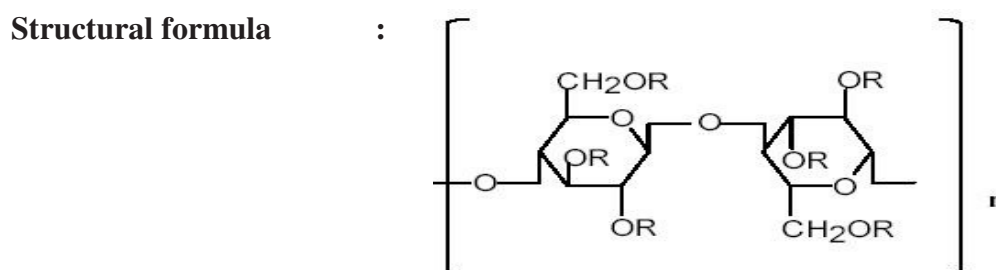
PhEur: Hypromellosum

USP: Hypromellose

Synonyms : Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Chemical Name : Cellulose hydroxypropyl methyl ether

Description : Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder



Functional Category : Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Typical Properties:

Density (bulk) : 0.341 g/cm³

Density (tapped) : 0.557 g/cm³

Density (true) : 1.326 g/cm³

Melting point : browns at 190–200°C; chars at 225–230°C

Solubility : Easily dispersed in water at all temperatures forming clear, colloidal solutions. The Aqueous solubility varies with the degree of substitution.

Practically insoluble in acetone, ethanol (95%), ether, and toluene.

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions.

Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative:

when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Applications

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-

coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

4.6 GLYCERINE⁽²²⁾

Non proprietary names: BP: Glycerol

USP: Glycerin

PhEur: Glycerolum

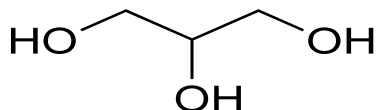
Synonyms: Croderol; E422; glycerine; Glycon G-100; Kemstrene; Optim; Pricerine; 1,2,3-propanetriol; trihydroxypropane glycerol.

Chemical Name: Propane-1,2,3-triol

Empirical Formula: C₃H₈O₃

Molecular Weight: 92.09

Structural Formula:



Functional Category: Antimicrobial preservative; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent

Description

Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

Typical Properties

Boiling point: 290°C (with decomposition)

Density: 1.2636 g/cm³ at 20°C

Flash point: 176°C (open cup)

Hygroscopicity: hygroscopic.

Melting point: 17.88°C

Solubility: Soluble in 95% ethanol, methanol, and water, slightly soluble in acetone, practically insoluble in benzene and chloroform

Applications

Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, topical, and parenteral preparation. In topical pharmaceutical formulations and cosmetics; glycerin is used primarily for its humectant and emollient properties. In parenteral formulations, glycerin is used mainly as a solvent. In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative, and viscosity increasing agent. It is also used as a plasticizer and in film coatings. Glycerin is additionally used in topical formulations such as creams and emulsions. Glycerin is used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories. Glycerin is

employed as a therapeutic agent in a variety of clinical applications, and is also used as a food additive.

Stability and Storage Conditions

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions but it decomposes on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol (95%), and propylene glycol are chemically stable. Glycerin may crystallize if stored at low temperatures; the crystals do not melt until warmed to 20°C. Glycerin should be stored in an airtight container, in a cool, dry place.

Incompatibilities

Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate, or potassium permanganate. In dilute solution, the reaction proceeds at a lower rate with several oxidation products being formed. Black discoloration of glycerin occurs in the presence of light, or on contact with zinc oxide or basic bismuth nitrate. An iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates, and tannin. Glycerin forms a boric acid complex, glyceroboric acid, that is a stronger acid than boric acid.

Safety

Glycerin occurs naturally in animal and vegetable fats and oils that are consumed as part of a normal diet. Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats. Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, parenteral, and topical preparations. Adverse effects are mainly due to the dehydrating properties of glycerin. Oral doses are demulcent and mildly laxative in action. Large doses may produce headache, thirst, nausea, and hyperglycemia. The therapeutic parenteral administration of very large glycerin doses, 70–80 g over 30–60 minutes in adults to reduce cranial pressure, may induce hemolysis, hemoglobinuria, and renal failure. Slower administration has no deleterious effects.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the recommended long-

term (8-hourTWA) exposure limit for glycerin mist is 10 mg/m³. Glycerin is combustible and may react explosively with strong oxidizing agents;

4.7 SUCRALOSE⁽²²⁾

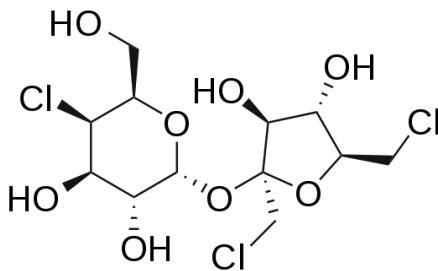
Nonproprietary Names

USPNF: Sucralose

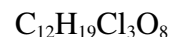
Synonyms: Splenda; TGS; 10, 40, 60-trichlorogalactosucrose; 4,10,60-trichloro-4,10,60-trideoxy-galacto-sucrose

Chemical Name: 1,6-Dichloro-1,6-dideoxy-b-D-fructofuranosyl-4-chloro-4-deoxy-a-D-galactopyranoside

Structural formulae:



Empirical Formula:



Molecular Weight: 397.63

Functional Category: Used as a sweetener in pharmaceutical formulations

Description

Sucralose is a white to off-white colored, free-flowing, crystalline Powder.

Typical Properties

Acidity/alkalinity: pH = 5–6 (10% w/v aqueous solution at 208C)

Density (bulk): 0.35 g/cm³

Density (tapped): 0.62 g/cm³

Density (true): 1.63 g/cm³

Melting point: 1308C (for anhydrous crystalline form); 36.5°C

Particle size distribution: 90% < 12 mm in size.

Partition coefficient: log₁₀ P = —0.51 (octanol:water)

Solubility: freely soluble in ethanol (95%), methanol, and water; slightly soluble in ethyl acetate.

Stability and Storage Conditions

Sucralose is a relatively stable material. In aqueous solution, at highly acidic conditions (pH < 3), and at high temperatures(4358C), it is hydrolyzed to a limited extent, producing 4-chloro-4-deoxygalactose and 1,6-dichloro-1,6-dideoxyfructose. In food products, sucralose remains stable throughout extended storage periods, even at low pH. However, it is most stable at pH 5–6. Sucralose should be stored in a well-closed container in a cool, dry place, at a temperature not exceeding 218C. Sucralose, when heated at elevated

temperatures, may break down with the release of carbon dioxide, carbon monoxide, and minor amounts of hydrogen chloride.

Safety

Sucralose is generally regarded as a nontoxic and nonirritant material and is approved, in a number of countries, for use in food products. Following oral consumption, sucralose is mainly unabsorbed and is excreted in the feces. The WHO has set an acceptable daily intake for sucralose of up to 15 mg/kg body-weight

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

5 EXPERIMENTAL METHOD

5.1 Analytical Method of Development

5.1.1 Identification of λ_{\max} for Isosorbide Mononitrate

Isosorbide mononitrate accurately weighed and dissolved in purified water and further diluted was made to get the required concentration. The wave length of maximum absorbance (λ_{\max}) of this clear solution was determined from 200-280nm using distilled water is used as blank.

5.1.2 Construction of Standard Curve for Isosorbide mononitrate

Procedure:

5.1.2.1 Preparation of stock solution

100mg of isosorbide mononitrate is weighed and dissolved in 100ml water. From this solution 1 ml was pipetted out and diluted with water up to 100ml mark as stock solution.

5.1.2.2 Preparation of sample solution:

Further dilution was carried out to obtain the concentration of 1, 2, 3,4,5,6,7,8,9 and 10 $\mu\text{g/ml}$ respectively. The absorbance was measured at 220 nm against the respective blank solution using UV visible spectrophotometer Perk-Elmer Lambda 40 P. The standard curves were plotted by putting the known concentration on X- axis and the obtained absorbance on Y- axis.

5.2 Drug Polymer Compatibility Studies:

Excipients are the essential component of a dosage form. The formulation of stable effective dosage forms depends on the care full selection of the excipient. Infrared spectroscopy for pure drug Isosorbide mononitrate and polymers used for formulation were testify to check the intactness of drug and polymer in the formulation using Perkin Elmer model furrier transform infrared spectrometer by KBr disk method.

5.4 Preparation of film

5.4 .1 Calculation of dose for Isosorbide mononitrate

The dose selected for development is 10mg. Isosorbide mononitrate contains lactose monohydrate by which each 12.5mg contains 10mg equivalent Isosorbide mononitrate.

Film diameter of 2.6 cm was selected for a single dose. Based on the petridish surface area, amount of drug required was calculated for every batch.

For example petridish with diameter of 8 cm (surface area: 5.31 sq.cm), 118.39 mg of isosorbide mononitrate with lactose was taken.

From the preliminary physical observation of the prepared placebo to optimize polymer concentration and composition films the best compositions were used for the incorporation of Isosorbide mononitrate. PVA, HPMC and combination of both PVA and HPMC was dissolved in water with continuous stirring. Calculated amount of Isosorbide mononitrate was dissolved in the polymeric solution. After complete dissolution of the drug, Sucralose, pineapple flavor and glycerin (plasticizer) were added and stirred to form a homogeneous solution. The solution was casted in a petridish then kept in microwave oven at 50°C for 45 minutes. Further drying was computed using vacuum oven at 35°C by applying vacuum. The film thus formed was cut into size of 2.6 cm diameter. Each film contains 12mg of Isosorbide mononitrate equivalent to 10mg of Isosorbide mononitrate. The detailed compositions of the Isosorbide mononitrate films are given in Table

Formulation	Isosorbide mononitrate (mg)	HPMC (mg)	PVA (mg)	Glycerine (mg)	Sucralose (mg)	Pine apple flavour	Purified Water (ml)
B1	12.5	200	-	60	50	0.05 ml	5
B2	12.5	-	250	-	50	0.05ml	5
B3	12.5	200	250	-	50	0.05ml	5

Table No.6 Composition of Oral Thin Film Formulation

5.5 EVALUATION OF FAST DISSOLVING FILM FORMULATION

5.5.1 Physical appearance and surface texture of films

These parameters were checked simply with visual infection of films and by feel or touch. The observation suggests that the films are having smooth surface and they are elegant enough to see.

5.5.2 Thickness:

All the batches were evaluated for thickness by using calibrated Thickness gauge Baker, typeK17 jeweled (0.001- 0.1 mm). Three samples from all the batches was withdrawn and evaluated for thickness.

5.5.3 Uniformity of weight:

Each film was weighed individually on electronic balance and average weight of three films was found.

5.5.4 Folding endurance:

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly

folding a small strip of the films at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

5.5.5 Tensile strength

Tensile strength of the films was determined by using Texture Analyzer (Stable micro system)

Tensile strength (kg/cm^2) = Force at break / Initial cross sectional area of the film

5.5.6 Percentage elongation

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.

$$\text{Percentage Elongation} = [L - L_0] \times 100 / L_0$$

Where, L was the Final length, L₀ was initial length.

5.5.7 Surface pH:

Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing pH paper near the surface of films.

5.5.8. Drug content

The films were tested for drug content by UV-Spectrophotometric method at 220nm. A film of 8 cm diameter was dissolved in purified water and diluted to get a concentration of 1 $\mu\text{g/ml}$. The absorbance was measured at 210 nm against blank. The amount of drug was calculated using standard graph. The drug content analysis was performed in triplicate.

5.5.9. Content Uniformity

Ten films were individually assayed for their drug content. Films of 2.6 cm diameter were dissolved in 10 ml water from this 1ml is taken and diluted to 100ml with water, from this 1ml is withdrawn and make up the volume up to 100ml with water to get a concentration of 1 $\mu\text{g/ml}$. The requirements for content uniformity are met if the amount of the active ingredient in each tablet within the range of 85-115% of the label claims.

5.5.10. *In-vitro* Dispersion Time

In-vitro dispersion time was measured by dropping a in petridish with 6 ml of water three films from each formulation were randomly selected and *in-vitro* dispersion time was performed

5.5.11 *In-vitro* dissolution studies

The release study was carried out in a USP dissolution apparatus type VI. The dissolution medium was 900 ml water maintained at 37⁰C and kept in a glass beaker fixed inside the USP dissolution flask. The film was fixed to the central axis, which rotated at 50 rpm. Filtered samples (2ml.) were manually collected at 2,5,10,15,20 and 30 min. The samples were compensated with an equal volume of purified water kept at the same temperature. The concentration of drug released in the medium was assayed spectrophotometrically at 220 nm after suitable dilution with the dissolution medium.

Dissolution parameters

Dissolution Medium : Purified water ,900ml

RPM : 50

Apparatus : Dissolution apparatus Type VI (CylinderApparatus)

Temperature : 37°C ± 0.5°C

Withdrawal time : 2,5,10,15,20,and 30min.

Volume withdraw : 2ml

6 Analytical Method Development

6.1 Construction of Standard Curve for Isosorbide mononitrate

The wave length of maximum absorbance of drug was found to be 220 nm. Beer lambertz law obeying range was found to be in the range of 1-10 μ g/ml at 210 nm against water is used as blank.

**Table No.6 Standard Curve of Isosorbide mononitrate
Absorbance of Isosorbide mononitrate in Distilled water**

CONCENTRATION (μ g/ml)	ABSORBANCE
1	0.027
2	0.053
3	0.083
4	0.103
5	0.135
6	0.156
7	0.18
8	0.215
9	0.235
10	0.265

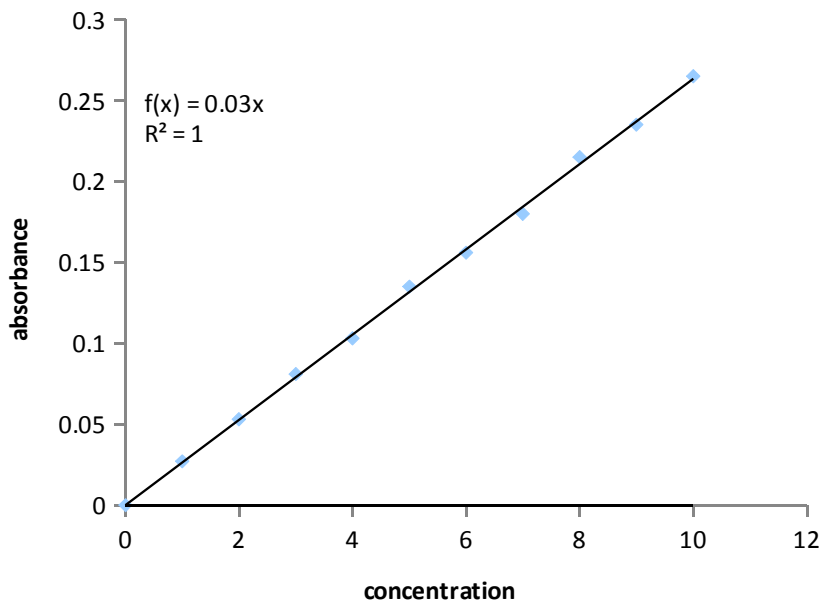


Figure No.3, Calibration Curve for Isosorbide mononitrate in distilled water in 220nm

6.2 Drug-Polymer Compatibility Study

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by using Perkin Elmer model furrier transform infrared spectrometer by KBr disk method.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for all formulations are shown below.

RESULTS AND DISCUSSION

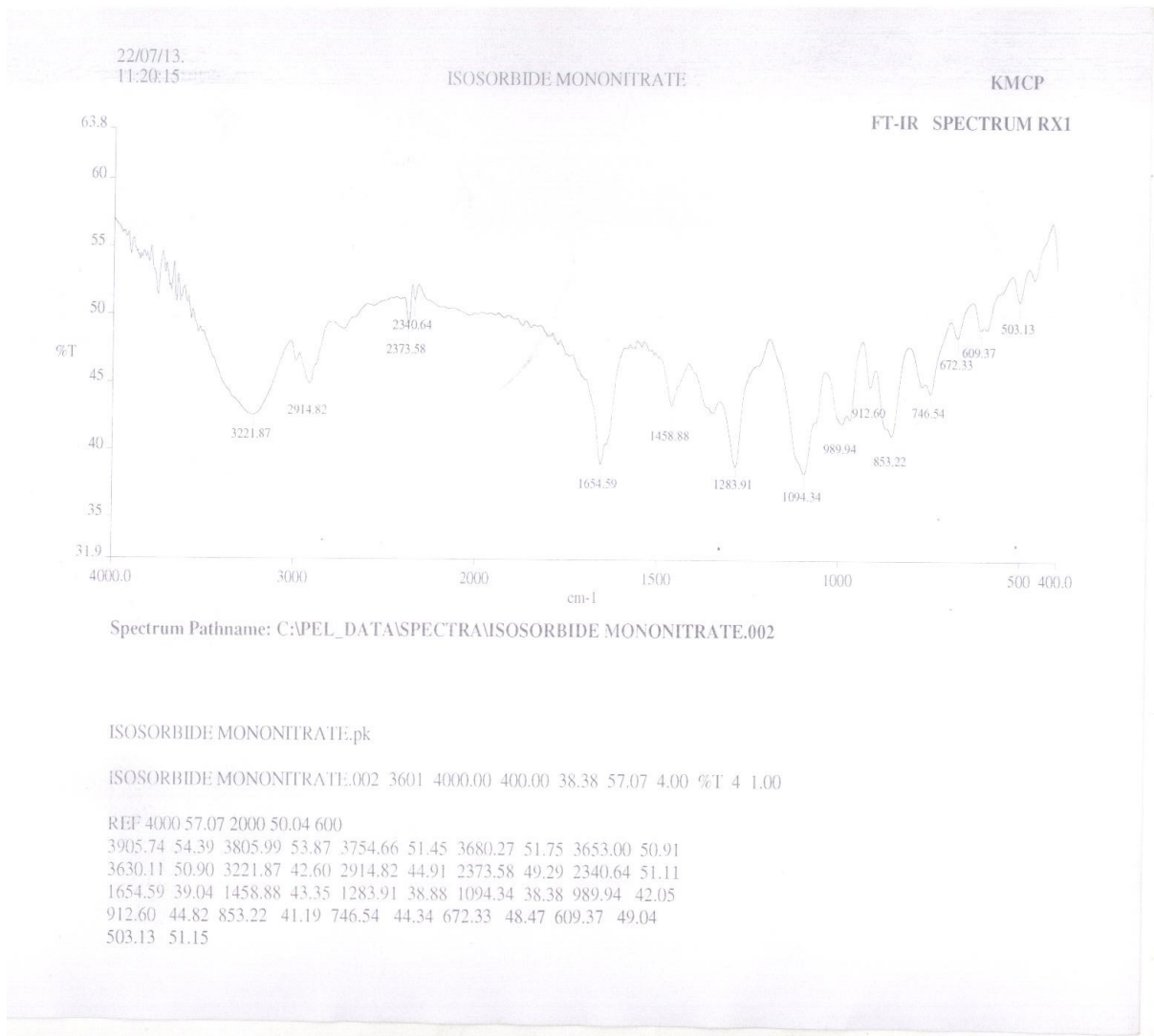


Figure No : 4 , FTIR studies for Isosorbide mononitrate

Wave number cm^{-1}	Characteristic band
3221.87	C-H alkyne
2914.82	C-H stretching
1458.88	-NO ₂
1904.34	C-O-C stretching

RESULTS AND DISCUSSION

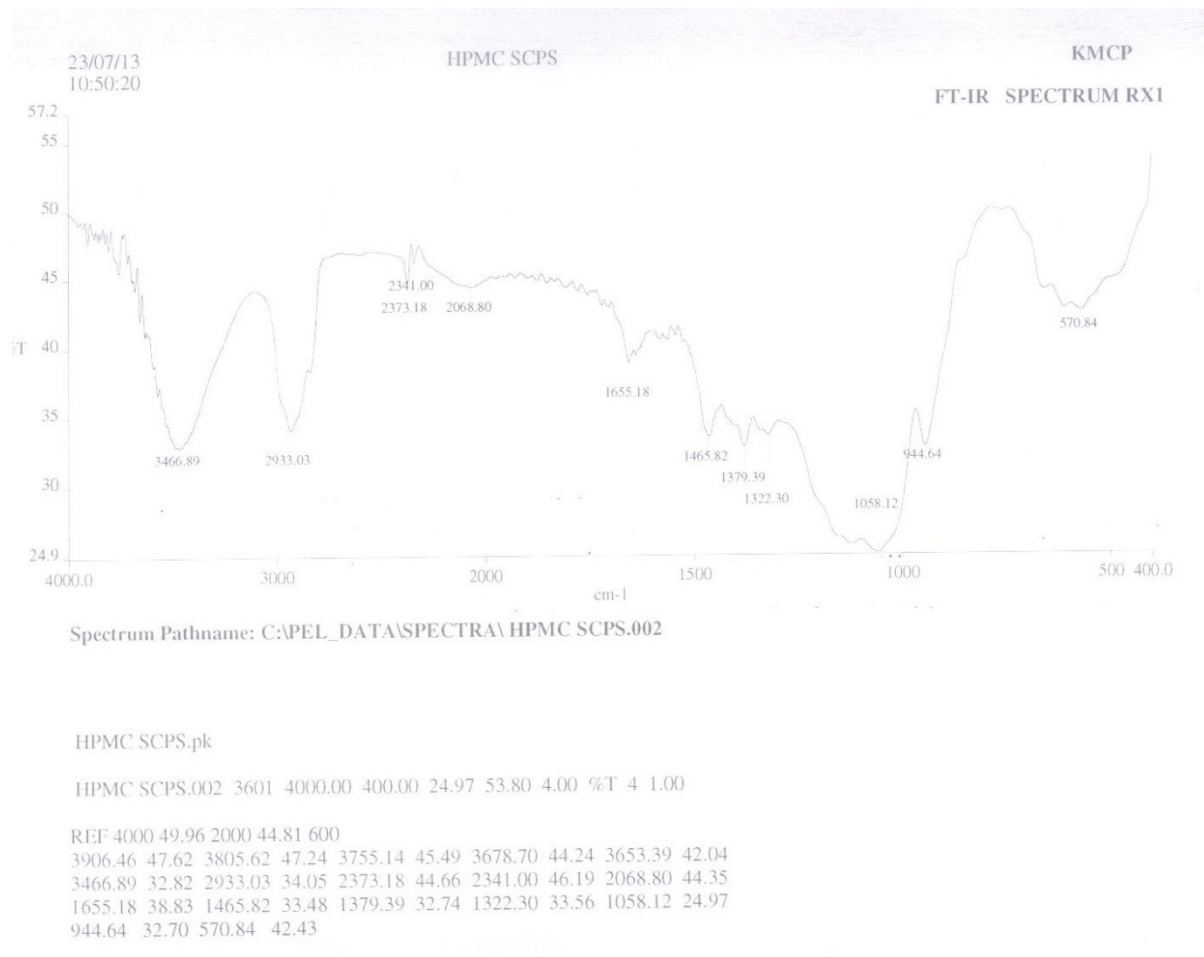


Figure No: 5, FTIR Studies for Hydroxy propyl methyl cellulose

Wave number in cm^{-1}	Characteristic band
3466.89	OH stretching
2933.03	C-H stretching
1655.18	C-O stretching
1465.82	C-H deformation
944.64	C-H deformation

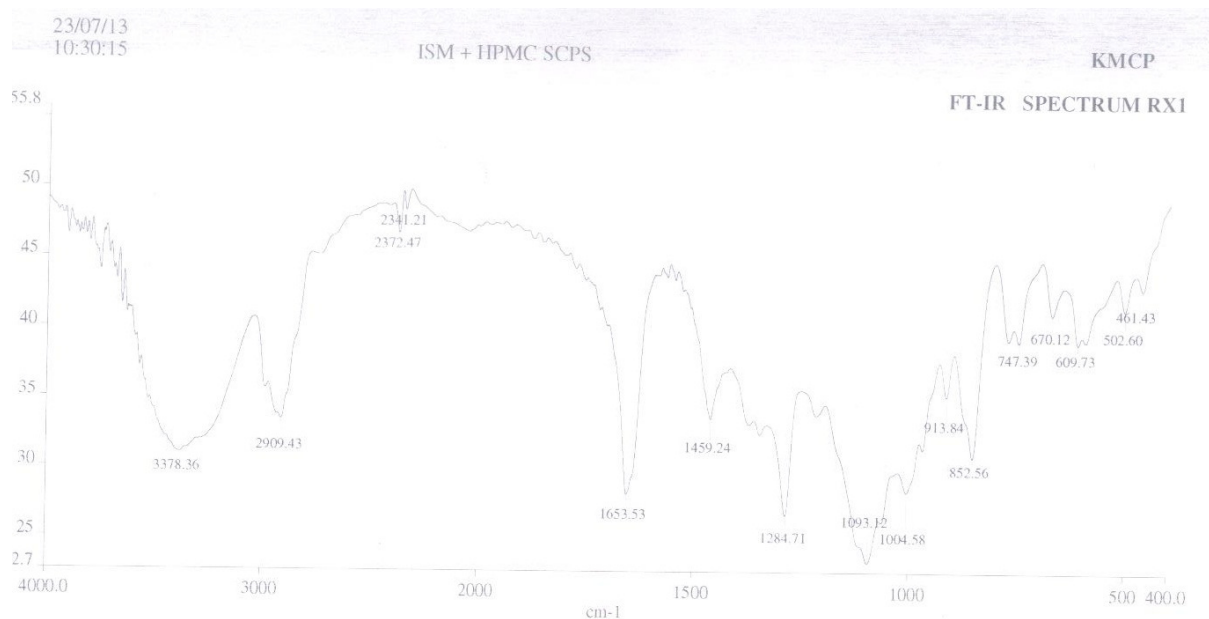
RESULTS AND DISCUSSION



Figure No: 6, FTIR studies for Poly vinyl alcohol

Wave number in cm^{-1}	Characteristic band
3452.33	O-H stretching
1582.79	C=C stretching
1093.99	C-C stretching

RESULTS AND DISCUSSION



Spectrum Pathname: C:\PEL_DATA\SPECTRA\ISM + HPMC SCPS.002

ISM + HPMC SCPS.pk

ISM + HPMC SCPS.002 3601 4000.00 400.00 23.33 49.83 4.00 %T 4 1.00

REF 4000 49.16 2000 47.23 600

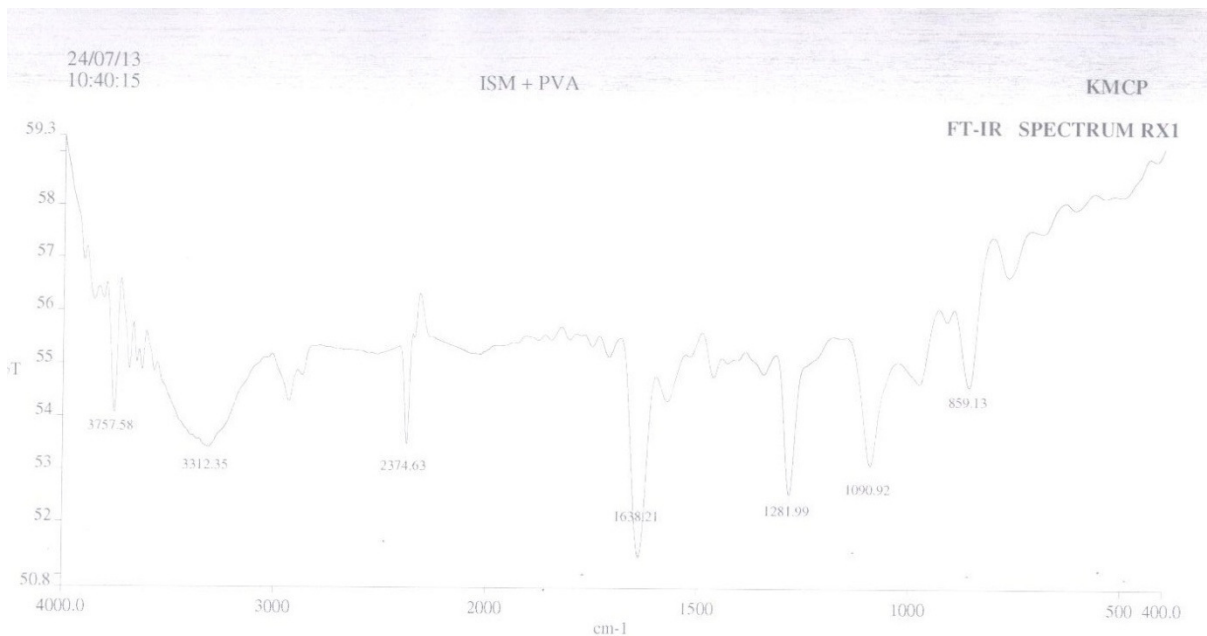
3906.22 46.54 3855.74 46.48 3805.51 46.00 3754.43 44.01 3678.32 43.34
 3653.51 41.58 3378.36 31.03 2909.43 33.47 2372.47 46.72 2341.21 48.39
 1653.53 28.18 1459.24 33.58 1284.71 26.71 1093.12 23.33 1004.58 28.41
 913.84 35.26 852.56 30.91 747.39 39.14 670.12 41.07 609.73 39.05
 502.60 41.48 461.43 42.92

Figure No.7, FTIR Studies for Isosorbide mononitrate and Hydroxy propyl methyl cellulose

Wave number in cm^{-1}	Characteristic band
3221.87	C-H alkyne
2914.82	C-H stretching
1904.34	C-O-C stretching
3466.89	OH stretching
2933.03	C-H stretching

RESULTS AND DISCUSSION

1655.18	C-O stretching
1465.82	C-H deformation
944.64	C-H deformation
1904.34	C-O-C stretching



Spectrum Pathname: C:\PEL_DATA\SPECTRA\ISM + PVA.003

ISM + PVA.pk

ISM + PVA.003 3601 4000.00 400.00 51.36 59.32 4.00 %T 4 1.00

REF 4000 59.32 2000 55.25 600

3757.58 54.06 3312.35 53.42 2374.63 53.49 1638.21 51.36 1281.99 52.55
1090.92 53.11 859.13 54.58

Figure No.8, FTIR Studies for Isosorbide mononitrate and Poly vinyl alcohol

Wave number cm^{-1}	Characteristic band
3221.87	C-H alkyne
2914.82	C-H stretching
1458.88	-NO ₂
1904.34	C-O-C stretching
3452.33	O-H stretching
1582.79	C=C stretching
1093.99	C-C stretching

Results shows that there is no interaction between drug and excioient

6.3 Evaluation of Fast dissolving film formulation

6.3.1 Physical appearance and surface texture of films:

These parameters were checked simply with visual infection of films and by feel or touch. The observation suggests that the films are having smooth surface and they are elegant enough to see.

6.3.2 Uniformity of weight

The weight of prepared films was determined using electronic balance and the average weight of all film was given in the table no.7

The weight of films measured with with HPMC,PVA and combination of both PVA and HPMC were about 40.51 ± 0.63 , 45.83 ± 0.95 and 43.43 ± 1.26 mg respectively.

In all the cases the calculated standard deviation values are very low which suggest that the prepared films were uniform in weight.

6.3.3 Thickness:

Thickness of the film was another parameter. Thickness of the all formulated film was given in the table no.7

RESULTS AND DISCUSSION

The thickness of films measured with HPMC, PVA and combination of both PVA and HPMC were about 51.2 ± 7.50 , 68 ± 3.012 and 67.5 ± 10.68 mm respectively.

In all the cases the calculated standard deviation values are very low which suggest that, the prepared films were uniform in thickness

6.3.4 Folding endurance:

Folding endurance is the index of ease of handling the film which reveals good film properties. All films exhibited folding endurance above proving the flexible nature of the film. Folding endurance of formulated film was given in the table no.7

The folding endurance of films prepared with HPMC, PVA and combination of both PVA and HPMC were about 237.3 ± 4.93 , 26.6 ± 7.6 and 256 ± 8.02 respectively.

6.3.5 Tensile strength

The tensile strength of all the formulation was carried out by texture analyzer. The result was shown in table no.7. Film with PVA showed higher tensile strength than other two formulations.

6.3.6 Percentage elongation

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.

$$\text{Percentage Elongation} = [L - L_0] / L_0$$

Where, L was the Final length, L₀ was initial length. The result was shown in table no.7

The results indicate that films PVA shown higher elongation (160%) time than other two formulations.

6.3.7 Surface pH

Surface pH was determined by the films were allowed in contact with 1ml of distilled

water. The surface pH of the films prepared with HPMC, PVA and combination of both HPMC and PVA were about 6.67 ± 0.154 , 6.89 ± 0.122 and 6.65 ± 0.111 respectively.

Considering the fact that acidic or alkaline pH may cause irritation to the oral mucosa and influence the degree of hydration of polymer, the surface pH of the fast films was determined to optimize drug permeation. Attempts were made to keep the surface pH as close to salivary pH as possible, by the proper selection of the polymer for developing the fast films. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of different films.

The standard deviation values calculated for all the films are very low which conclude that the surface pH of all the films was uniform and within the ranges. The result was shown in table no.7

6.3.8 Drug content and content uniformity

Isosorbide mononitrate films prepared with various polymers were analyzed for drug content and content uniformity. The average drug content and content uniformity results were shown in Table no.7. The drug content was in the range of 99.8 to 100.6%. The drug content and content uniformity were found within pharmacopeial limit. Both the result suggesting that drug was uniformly dispersed throughout all films.

6.3.9 *In-vitro* Dispersion Time

In-vitro dispersion time of formulated film was given in the table no.7

The *In-vitro* dispersion time of the films prepared with HPMC, PVA and combination films were about 6.3 ± 1.53 , 24.6 ± 1.53 and 16.7 ± 2.52 respectively.

RESULTS AND DISCUSSION

Formulation code	Weight (mg) (n=10)	Thickness (μ m) (n=10)	Folding endurance (n=10)	Surface pH (n=10)	Drug content (mg)%	Content Uniformity (n=10)	Tensile strength Kg/cm ² (n=4)	Percentage Elongation (n=4)	Invitro Dispersion Time in sec (n=4)
Batch-1	40.51 \pm 0.43	51.2 \pm 2.50	237.3 \pm 4.9	6.67 \pm 0.154	99.8 \pm 1.10	98.9 \pm 1.2	0.25 \pm 0.39	4.3 \pm 23.79	6.3 \pm 1.53
Batch-2	45.83 \pm 0.35	68 \pm 2.012	326.6 \pm 2.6	6.89 \pm 0.122	100.6 \pm 1.23	99.3 \pm 2.5	0.58 \pm 0.72	160 \pm 53.31	24.6 \pm 1.53
Batch-3	43.43 \pm 1.16	67.5 \pm 4.68	256 \pm 2.02	6.65 \pm 0.111	99.6 \pm 1.25	99.0 \pm 1.58	0.25 \pm 0.40	3.8 \pm 60.19	16.7 \pm 2.52

Table No: 7, Physicochemical Evaluations of Oral Thin Films

6.3.10 *In vitro* Dissolution Study

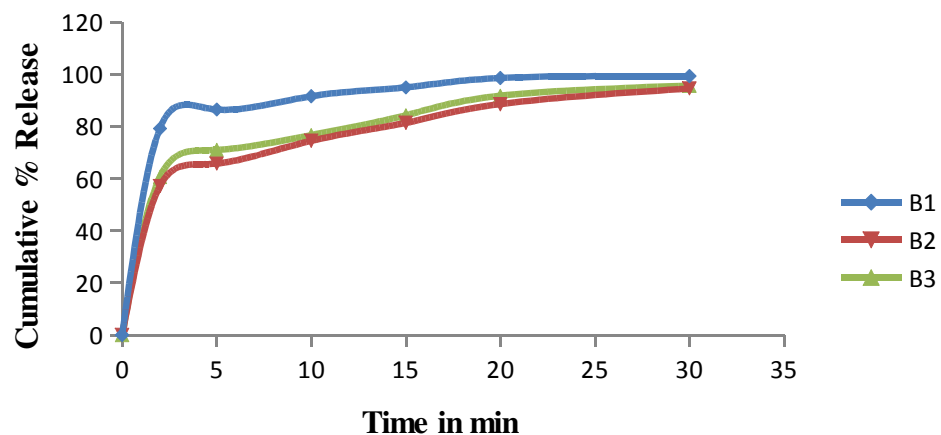


Figure No .8, Comparative Dissolution Profiles of B 1, B 2, B3.

Time (min)	Cumulative percentage of drug release		
	B1	B2	B3
2	79.2	57.1	60.6
5	86.4	65.7	70.9
10	91.5	74.4	76.6
15	94.9	81.3	84.2
20	98.5	88.5	91.7
30	99.2	94.5	95.6

Table No : 8, Dissolution Study in Distilled water

RESULTS AND DISCUSSION

The dissolution results indicate that rate and extent of films formulated with HPMC was better than other 2 formulations. Hence film formulated with HPMC was selected as a final formula.

7. SUMMARY AND CONCLUSION

Summary

Formulation and Evaluation of fast dissolving oral film of Isosorbide mononitrate of initiated with determination of λ_{\max} using UV spectroscopy and it was found that λ_{\max} & it obeys Beer's Lamberts law. The FTIR characterization of Isosorbide mononitrate and the physical mixture of drug and polymer indicate the absence of interaction between them.

Initial placebo trials of polymers were taken to optimize the concentration of polymer and composition. Fast dissolving oral thin films with selected polymer concentration, films with HPMC, PVA and combination of both PVA and HPMC were formulated by solvent casting method. Sucralose and pineapple flavour were used to improve the palatability of films.

All the formulation were evaluated for the uniformity of weight, thickness of film, drug content, content uniformity, tensile strength, percentage elongation, folding endurance, surface pH, Invitro dispersion time and Invitro dissolution studies.

The weight of films with HPMC, PVA and combination of both PVA and HPMC were about 40.51 ± 0.63 , 45.83 ± 0.95 and 43.43 ± 1.26 mg respectively. In all the films the calculated standard deviation values are very low which suggest that, the prepared films were uniform in thickness. All films exhibited folding endurance above proving the flexible nature of the film. The oral thin films of Isosorbide mononitrate prepared with HPMC, PVA and combination films prepared by solvent casting method possesses good mechanical properties. Results of texture analysis proved that films with PVA showed higher tensile strength than other two formulations. The standard deviation values of surface pH indicate that all the films all the films were uniform and as close to salivary pH. The drug content and content uniformity results suggesting that drug was uniformly dispersed throughout all films.

The Invitro dispersion time of all the films were within 30 sec .The dissolution results indicate that rate and extent of films formulated with HPMC was greater than other two formulations. Hence film formulated with HPMC was selected as a final formula.

Conclusions

Film dosage form typically the size of a postage stamp that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension without the need for the administration of water is known as an oral fast dispersing dosage form.

There is an unmet need in the art for an oral dosage form which includes Isosorbide mononitrate which can be administered conveniently without requiring water for ingestion, which can disintegrate rapidly, and which has a decrease potential for a patients to expel the dosage form after administration and placement of the dosage form in the oral cavity. This dosage form is convenient for the geriatric patients and bedridden patients are unwilling to take solid do solid dosage form.

Isosorbide mononitrate is not available as patient compliance orally disintegrating dosage form. Thus present attempt of developing Isosorbide mononitrate oral thin film was successful and the developed Isosorbide mononitrate oral thin film is a viable alternative for Isosorbide mononitrate immediate release tablets.

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