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FORMULATION & EVALUATION OF FAST DISSOLVING ORAL FILM

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INTRODUCTION

1.1 Oral drug delivery system

Mouth dissolving films offers an elegant route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage. Also, large surface areas of absorption, easy ingestion and swallowing, pain avoidance make the oral mucosa a very attractive and selective site for systemic drug delivery. Recent developments in the technology have presented viable dosage alternatives from oral route for wide variety of group of patients. Buccal drug delivery has lately become an important route of drug administration. Various Bioadhesive mucosal dosage forms have been developed. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experienced difficulties in swallowing traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is also known as fast dissolve, rapid dissolve, rapid melt or quick disintegration. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing or fast-dissolving dosage form**. [Ghodake, P.P.*et al.*, 2013].**

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal

tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Despite of so much of advancements in various delivery system developed for administration of various drugs through different routes such as oral, parental, transdermal and nasal etc., the oral route is considered as the preferred route of administration which includes painless, ease of administration, patient friendly and so on. Several new technologies had been developed for oral delivery is being available to address to improve the patient compliance. Fast dissolving drug delivery system (FDDS) is gaining popularity in pharmaceutical companies as they are new drug delivery technique in order to provide the patient with medicine without obstacles in swallowing.

Thin-film and strip intraoral dosage forms have been developed by several companies including LTS (Lohmann Therapie-System) AG, Zengen Inc., and Lavipharm Laboratories (Quick-Dis™ and Slow-Dis™ technology), Pfizer's Warner-Lambert consumer healthcare division (Listerine® PocketPaks™). Chloraseptic® Relief Strips™ were the first oral thin-film product to incorporate a drug and were introduced in the United States in September 2003 by Prestige Brands International for relief of sore throat.

Domperidone is a white crystalline, odorless substance, freely soluble in water and is used in the treatment of some forms of nausea and vomiting by inhibition of dopamine and 5-HT3 receptors in the CTZ (Chemoreceptor trigger zone of the CNS). It promotes gut motility by inhibiting presynaptic and postsynaptic D2 receptors as well as presynaptic 5-HT4 receptors. Commercially, it is available in tablet form. Patients with gastroparesis often have symptoms such as vomiting and nausea as well as fullness and bloating, each of which can lead to patient discomfort with or unwillingness to swallow the available oral tablet. It is absorbed orally, however it undergoes hepatic first pass metabolism, which varies considerably between subjects and hence absolute bioavailability and plasma concentration are subject to inter individual variation. Hence, Domperidone is suitable candidate for fast dissolving oral film**. [Amal, S. M. *et al*., 2015].**

1.2 Special features of fast dissolving oral film

- Thin elegant film
- Available in various size and shapes

- Unobstructive
- Excellent mucoadhesion
- Fast disintegration and rapid release

1.3 Ideal characteristics of a suitable Drug candidate

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

1.4.1 The advantages of oral film

- The film administered sublingually and buccally deliver the drug with high potential to improve the onset of action, lower the dose, and enhance the efficacy and safety profile of the medicament.
- All single unit dosage forms, soft gels and liquid formulations primarily enter the blood stream via the gastrointestinal tract, which subjects the drug to degradation from stomach acid, bile, digestive enzymes and other first pass effects. As a result, such formulations often require higher doses and generally have a delayed onset of action, which can be overcome using current oral film drug delivery systems that avoid these issues and yield quicker onset of action at lower doses.
- Oral film is more stable, durable and quicker dissolving than other conventional dosage forms.
- Oral film enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain precise amount of drug.
- Oral film ensures more accurate administration of drugs.
- Oral film can improves compliance due to the intuitive nature of dosage form and its inherent ease of administration. These properties are especially beneficial for pediatric, geriatric and neurodegenerative disease patients where proper and complete dosing can be difficult.
- Oral films ability to dissolve rapidly without the need for water provides an alternative to patients with dysphasia and to patients suffering from nausea, such as those patients receiving chemotherapy.

- Oral film drug delivery has the potential to allow the development of sensitive drug targets that may otherwise not to be possible in tablet or liquid formulations.
- From a commercial perspective oral film drug delivery technology offers an opportunity to extend revenue lifecycles for pharmaceutical companies whose drug patent is expiring and will soon be vulnerable to generic competition.
- Sublingual film delivers a convenient, quick dissolving therapeutic dose contained wioraian abusedeterrent film matrix that cannot be crushed or injected by patients , and rapidly absorbs under the tongue to ensure compliance.

1.4.2 The disadvantages of oral film

- Oral disintegrating films have limitations in terms of the amount of drug that can be incorporates in each unit dose. For lyophilized dosage forms, the drug dose must generally be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. Also, due to the nature of fast dissolving oral films, special packaging is needed for products that are fragile, which may add to the cost.
- Dose uniformity is a challenge.
- It takes moisture from atmosphere.
- It requires special packaging for product's stability and safety.

1.5 Overview of the oral cavity

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 oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. There are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa.

1.5.1 Sublingual gland

Salivary glands are present in the floor of the mouth underneath the tongue. Sublingual glands are also known as the salivary glands that are located beneath the tongue secrete saliva which gets mixed with the food, so that the food gets lubricated, formed into a soft bolus and can be easily swallowed. Absorption of drugs is directly from the site into systemic circulation owing to its relatively lesser thickness, high permeability and rich blood supply they are also known as sublingual glands. They produce mucin in turn produces saliva. The

oral cavity is lined with mucous membrane which comprises of squamous cells and mucous glands. Salivary gland contains the group of cells which secrete saliva into the mouth through salivary ducts. Salivary gland includes comprises of Parotid, Submandibular and Sub-maxillary glands. The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional layer thickness. The absorption of the drug follows in this way Sublingual > Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent.

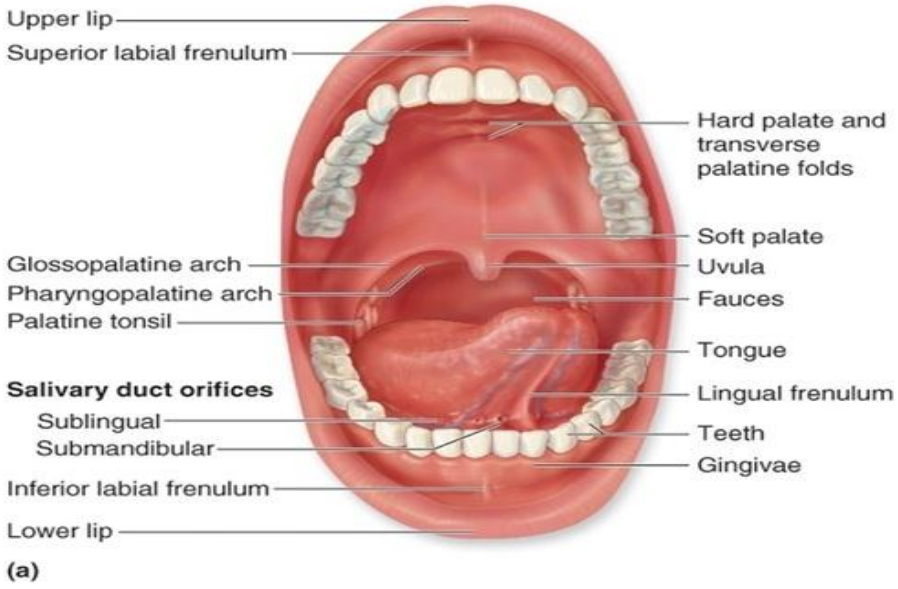


Figure No. 01: Overview of Oral Mucosa.

1.5.2 Mechanism of absorption

Sublingual administration drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein, and braciocephalic vein and are then drained into the systemic circulation. Upon sublingual administration drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane .The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection.

1.5.3 Factors affecting absorption

- Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.
- Binding to the oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.
- PH and pKa of the saliva: As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- Lipophilicity of the drug
- For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
- Thickness of the oral epithelium: As the thickness of sublingual epithelium is 100-200 µm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

1.6 Comparison Between Orally Fast Dissolving Films and Oral Disintegrating Tablet.

Orally Fast Dissolving Films	Orally Disintegrating Tablets
1. Larger surface area gives greater dissolution.	1. Less surface area gives less dissolution than ofdf.
2. These are flexible and durable.	2. These are brittle and less durable than ofdf.
3. Only low dose can be incorporated.	3. High dose can be incorporated.
4. Ofdf thicknes are 50 to 500 µm.	4. Odt thickness as like convention tablet.
5. Patient compliance is more.	5. Patient compliance is less than odf.

1.7 Formulation ingredients

Following general composition of drug and excipients in percentage

- Drug 1-25%
- Water soluble polymer 40-50%
- Plasticizers 0-20%
- Fillers, colours, flavours etc. 0-4

1.7.1 Drug (1-25%)

The drugs selected oral films should possess good stability in saliva and water with low dose. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the oral fast dissolving films. Several class of

drugs can be formulated as mouth dissolving films including antiasthamatics (Salbutamol sulphate, Montelukast), antihistamine (Levicitrizine), antianginal (Verapmil), antiulcer (Omeprazole), antiemetic (Domperidone) , expectorants, antitussives, NSAID'S (Valdecoxib, Meloxicam, paracetamol).

1.7.2 Water Soluble Polymers (40-50%)

To obtain the desired film properties, polymers can be used alone or in combination. Generally water-soluble polymers are used as film formers as they achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The strength of the film depends on the type of polymer and the amount in the formulation. By increasing the molecular weight of polymer film bases, disintegration rate of the polymer decreases. Polymers frequently used as film formers are water soluble grades of cellulose ethers, polyvinyl alcohol, polysaccharides, polyvinylpyrrolidone K-90, polyethylene glycols, pullulan, gelatin, carboxy methyl cellulose cekol 30, hydroxy propyl methyl cellulose E-3 and K-3, methyl cellulose A- 3, A-6 and A-15, pectin, sodium alginate, hydroxyl propyl cellulose, maltodextrins and eudragit RD10,11.

1.7.3 Plasticizers (0-20%)

Plasticizer is used for improve Flexibility with reduce Brittleness of films. Plasticizer enhances mechanical properties such as tensile strength and elongation to the film by reducing the glass transition temperature of the polymer. It also reduces brittleness of the strip as a result improves its flexibility. Choice of plasticizer depends upon type of solvent used and its compatibility with the polymer. Some of the commonly employed plasticizers are phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and glycerol. Improper use of plasticizer may lead to blooming, film cracking, splitting and peeling of the strip.

1.7.4 Surfactants

Surfactants are used as wetting or solublising or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Commonly employed are polaxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactant is polaxamer 407.

1.7.5 Sweetening agents

Sweetners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Some of the commonly employed sweeteners are dextrose, sucrose, fructose, glucose, isomaltose, polyhydric alcohols (sorbitol, mannitol), etc. Artificial sweeteners like saccharin, cyclamate, aspartame (first generation) and acesulfame K, sucralose, alitame, neotame (second generation) can also be used.

1.7.6 Saliva stimulating agents

Saliva stimulating agents are used to increase the rate of production of saliva that would help in the faster disintegration of the rapid dissoving strip formulations. Examples of salivary stimulants are citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. Among these the most preferred one is citric acid.

1.7.7 Flavouring agents

The quantity of flavouring agent required to mask the taste depends on the flavour type and its strength. Commonly employed are fruity flavours (vanilla, cocoa, coffee, chocolate, citrus), flavor oils (peppermint oil, cinnamon oil, oil of nutmeg). Flavours can also be chosen from oleo resins, synthetic flavour oils and extract derived from various parts of the plants like fruits, flowers etc.

1.7.8 Colouring agents

Generally incorporated colouring agents are FDandC colours, natural colours, pigments such as titanium dioxide etc.

1.8 Different Technologies used in film formulation (Patented technologies)

1.8.1 XGel

XGel™ film provides unique product benefits for healthcare and pharmaceutical products: It is non-animal derived, approved on religious grounds, and is suitable for vegetarians; the film is genetically modified organism (GMO) free and continuous production processing provides an economic and competitive manufacturing platform. XGel™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients.

1.8.2 Soluleaves

This technology is applied to flavor-release products such as mouth fresheners and vitamin products. For pharmaceutical uses, this method of administration is especially useful for pediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. Soluleaves™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 min.

1.8.3 Wafertab

Wafertab™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible film strip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The Wafertab™ filmstrip can be flavored for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre manufactured XGel™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The Wafertab™ system lends itself to many possibilities for innovative product design, enabling multiple 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.

1.8.4 Foamburst

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

1.8.5 Micap

Micapplc signed an option agreement in 2004 to combine its expertise in microencapsulation technology with the Bio Progress water soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4 billion global market for smoking cessation products (SCPs). **[Venkata, A.M.*et al*., 2014.]**

1.9 Methods of preparation

Following methods can be used for the preparation of fast dissolving oral films:

1. Solvent casting method
2. Semisolid casting method
3. Hot melt extrusion

4. Solid dispersion extrusion
5. Rolling method

1.9.1 Solvent Casting Method

It is very old film making method. In this method the drug is either dissolved or suspended in a solution containing polymers, plasticizers and other excipients which are dissolved in a volatile solvent, like ethanol or water. It is referred as film dope, it is then casted in petri plate and passed through drying equipment like oven to remove all the volatile solvents. Then the dried film is die cut into strips and packed in sealed atmospherically resistant pouches. This method is suitable for films containing heat sensitive drug/API as the temperature needed to remove the volatile solvents is comparatively low than hot melt extrusion method.

Advantages

- Better film clarity and thickness uniformity than extrusion method.
- Fine gloss on film and lack of die lines.
- Films with more flexible and better physical properties are produced by this method.

Disadvantages

- Polymers to be used should be soluble in volatile solvents.
- Formation of a stable solution with considerable minimum solid content and viscosity is required, which is difficult to attain.
- Homogenous film preparation with proper drug release from casting support must be attained.

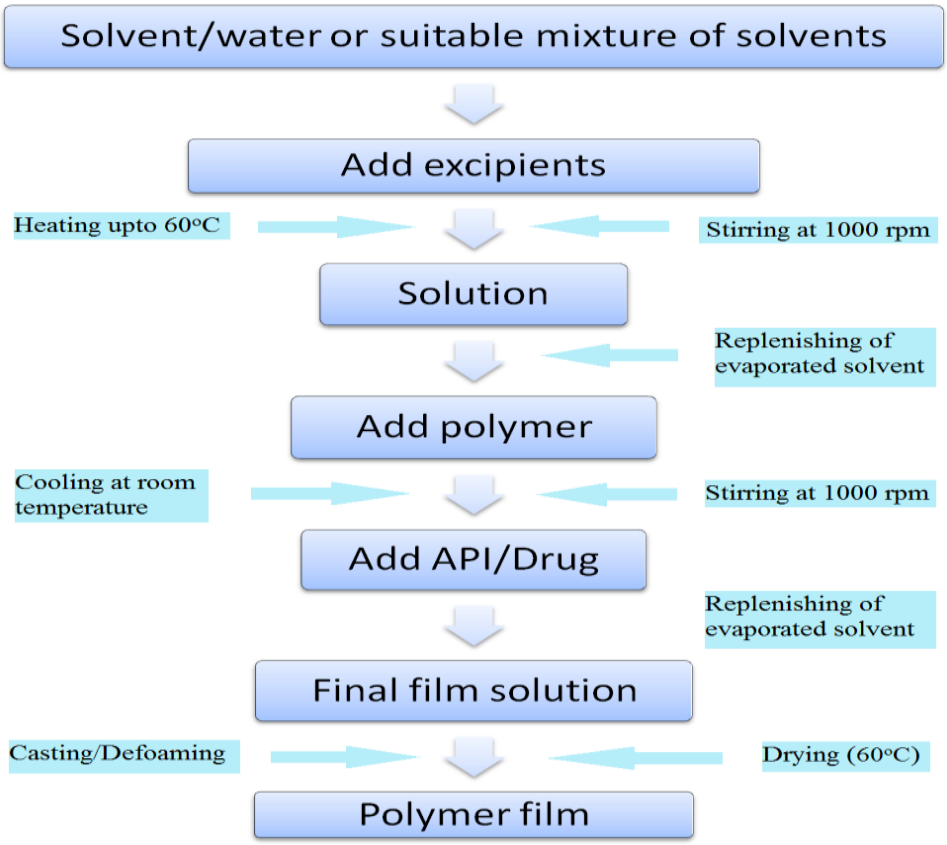


Figure No. 02: Solvent Casting Method.

1.9.2 Semisolid Casting Method

Semisolid casting method is generally used when acid insoluble polymers are used. In this method a solution of water soluble film forming polymer is made then this solution is poured in the solution of acid insoluble polymer, which is prepared in sodium or ammonium hydroxide. After this plasticizer is added to form the gel mass. Amount of plasticizer added affect the property of gel mass formed. The gel mass formed is then casted into film or ribbons using heat controlled rollers/drums. The ratio of acid insoluble polymer and film forming polymer should be 1:4. The films thickness formed by this method is about 0.015-0.05 inches.

1.9.3 Hot Melt Extrusion

This method involves shaping polymer into film through heating process. Firstly the drug - polymer mixture is filled in hopper and is conveyed, mixed and melted by the extruder. A die gives shape to the melt in required form. This method involves lower temperature and short residence time (< 2 min.) for the drug polymer mixture. Organic solvents are not used in this method and it can operate continuously with minimum product wastage. Operating parameters can be controlled efficiently by this method.

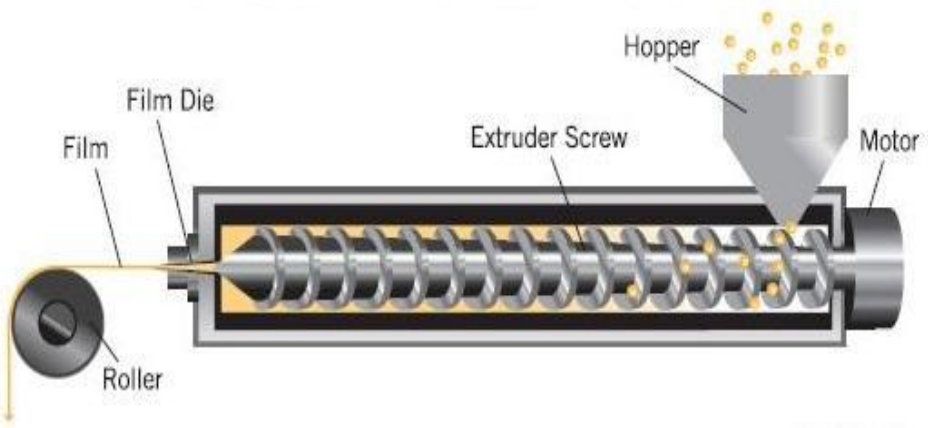


Figure No. 03: Hot Melt Extrusion Method.

Advantages

- Less processing steps.
- No need of solvent or water.
- Less energy is required compared to high shear methods.
- Uniform dispersion of fine particles due to intense mixing and agitation.
- No importance of drug compressibility properties.

Disadvantages

- Number of polymers is limited.
- Polymer flow properties are essential to processing.
- Drug/polymer stability problem as it is a thermal process.

1.9.4 Solid Dispersion Extrusion

Term solid dispersion refers to dispersion of active ingredients in an inert carrier in solid state in the presence of amorphous hydrophilic polymers. In starting, the drug is dissolved in suitable liquid solvent and later this solution is added in the melt of polyethylene glycol at below 70oC without removing the liquid solvent. And at last the solid dispersions are passed through dies to shape them in form of film.

Precautions while preparing solid dispersions

The selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol and polymeric form of drug precipitated in the solid dispersions may get affected by the liquid solvent used.

Advantages

- Low shear method.
- Uniform dispersion of fine particles.
- Less processing steps.

1.9.5 Rolling Method

In rolling method a pre-mix is prepared for preparation of film, later active drug is added and film is prepared. Pre-mix batch include film forming polymer, polar solvent, plasticizer and other excipients except the drug, which is added in to the master batch. Master batch and pre-mix of required quantity are pumped into separated containers and later drug is blended with master pre-mix for specific time to provide uniformity. The mixture so formed is then fed to the roller; metering roller controls the thickness and applies the mixture to the roller. The film is formed and it is carried away by the support roller. A specific amount of matrix is fed into pan through second metering pump. The metering roller determined thickness of film. The film is finally formed on substrate and carrier away by the support roller As the film formed is wet so it is then dried using controlled bottom drying, it is desirable to avoid presence of external air while drying. After drying, film is cut into different sizes and shapes according to need. [**Jangra, P.K. *et al*., 2014]**

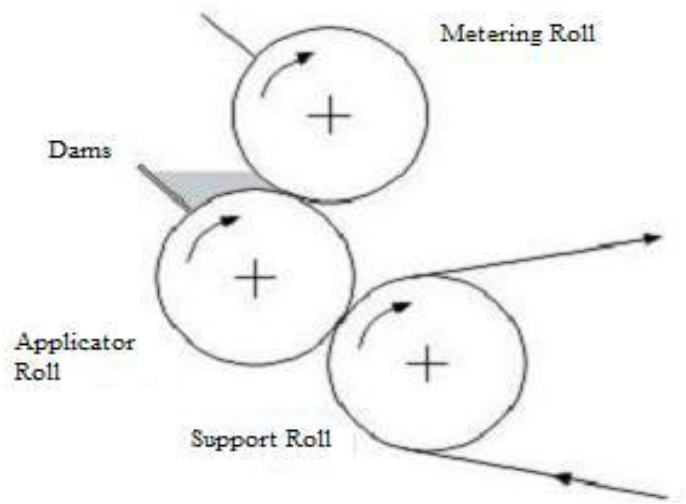


Figure No. 04: Rolling Method.

1.10 Classification of Fast Dissolving Technology

For ease of description, fast-dissolve technologies can be divided into three broad groups:

- Lyophilized systems
- Compressed tablet-based systems

- Thin film strips

1.10.1 Lyophilized systems

The technology around these systems involves taking a suspension or solution of drug with other structural excipients, through the use of a mould or blister pack, forming tablet shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration.

1.10.2 Compressed tablet-based systems

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

1.10.3 Thin film strips

Oral films also called oral wafers, 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. Today, FDFs are a proven and accepted technology for the systemic delivery of APIs for over-the counter (OTC) medications and are in the early- to mid development stages for prescription drugs. This has been attributed to the success of the breath freshener products by consumers such as Listerine Pocket Paks in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50- 200 mm film. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats. **[Kaur, M. *et al*.,2013.]**

1.11 Classification of Oral Films

There are three different subtypes of oral films:

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

Table No. 01: Types of Oral Films and Their Properties.

Property/Sub Type	Flash Release Wafer	Mucoadhesive Melt-Away Wafer	Mucoadhesive Sustained Release Wafer
Area (cm2)	2-8	2-7	2-4
Thickness (µm)	20-70	50-500	50-250
Structure	single layer	Single or multilayer System	Multi layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid Solution
Application	Tongue (upper palate)	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

1.12 Packaging of oral film

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used packaging format. APR- Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually.

The material selected must have the following characteristics:

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper-resistant requirement
- They must be non-toxic.
- They must not be reactive with the product.

They must not impart to the product tastes or odors

1.12.1 Single pouch and Aluminum pouch

Soluble film drug delivery pouch is a peelable pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure

combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

1.12.2 Foil, paper or plastic pouches

The flexible pouch is a packaging concept capable of providing not only a package that is temper- resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.

1.12.3 Blister card with multiple units

The blister Container consists of two components: the blister, Which is the formed cavity that holds the product, and The lid stock, which is the material that seals to the Blister. The film selection should be based upon the Degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form The cavity is typically a plastic, which can be Designed to protect the dosage form from moisture.

1.12.3.1 Barrier Films

Many drug preparations are extremely sensitive to moisture and therefore require High barrier films. Several materials may be used to provide moisture protection such as Polychlorotrifluoroethylene film, Polypropylene.

1.12.3.2 Continuous roll dispenser

An automatic drug tape Dispensing and metering device and a disposable Cassette containing a roll of drug tape housed in a Small reusable portable dispenser unit. The dispenser contains a measurement device for carefully measuring the length of tape as it is dispensed. A Counter monitors the remaining doses of drug tape remaining within the dispenser. A timer device may be provided to alert the patient that it is time for the Medicament to be dispensed. As the lid of the dispenser unit is opened, the measured length of drug Tape is severed from the roll by a cutter blade incorporated into the lid. The dosage and Administration of the medicament to be given a Patient may be set by adjusting the tape length released for each single dose and

selecting the time Intervals between dosages. The invention comprises also ingestible tapes of medicament**. [Raghavendra Rao, N.G *et al*., 2013].**

Table no. 02: Patented packaging systems.

Packaging	Company
RapidCard	Labtec
Core-Peel®	Amcor Flexibles

1.13 Marketed Films

Table No. 03: List of Marketed Films.

Sr.No.	Product	Manufactured By
1.	Donepezil rapid dissolving films, Ondansatron rapid dissolving films	Labtec Pharma
2.	Altoid cinnamon strips, Boots vitaminc strips, Cool shock peppermint strips, Benzocaine films, Caffeine films.	Dow chemical company
3.	Listerine Pocket Paks, Breath Freshening Strips	Pfizer's Warner-Lambert consumer healthcare division
4.	Klonopin Wafers	Solvay Pharmaceuticals
5.	Listerine Cool Mint Pocket Paks	Pfizer,Inc.
6.	Triaminic	Novartis

2. Aim and objective

2.1 Aim

Formulation and evaluation of fast dissolving oral films.

2.2 Objective

The primary objectives of the work were:

- To formulate and evaluate oral fast dissolving films of Domperidone.
- To study the effect of various polymers and plasticizers in different concentrations on the release of Domperidone

3. PLAN OF WORK

1. **Literature review**
2. **Selection of drug and excipients**
3. **Procurement of Domperidone and excipients**
4. **Preformulation studies**

- Compatibility studies between Domperidone and excipients by IR.

5. Identification of Domperidone

- Description
- Solubility
- Melting point
- Standard calibration curve of Domperidone
- Study of IR spectrum of Domperidone

6. Formulation of fast dissolving oral films of Domperidone by solvent casting method

7. *In vitro* evaluation of fast dissolving oral films of Domperidone

- Appearance
- Thickness
- Weight of film
- Folding endurance
- Disintegration time
- *In vitro* dissolution study
- Selection / optimization of batch

8. Result and data interpretation.

4. Literature review

Pathan, A. *et al*, [2016]: They formulated fast dissolving Oral film of Promethazine hydrochloride as a strong antihistamine which are used to reduce nausea, motion sickness and improved bioavailability of drugs as compared to conventional solid oral dosage forms. The films were prepared Hydroxypropylmethyl cellulose E15 as a film base synthetic polymer and PEG400 (Poly Ethylene Glycol 400) as a plasticizer. SLS (Sodium Lauryl Sulfate) and MCC (Micro Crystalline Cellulose) used as a surfactant in different concentration. The in vitro drug release in optimized formulation F2 was found to be 14.36% in 2 min. The optimized formulation F2 also showed satisfactory pH, drug content, effective in vitro drug release, disintegration time of 09 seconds and satisfactory stability. The folding endurance of the all the batches were and disintegration time of all batch.

Shrimali, C. *et al*, [2015]: Meloxicam fast dissolving films were prepared by solvent casting method using PVA, PEG-400, Glycerol, Aspartame, Citric acid. Tensile strength of all the films was in the range in gm/cm2. The results of % elongation from various formulations were in the range. This represents the elasticity of the film. The films were showing folding endurance in the range.

Jelvehgari, M. *et al*, [2015]: Buccal films of Ergotamine Tartrate and Caffeine Anhydrous were prepared by solvent casting technique using film forming mucoadhesive polymer. ET film was prepared using different ratios of drug (ET/CA) to polymer (HPMC-E15) and CA film was formulated using various ratios of drug to polymers. The best drug of polymer ratio in ET/CA films was (E2) and (C2), respectively. Moreover, the film had acceptable physical properties and drug content. The films were non-irritating with favorable film properties and showed sufficient mucoadhesive potential until the drug was absorbed from the formulation. Further, it was confirmed that the combination of ET and CA films for a buccal delivery was a cure for migraine headaches that avoided the disadvantages of oral routes.

Pawar, S.V. *et al*, [2015]: They prepared mouth dissolving film of risperidone, which is first generation antipsychotic. Schizophrenia is a severe, disabling disorder that affects about 1% of the world's Population. Risperidone is effective for treating the positive and negative symptoms of schizophrenia compared to first generation antipsychotics. Oral administration of Risperidone has drawbacks such as hepatic first pass metabolism which is overcome by means of mouth dissolving film formulation. Diseases which cannot be treated by other oral formulations can be cured by preparing oral fast dissolving oral films. In evaluation study, The percentage elongation of optimized formulation was 120%. Generally elongation of film increases as the plasticizer content increases. *In-vitro* drug release study results showed that as the concentration of polymer increases, drug release from mouth dissolving films decreases. An immediate drug release was successfully observed for all HPMC films.

Talele, S. G. *et al*, [2015]: They formulated mouth dissolving films of Almotriptan malate using polymers HPMC E-15, HPMC E-4 and Gelatin as the film forming agents. PEG 400 was incorporated as plasticizer to improve flexibility of films. Aspartame used as sweetner. Sodium Starch glycolate used as a disintegrant. Single polymer HPMC E-15showed best results, Intermsot tensile Strength, percentage elongation Folding endurance, in-vitro disintegration time, Surface pH , thickness and percentage content uniformity . Satisfactory dissolution profile was obtained with maximum release of drug within sec. The stability studies showed that there was no appreciable change in parameters when stored at three different temperatures. Finally it is concluded that the drug release from the mouth dissolving film was increased by using the increased concentration of superdisintegrant thus assisting in faster disintegration in the buccal cavity. The high % drug release of the film in simulated

saliva indicated that it could be helpful for the treatment of acute migraine where quick bioavailability of the drug is desired.

Krishna, R. K. *et al,* [2014]: Loratidine oral disintegrating films were prepared using HPMC E3, E6 and pullulan gum as film forming polymer and PEG 400 is used as plasticizer. The prepared films were evaluated for various evaluation parameters like weight variation, folding endurance, thickness, drug content etc. The results showed that all the films have a smooth surface texture. The weight variations of the films were found to be uniform within all batches. The thickness of the films was found to be in the range of mm. The folding endurance was found to be above 300 which indicate that the plasticizer concentration was adequate. Thus drug was uniformly distributed in the films. The disintegration time of the films was evaluated using 0.01 N HCl buffer. It was observed that the disintegrating time was increased as the concentration of polymer was increased.

Birari, A. E. *et al,* [2014]: Atenolol films were prepared by solvent casting method. The hydrophilic polymer such as HPMC and PVA used as film forming polymer, Glycerin used as plasticizer, Vanillin used as flavoring agent and SLS used as surfactant which provide uniform dispersion of Atenolol in polymeric solution. All the prepared films were evaluated for different parameters. All the formulations show satisfactory result.

Vamshi, K. M. *et al,* [2014]: Fast dissolving films of Timolol maleate were prepared by solvent casting method. HPC, HPMC E5 and HPMC E15 polymers were used in preparation of film. All the fabricated film formulations were smooth and almost transparent with good flexibility. As the viscosity of the polymer increases the rate of drug release from the film decreases.

Gade, R. *et al,* [2014]: The Pravastatin Sodium films were prepared by solvent-casting method. HPMC E3, HPMC E5, HPMC E6, PVA, xylitol, mannitol, sorbitol, PEG 400, glycerin, propylene glycol were used in the preparation of film. The films were evaluated for imperfections and cuts, peelability without rupturing, folding endurance and cracking and surface roughness. Films were found to be stable at accelerated stability conditions. The thickness was gradually increases with the amount of polymers. Films containing HPMC were thicker than films containing PVA.

Pandey, G. S. *et al,* [2014] : They prepared Salbutamol Sulphate fast dissolving oral films. Prepared mouth dissolving film with excellent mechanical properties by employing design of experiment based on factorial designs. The optimized mouth dissolving film was made with % w/w Maltodextrin and % w/w Glycerine. This developed optimized oral fast dissolving film showed rapid disintegration and dissolution of OFDF with good flexibility and tensile strength, thus the oral fast dissolving film as one of the promising tool for delivery of salbutamol in order to achieve rapid disintegration, improved patient compliance and bioavailability. They studied effect of maltodextrin and glycerin on fast dissolving oral film of salbutamol sulphate.

Marzia, A. *et al,* [2014]: They prepared metaclopramide HCl swellable oral thin films. Quantity of glycerin and Povidone K90 affected the appearance and peeling of the films. It was observed that thickness and weight of film was directly proportional to the total solid content of the film. Swelling behavior of film was inversely proportional to the quantity of Povidone K90 in the film. The folding endurance of the formulated films was above of folding which indicates satisfactory mechanical strength.

Krishna, R. K. *et al,* [2014]: He prepared oral fast dissolving films of atazanavir. Atazanavir acts by selectively inhibiting the virusspecific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells by binding to the active site of HIV-1 protease. The prepared films were clear and found to have smooth surface and texture. The film forming capacity of HPMC polymer was good. The folding endurance was and thickness ranged from mm. the weight variation of the films was within in the limits. The in vitro disintegrating time of the films was in the range of sec. The release of drug from the film prepared by using grade HPMC E3 is the best one.

Shah, H.P. *et al,* [2014]: The oral fast dissolving film of Terbutaline Sulphate prepared to avoid first pass metabolism and thus improving bioavailability of Terbutaline Sulphate. The polymers selected were HPMC E 15, Sodium alginate and PVP K-30. Most efficient film was of 4% HPMC E 15. The selected film which was disintegrated in less than 3 minutes and releasing 100% of drug within 5 minutes. From that it was found that placebo Film containing formula passed all the criteria regarding to the evaluation parameters so that film was selected. Selected film was prepared again by adding the terbutaline sulphate and evaluated (3x2 film) all the parameter. It was found that all the criteria passed.

Kuchana, V. *et al,* [2014]: The fast dissolving films containing buclizine were prepared with an aim to have rapid onset of action and increased bioavailability in allergic conditions. PEG and PVA showed promising physiochemical properties as compared to all other grades of plasticizers. Prepared films were transparent with smooth surface and acceptable mechanical properties. Oral thin strips of buclizine can be prepared using the polymer combinations of B4 and B5. Depending on physical evaluation and drug release it was concluded that B4 [PVA 4mg and PVP 58mg] is optimized among all the formulations. Oral thin strips of buclizine were prepared by solvent casting method using 1:1 and 1:2 ratios of drug and polymers.

Swamy, N.G.N. *et al,* [2014]: They formulated fast dissolving oral film of palonosetron HCl using various polymers. Tween-80 and Polaxomer-407 were selected as surfactants. Formulation containing Tween-80(10%) revealed high degree of folding endurance, more percentage moisture loss, high tensile strength and more percentage elongation and it was also noticed that the increase in the concentration of Tween-80 increased the folding endurance, percentage moisture loss, tensile strength and percentage elongation, but in formulations withPolaxomer-408 there was decrease in folding endurance and percentage elongation and slight increment in tensile strength and percentage moisture. The formulation with Polaxomer-408(10%) showed lesser *in vitro* disintegration time. It was found that the increase in the surfactant concentration decreased the *in vitro* disintegration time.

Dr. Kumari, A. *et al,* [2014]: They formulated fast dissolving films by using various film formers alone or in combination such as HPMC, PVA, PVPK30, Maltodextrin (DE 18-20) at different concentrations and glycerol as plasticizer. All the films have the smooth textured and possess the adequate mechanical strength. Amongst all the prepared formulations from F1 to F12, the formulation F6 possessing PVA and PVPK30 as a film former at a concentration of 60% in 2:1 ratio and glycerol as plasticizer at 10% concentration considered as optimized formulation on the basis of % drug release, mechanical strength and surface morphology. The optimized formulation F6 releases almost 100% of drug at the end of 8th minute. The mechanical strength is also high for the optimized formulation F6 and has the clear surface morphology compared to other formulations. The study clearly evident that the Losartan potassium fast dissolving films provide the fast onset of action by bypassing the first pass metabolism, which is essential requirement for the hypertension patients.

Mishra, R. *et al,* [2013]: Rapidly dissolving films were prepared using HPMC E3 LV as a film forming polymer. Taste masking of Cetirizine hydrochloride was done using Hydroxypropyl β-cyclodextrin as a taste masking agent. It was found out that at optimized ratio of 1:3 of Cetirizine hydrochloride to Hydroxypropyl β-cyclodextrin desired taste masking could be obtained. As amount of HPMC E3 LV and plasticizer PEG 400 had critical role in film properties. Excellent taste masking was achieved using cyclodextrins as complexing agent.

Goud, A. *et al.* [2013]: Fast dissolving films of Propanolol hydrochloride were prepared by solvent casting technique using film forming polymer. HPMC E 15, Propylene glycol and Aspartame were used in the preparation of the film. The thickness was gradually increased with the increasing amount of polymers. All the prepared films were found to be non tacky. *In-vitro* disintegration time of the films was found to be increased with increase in the amount of the polymer. The prepared films were clear, homogenous, devoid of particulate matter, showed good folding endurance and all the prepared bathes were showed good mechanical properties with *in-vitro* disintegration time.

Shelke, P.V. *et al,* [2012]: Fast dissolving films were prepared using sodium alginate as film forming polymer and sodium starch glycolate as disintegrating agent. The result showed that all the films have a smooth surface and good folding endurance. Drug content of all the films was between mg. The disintegration time of the films was evaluated using simulated salivary fluid. The result indicates that disintegration of films initialized in about sec. The % cumulative drug release after 6 minutes is inversely proportional to the concentration of sodium alginate and directly proportional to concentration of sodium starch glycolate. The disintegration time is inversely proportional to concentration of sodium starch glycolate and directly proportional to concentration of sodium alginate.

Sakhare, A. V. *et al,* [2012]: They were prepared oro dissloving films of losartan potassium. The Films of Losartan Potassium were prepared by using polymer as HPMC 15 Cps and Glycerin as plasticizer. *In-vitro* drug release shown by the batch in which concentration of plasticizer used is in large quantity. The glycerin used as in that batch in mg and remaining all concentrations were same, so disintegrate rapidly and release is fast. Hence, as the concentration of plasticizer increases drug release increases.

Bushetti, S.S. *et al,* [2011]: They developed mucoadhesive buccal films of nebivolol. The films of nebivolol using hydroxyl propyl methyl cellulose and methyl cellulose were smooth, elegant and uniform in thickness and weight. Among the two polymers used hydroxyl propyl methyl cellulose showed an increased *in-vitro* residence time due to mucoadhesion nature of the hydroxyl propyl methyl cellulose. The thickness of the film prepared measured in the range of mm, suggested that the films were thin enough and they did not cause any inconvenience after their application into the buccal cavity. the pH of films was nearer to the salivary pH, hence any irritation was not observed to the mucus membrane of the buccal cavity.

Koland, M. *et al,* [2010]: The films were prepared from polymers such as polyvinylalcohol, polyvinyl pyrrolidone, Carbopol 934P in different ratios by solvent casting method. Propylene glycol or PEG 400 as plasticizers and mannitol or sodium saccharin as sweeteners were also included. The films showed Satisfactory results were obtained when subjected to physico-chemical tests such as uniformity of weight, thickness, surface pH, folding endurance, uniformity of drug content, swelling index, bioadhesive strength, and tensile strength. Films were also subjected to *in vitro* drug release studies by using USP dissolution apparatus. The stability studies conducted for a period of 8 weeks showed no appreciable change in drug content, surface pH, and *in vitro* drug release.

Sumitha, C. *et al,* [2009]: The purpose of this research was to mask the intensely bitter taste of Ondansetron HCl and to formulate rapid disintegrating films (RDFs) of the taste-masked drug using methocel E15.Taste masking could be achieved using suitable ion exchange resins, sweeteners and flavors. Taste masking was done by complexing Ondansetron HCl with ion exchange resin (Polacriline Potassium) which also has disintegrating property, in different ratios and by using sucralose as sweetening agent in very low concentrations. Taste was further masked using vanilla flavor in combination with lychee and banana flavor. The RDFs were transparent, without any air entrapment. The drug-release profiles indicated that it could be used for the oral delivery of ONDCT in chronic and acute postoperative or chemotherapy- or radiotherapy-induced emesis.

5 MATERIALS AND METHODS

- **Materials**

Table No. 04: List of Chemicals and Their Suppliers.

Sr.No.	Name of The Ingredient	Name of Supplier / Manufacturer
1	Domperidone	Ipca laboratories, India.
2	Hydroxypropyl methylcellulose E-5	Ajanta pharma, Mumbai.
3	Hydroxypropyl methylcellulose E-15	Ajanta pharma, Mumbai.
4	Hydroxypropyl methylcellulose K-4M	Ajanta pharma, Mumbai.
5	Hydroxypropyl methylcellulose K-15	Ajanta pharma, Mumbai.
6	Maltodextrin	Ajanta pharma, Mumbai.
7	Xanthum gum	Moly Chem. Pvt. Ltd, Mumbai.
8	Guar gum	Moly Chem. Pvt. Ltd, Mumbai.
9	Polyethylene glycol 400	Research-Lab fine Chem. Industries, Mumbai
10	Glycerol	Moly Chem. Pvt. Ltd, Mumbai.
11	Saccharin	Hindustan chemicals and pharmaceuticals, Mumbai.

- **Equipments**

Table No. 05: List of Equipments With Their Suppliers.

Sr. no.	Name of equipments	Suppliers / Model
1	Electronic digital balance	Eagle
2	Melting point apparatus	Dolphin
3	Digital pH meter	Hanna instrument
4	UV Visible spectrophotometer	Shimadzu UV 1800,Japan
5	Sonicator	Leelasonic
6	Mechanical stirrer	Remi equipments, Mumbai
7	USP dissolution apparatus	Electro lab EDT-08LX
8	Micrometer screw gauze	Matoshri college of Engineering.
9	FTIR spectrophotometer	FTIR-4100, Jasco, Japan

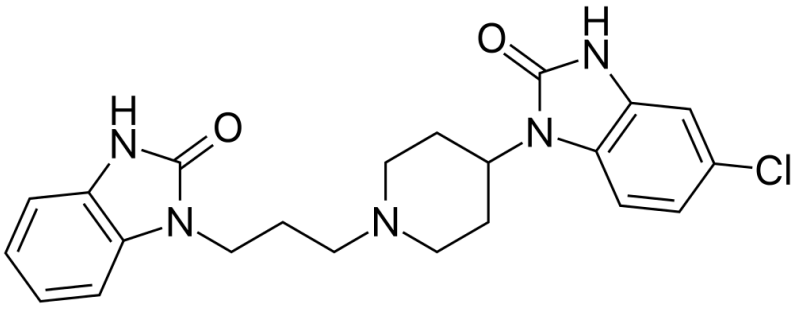
- **Ingredients and their category**

Table No. 06: List of Ingredients Used In Formulation and Their Category.

Sr.no.	Ingredients	Category
1	Domperidone	Antiemetic
2	Hydroxypropyl methyl cellulose E-5, E-15, K-4M, K-15	Polymers
3	Maltodextrin, Xanthum gum, Guar gum	Polymers
4	Polyethylene glycol 400, Glycerol	Plasticizer
5	Saccharin	Sweetener
6	Distilled water	Solvent

5.1 Drug Profile

Domperidone



IUPAC Name: 5-chloro-1-(1-(3-(2-oxo-1-Benzimidazolinyl)propyl)-4-piperidyl)-2-benzimidazolinone

Molecular formula: $C_{22}H_{24}ClN_5O_2$

Molecular weight: 425.9

Description: white crystalline, odorless substance

Solubility: Freely soluble in water and ethanol

pKa: 12.52

Half life: 7.5 hours

Category: Antiemetic.

Bcs class: II

Melting point: 242.5^0c

Dose of drug: 10 mg

Storage: Store protected from light and moisture.

Assay

Weigh accurately about 0.25 g, dissolve in a mixture of 50 ml of ethanol (95 per cent) and 5.0 ml of 0.01 M hydrochloric acid. Titrate with 0.1 M sodium hydroxide, determining the end-point potentiometrically (2.4.25). Note the volume added between the two inflections.

1 ml of 0.1 M sodium hydroxide is equivalent to 0.03363 g of $C_{22}H_{24}ClN_5O_2$

Pharmacological profile

Mode of action

Domperidone acts by increasing the gastrointestinal motility by inhibiting dopaminergic mechanisms and thus manifest the unopposed central cholinergic activity. This leads to an increased release of acetylcholine from enteric neurons, suppress the interneurons by the

antagonism of 5-HT_3 receptors and stimulation of excitatory neurons via 5-HT_4 receptors. The prokinetic effect of compound was due to the blocking of both central and peripheral dopaminergic receptors, by the 5-HT3 receptors blocking and 5-HT4 receptors stimulating effects. The anti-emetic and anti-nauseant effects of the compound were predominantly by blocking the central dopaminergic D2 receptors on cholinergic enteric neurons and chemoreceptor trigger zone (CTZ).

Pharmacokinetics

Absorption

Domperidone is rapidly and well absorbed from the GI tract, from rectal mucosa, and from IM sites. Relative to an intravenous dose of drug, The absolute oral bioavailability of Domperidone is 80% ± 15.5% as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state.

In a single dose study, The area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same.

Distribution

Domperidone Widely distributed into body tissues and fluids. It crosses blood-brain barrier and placenta. It also enters breast milk in concentrations greater than plasma.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

Metabolism

The cytochrome P450 (CYP450) system is a major enzyme system responsible for drug metabolism and consists of more than 20 families of enzymes that primarily are located in the hepatocytes of the liver and mucosal tract. Each CYP isoform possesses a characteristics broad spectrum of catalytic activities of substrates. Domperidone is a substrate for CYP2D6.

Elimination

About 80% of the drug is excreted in the urine in the first 24 hours, approximately half as the glucuronide and sulfate conjugates and half as unchanged drug. Elimination half-life varies in

different studies from 2.5 to 5 hours. Impaired renal function results in reduced clearance of Domperidone and an increased half-life (15 hours).

Precaution

Tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and can oftentimes appear to be irreversible. The syndrome is characterised by rhythmical involuntary movement of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movement of extremities. There is no known effective treatment for tardive dyskinesia, however, in some patients symptoms may lessen or resolve after Domperidone treatment is stopped. Antiparkinsonism agents usually do not alleviate the symptoms of this syndrome.

Side effects

- The most frequent adverse reactions to Domperidone are restlessness, drowsiness, fatigue and lassitude, which occur in approximately 10% of patients.
- Less frequently, insomnia, headache, dizziness, nausea, or bowel disturbances may occur. Rare (less than 1 in 1,000) cases of acute depression have been reported. Anxiety or agitation may occur (especially after rapid injection).
- A single instance of supraventricular tachycardia following intramuscular administration has been reported. There have been very rare (less than 1 in 10,000) cases of abnormalities of cardiac conduction (such as bradycardia and heart block) in association with intravenous Domperidone
- Raised serum prolactin levels have been observed during Domperidone therapy: this effect is similar to that noted with many other compounds.
- Parkinsonism symptoms, including tremor, rigidity, bradykinesia and akinesia, occur rarely in patients receiving Domperidone but may be associated with usual or excessive doses or with decreased renal function.

Interactions with other drugs

- The effects of Domperidone on gastrointestinal motility are antagonised by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when Domperidone is given with alcohol, sedatives, hypnotics, narcotics or tranquillizers.

- Since Domperidone accelerates abnormally slow gastric and small bowel peristaltic activity, it may change absorption of orally administered drugs. The absorption of drugs from the small bowel may be accelerated (e.g. paracetamol, tetracycline, levodopa), whereas absorption of drugs from the stomach may be diminished (e.g. digoxin).
- Domperidone may cause extrapyramidal symptoms in some patients. Therefore, when Domperidone is used concomitantly with other drugs that are likely to cause extrapyramidal reactions (e.g. neuroleptics such as phenothiazines), caution should be exercised.
- The decrease in gastric emptying time caused by Domperidone may increase the bioavailability of cyclosporin. Monitoring of cyclosporin concentrations may be necessary.
- When Domperidone is given concurrently with suxamethonium the recovery time is prolonged.
- Since Domperidone influences the delivery of food to the intestine and thus the rate of its absorption, the administration of Domperidone may result in poor diabetic control in some patients. Therefore adjustment in or timing of, insulin dosage may be necessary in insulin controlled diabetics.
- The finding that Domperidone releases catecholamine in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Uses

- To control nausea and vomiting associated with the following conditions: intolerance to essential drugs possessing emetic properties; uraemia; radiation sickness; malignant disease; postoperative vomiting; infectious diseases. There is no clear benefit in motion sickness or other labyrinth disturbances.
- Domperidone has been found useful in the management of gastric retention after gastric surgery.
- Domperidone may be useful in the treatment of diabetic gastroparesis of mild to moderate severity. Once control of diabetes has been established by diet and/or insulin, Domperidone should be discontinued.

5.2 Hydroxypropyl methylcellulose

Synonym

Methyl Hydroxypropyl cellulose; Benecel MHPC; E464; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether;methyl Hydroxypropylcellulose; Metlose; MHPC; Pharmacoat; Tylopur; Tylose MO.

Chemical Name

Cellulose 2-hydroxypropyl methyl ether.

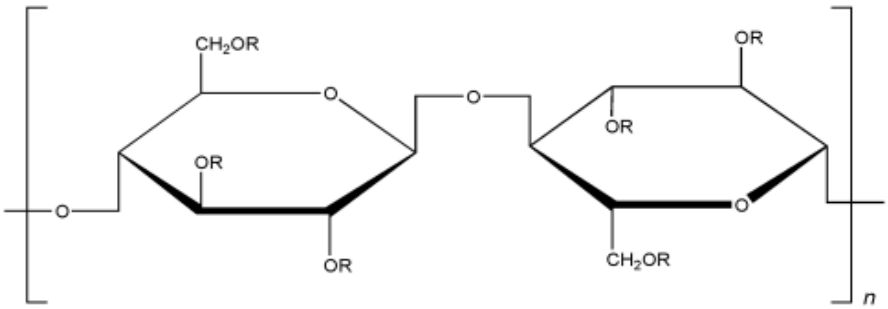
Nonproprietary Names

BP: Hypromellose

JP: Hydroxypropyllmethylcellulose

USP: Hypromellose

Structural formula



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Mixed ether of cellulose with some of hydroxy groups in the form of methylether and some in the form of the 2- hydroxy propyl ether. Several grades of HPMC are distinguished by appending a number indicative of the apparent viscosity, in milipascal, of a 2% w/w solution measured at 20^0C. Hypromellose defined in the USP 25 specifies the substitution type by appending a four digit number to the nonproprietary name, e.g.: hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of hydroxypropoxy group [$OCH_2CHC(OH)\ CH_3$], calculated on a dried basis.

Empirical Formula

HPMC is propylene glycol ether of methylcellulose. It contains methoxy ($-OCH_3$) and hydroxypropoxy ($-OCH_2CHOHCH_3$) groups confirming to the limits for the types of HPMC.

Molecular Weight

Approximately 10,000 – 15, 00,000.

Functional Category

Emulsifying agent, suspending agent and stabilizer in gel and ointments, adhesive in plastic bandages, binder in tablet granulation (2-5%); high viscosity grades are used to retard the release the release of water soluble drugs.

Description

An odorless, tasteless, white or creamy white fibrous or granular powder.

Physical Properties

Viscosity

Wide ranges of viscosity types are commercially available. Typical viscosity values for 2% (w/v) aqueous solutions of Methocel. K4M Premium 4000 (mPas) Methocel K15M Premium 15000 (mPas).

Stability and Storage Conditions

Powder is stable, although hygroscopic after drying. Solutions are stable at pH 3-11. 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. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Safety

Hydroxypropyl methylcellulose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.

Applications in Pharmaceutical Formulation

Hypromellose is used in oral and topical pharmaceutical formulations. In oral products it is primarily used as a tablet binder, in film coating and as an extended release tablet matrix. It is also used as suspending and thickening agent in topical formulations, particularly ophthalmic preparations.

Table No. 07: Grades Of HPMC With Their Viscocity.

HPMC product	USP 28 designation	Nominal viscocity (mPas)
HPMC K4M	2208	4000
HPMC K15M	2208	15000
HPMC E5 LV	2906	5
HPMC E15 LV	2906	15

5.3 Polyethylene Glycol 400

Synonyms: Carbowax, Carbowax Sentry, Lipoxol, Lutrol E, PEG, Pluriol E, polyoxyethylene glycol.

Chemical Name and CAS Registry Number: α-Hydro-ω-hydroxypoly (oxy-1, 2-ethanediyl) [25322-68-3].

Empirical Formula and Molecular Weight: $HOCH_2(CH_2OCH_2)m\ CH_2OH$ where m represents the average number of oxyethylene groups.

Table No. 08: Grade and Molecular Weight of PEG.

Grade	Average molecular weight
PEG 200	190-210
PEG 300	285-315
PEG 400	380-420
PEG 600	570-613

Functional Category: Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.

Description: Polyethylene glycol grades 200–600 are liquids, grades 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. Grades of PEG 6000 and above are available as free-flowing milled powders.

Moisture content: Liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades e.g. PEG 4000 and above, are not hygroscopic.

Solubility: All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols.

Table No. 09: Specifications For Various Grades of PEG.

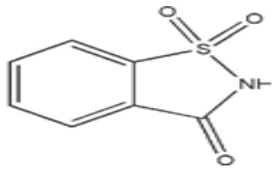
PEG	Density (g/cm3)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPas(cP)]
300	1.120	—	340–394	80–105
400	1.120	—	264–300	105–130
600	1.080	15–25	178–197	15–20

5.4 Saccharin

Synonyms

Garantose; gluside; Hermesetas; sacarina; saccarina;

Structural Formula



Molecular Formula: $C_7H_5NO_3S$

Molecular Weight: 183.18

PH: 2.0 (0.35% w/v aqueous solution)

Functional Category: Sweetening agent.

Applications in Pharmaceutical Formulation or Technology

- Saccharin is an intense sweetening agent used in beverages, food products, table-top sweeteners, and oral hygiene products such as toothpastes and mouthwashes. In oral pharmaceutical formula-tions, it is used at a concentration of 0.02–0.5% w/w. It has been used in chewable tablet formulations as a sweetening agent.
- Saccharin has been used to form various pharmaceutical cocrys-tals.
- Saccharin can be used to mask some unpleasant taste character-istics or to enhance flavor systems. Its sweetening power is approximately 300–600 times that of sucrose.

Description

Saccharin occurs as odorless white crystals or a white crystalline powder. It has an intensely sweet taste, with a metallic or bitter aftertaste that at normal levels of use can be detected by approximately 25% of the population. The aftertaste can be masked by blending saccharin with other sweeteners.

Stability and Storage Conditions

Saccharin is stable under the normal range of conditions employed in formulations. In the bulk form it shows no detectable decomposition and only when it is exposed to a high temperature (1258C) at a low pH (pH 2) for over 1 hour does significant decomposition occur. The decomposition product formed is (ammonium-o-sulfo) benzoic acid, which is not sweet. The aqueous stability of saccharin is excellent.

Saccharin should be stored in a well-closed container in a dry place.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended.

Safety

There has been considerable controversy concerning the safety of saccharin, which has led to extensive studies since the mid-1970s. Two-generation studies in rats exposed to diets containing 5.0–7.5% total saccharin (equivalent to 175 g daily in humans) suggested that the incidence of bladder tumors was significantly greater in saccharin-treated males of the second generation than in controls. Further experiments in rats suggested that a con-taminant of commercial saccharin, o-toluene sulfonamide, might also account for carcinogenic effects. In view of these studies, a ban on the use of saccharin was proposed in several countries. However, in 1977 a ban by the FDA led to a Congressional moratorium that permitted the continued use of saccharin in the USA.

From the available data it now appears that the development of tumors is a sex-, species-, and organ-specific phenomenon, and extensive epidemiological studies have shown that saccharin intake is not related to bladder cancer in humans. The WHO has set a temporary acceptable daily intake for saccharin, including its calcium, potassium, and sodium salts, at up to 2.5 mg/kg body-weight. In the UK, the Committee on Toxicity of Chemicals in Food, Consumer

Products, and the Environment (COT) has set an acceptable daily intake for saccharin and its calcium, potassium, and sodium salts (expressed as saccharin sodium) at up to 5 mg/kg body-weight. Adverse reactions to saccharin, although relatively few in relation to its widespread use, include: urticaria with pruritus following ingestion of saccharin-sweetened beverages and photosensitization reactions.

LD_{50} (mouse, oral): 17.5 g/kg

LD_{50} (rat, IP): 7.10 g/kg

LD_{50} (rat, oral): 14.2 g/kg

6. PREFORMULATION STUDY

6.1 Characterization of Domperidone.

6.1.1 Description

Color and physical form of Domperidone was checked visually.

6.1.2 Solubility

Solubility of Domperidone was checked in water and ethanol

6.1.3 Melting point of Domperidone

The melting point was determined by introducing small amount of the Domperidone in the capillary attached to the graduated thermometer and constant heat was applied with assembly suspended in melting point apparatus. The sample was tested in the temperature to melt the substance, was noted.

6.1.4 Study of UV Visible spectrophotometric characteristics of Domperidone (Determination of λ max)

Weight accurately 10 mg of Domperidone, transfer in the 100 ml volumetric flask and volume was made up to 100 ml with phosphate buffer (pH 6.8). From this solution, 1 ml was withdrawn and added to the 10 ml volumetric flask and diluted up to 10 ml with phosphate buffer (pH 6.8). Finally, sample was scanned in the range of 200-400 nm. The wavelength of the maximum absorption was noted and UV spectrum was recorded.

6.2 Standard calibration curve of Domperidone

6.2.1 Standard calibration curve of Domperidone in distilled water

Accurately weighted 100 mg of Domperidone was added to the 100 ml volumetric flask. Volume was made up to 100 ml with distilled water (1000 µg/ml). From this solution 1 ml

was withdrawn and added into 10 ml volumetric flask and volume was made to 10 ml with distilled (100µg/ml). This solution was used as stock solution. From the stock solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4 ml solution was withdrawn and added into the 10 ml volumetric flask and finally diluted up to 10 ml with distilled water to get the solution with concentration of 2-14 µg/ml respectively. The absorbance was measured for each solution at 272 nm using UV visible spectrophotometer. The graph was plotted for absorbance Vs concentration.

6.2.2 Standard calibration curve of Domperidone in phosphate buffer (pH 6.8)

Accurately weighted 100 mg of Domperidone was added to the 100 ml volumetric flask. Volume was made up to 100 ml with phosphate buffer (pH 6.8) (1000 µg/ml). From this solution 1 ml was withdrawn and added into 10 ml volumetric flask and volume was made to 10 ml with phosphate buffer (pH 6.8) (100 µg/ml). This solution was used as stock solution. From the stock solution 0.4, 0.8, 1.2, 1.6, 2.0, 2.4, 2.8 ml solution was withdrawn and added in to 10 ml volumetric flask and finally diluted up to 10 ml with phosphate buffer (pH 6.8) to get the solution with concentration of 4-28 µg/ml respectively. The absorbance was measured for each solution at 272 nm using UV visible spectrophotometer. The graph was plotted for absorbance Vs concentration.

6.2.3 Standard calibration curve of Domperidone in 0.1 N HCl

100 mg of Domperidone was weighed accurately and transferred to 100 ml of calibrated volumetric flask. 50 ml of previously prepared and standardized 0.1 N HCl was transferred to same flask and swirled for solublization. Volume was made upto 100 ml mark by 0.1 N to obtain solution of 1mg/ml (1000 µg/ml) concentration. This solution was used as standard stock solution. From this solution 10 ml was withdrawn and diluted to 100 ml with 0.1 N HCl, (100µg/ml). This solution was used as working standard solution. For calibration curve dilutions were made from 2-26µg/ml. The absorbance of solutions containing 10µg/ml was determined in UV range 200-800 nm using 0.1 N HCl as blank. The λ max was found to be 272 nm. At this wavelength maximum, calibration curve was drawn by plotting graph between absorbance Vs concentration.

6.3 Drug excipients compatibility study

The oral films are prepared by using drug and other excipients. There are chances of degradation and unstable product formulation because of chemical interaction between drug and excipients. Hence, drug:excipients compatibility study is essential. Formulator must know which excipients are compatible with the drug.

Table No. 10: Ratio of Domperidone: Excipient For Compatibility Study By IR Spectroscopy.

Sr.No.	Domperidone / excipients	Ratio of Drug with excipients
1	Domperidone	----
2	HPMC E-5	----
3	HPMC E-15	----
4	HPMC K-4M	----
5	HPMC K-15	----
6	Domperidone + HPMC E-5	1:1
7	Domperidone+ HPMC E-15	1:1
8	Domperidone + HPMC K-4M	1:1
9	Domperidone + HPMC K-15	1:1

6.4 Formulation of fast dissolving oral films

6.4.1 Dose calculation

The drug to be loaded in the film was determined by the dose of the drug and the drug loading in the glass plate was determined by the area of the glass plate.

6.4.2 Exploration of polymers for preparation of films

Different polymers were used for the preparation of films. Films were prepared by the solvent casting method. They were screened for their film forming capacity, appearance and disintegration time.

6.4.3 Selection of plasticizer for optimization of films

Different plasticizers were used for the preparation of films. They were screened for their film forming capacity, appearance and disintegration time.

6.5 Method of preparation of fast dissolving oral films (Trial batch)

6.5.1 Preparation of film with different polymers

All the ingredients were weighed accordingly. The polymer was dissolved in quantity sufficient (5) ml water. The drug and saccharin were dissolved in quantity sufficient (5) ml water. The resultant solution is plasticized with using suitable plasticizer (PEG-400 and glycerol) and stirred for 15 minutes to produce a clear solution, which kept aside for 15 minutes to get bubble free solution. These solutions were casted slowly and with continuous flow on glass plate to prevent formation of bubbles then it kept for drying. The dried film was gently separated from glass plate and evaluated.

6.6 Preparation of the fast dissolving oral films of HPMC (Formulation batch)

Method

The fast dissolving oral film was prepared by dissolving (HPMC grade) film forming polymer in the distilled water (5 ml) then solution was continuously stirred up to 15 min and kept aside for 5 min to remove all the air bubbles entrapped. Meanwhile, in the separate container remaining excipients i.e. plasticizer PEG-400 and sweetener saccharin along with drug were dissolved in 5 ml of distilled water with constant stirring for 15 min. when the stirring was over both the solution were mixed together and stirred for another 15 min. Then the solution was kept stationary for 10 min to remove the air bubbles. The formulation was casted on a suitable platform and dried to form a film. The film was preferably air-dried or dried in the oven then the film was carefully removed and cut into suitable size i.e. 2cm X 2cm.

6.7 Evaluation parameters of oral fast dissolving film

6.7.1. Appearance

The formulated films should be checked for their appearance. Film should be checked visually for their appearance.

6.7.2. Thickness of films

The thickness of the film was measured by micrometer screw gauge at three different places and average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film which is directly related to the accuracy of dose in the film.

6.7.3. Weight of films / weight variation

Oral fast dissolving films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

6.7.4. Folding endurance

Folding endurance of the film is essential to study the elasticity of the film during storage and handling. The folding endurance of the film films was determined by repeatedly folding one film at the same place till it broke. This is considered to reveal good film properties. A film (2 X 2 cm) was cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance. All determination were performed in triplicate.

6.7.5. pH value

The pH value was determined by dissolving one oral film in 10 ml distilled water and measuring the pH of the obtained solution. All determinations were performed in triplicate. It is necessary that strip should have nearly uniform pH value.

6.7.6. Dryness / Tack test

Tack is the tenacity with which strip adheres to an accessory or a piece of paper that has been pressed into contact with the strip.

6.7.7. Content uniformity

Drug content was determined by dissolving the film containing 10 mg of drug in 100 ml water to get 100 µg/ml solutions. An aliquot of 01 ml sample was withdrawn and diluted to 10 ml with water. Then solution was filtred through whatman filter paper and analyzed by UV-spectrophotometer at 272 nm against blank prepared by using dummy film treated in same manner. Content uniformity studies were carried out in triplicate for each batch of the film. Limit of content uniformity is 85-115%.

6.7.8. Disintegration time

It was determined visually in a glass beaker filled with 25 ml distilled water with swirling every 10seconds. The time at which film started to break or disintegrate was recorded as the *in-vitro* disintegration time. It was performed in triplicate.

6.7.9. *In-vitro* dissolution studies

The *In-vitro* dissolution study was carried out in 500 ml pH 6.8 phosphate buffer using (USP) XIV basket apparatus II at 37^0 $\pm 0.5^0$C and at 50 rpm. Each square cut film sample (dimension: 2cm x2cm) was submerged into the dissolution media and appropriate aliquots were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 minute time intervals and again replaced with same volume of dissolution media. The sample were filtered through whatman filter paper for all the batches and analyzed spectrophotometrically at 272 nm (Model UV-1800 UV-Visible spectrophotometer, Shimadzu, Japan). Sink conditions were maintained throughout the experiment. The dissolution test was performed in triplicate for each batch.

7 RESULT AND DISCUSSION

7.1 Characterization of Domperidone

7.1.1 Description

Table No.11: Description of Domperidone.

Color	White
Odour	Odourless
Taste	bitter

7.1.2 Solubility

Domperidone was highly soluble in water and ethanol.

7.1.3 Melting point

Melting point of Domperidone was found 180^0. Thus it indicates the purity of sample.

7.1.4 Determination of λ max of Domperidone

The λ max of Domperidone was found to be 272 nm.

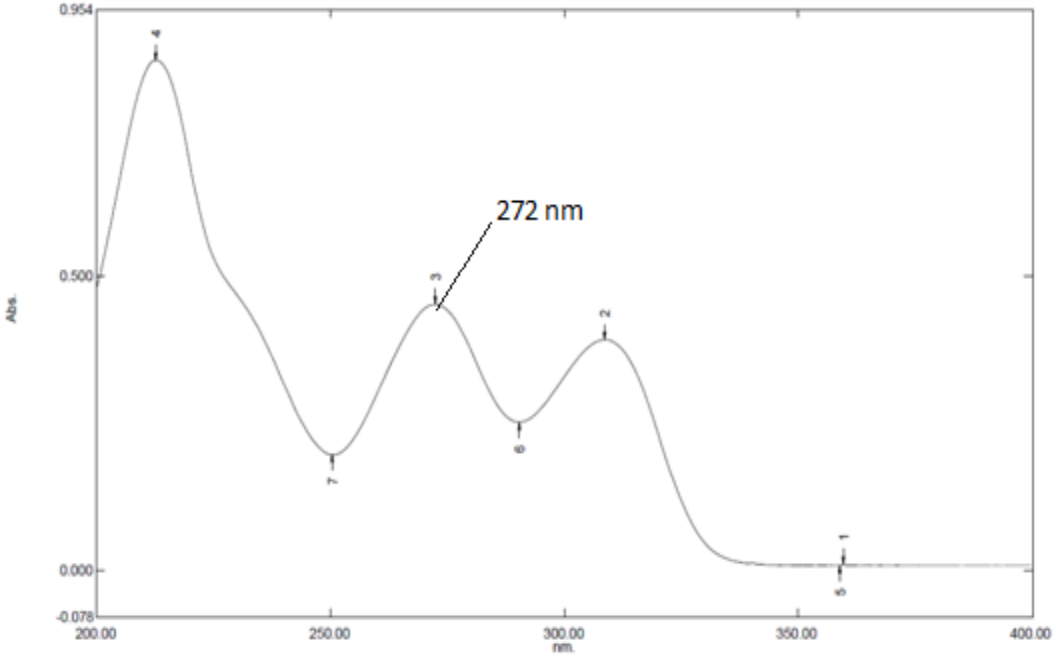


Figure No. 05: UV Spectrum of Domperidone.

7.2 Standard calibration curve of Domperidone

7.2.1 Standard calibration curve of Domperidone in Distilled water

Domperidone showed maximum absorption at wavelength 272 nm in Distilled water. Standard curve was plotted by taking absorption of diluted stock solutions (2, 4, 6, 8, 10, 12, 14 µg/ml) at wavelength 272 nm.

Table no. 12: standard calibration curve of Domperidone in distilled water.

Sr.No.	Concentration in µg/ml	Absorbance at 272 nm
1	0	0.00
2	2	0.151
3	4	0.291
4	6	0.397
5	8	0.541
6	10	0.682
7	12	0.844
8	14	0.991

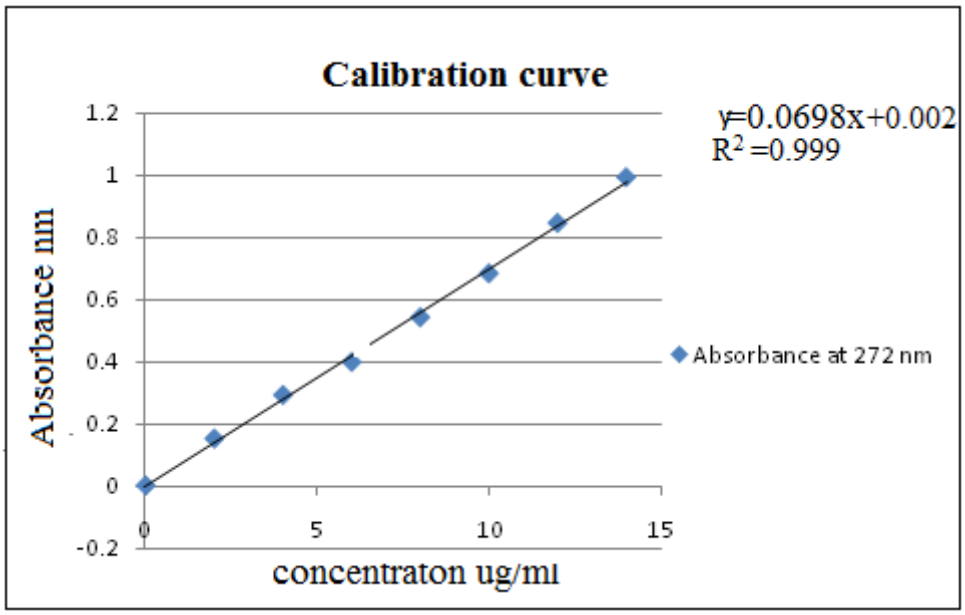


Figure No. 06: Calibration Curve of Domperidone in Distilled Water.

Table No. 13: Standard Calibration Curve of Domperidone Parameters in Distilled Water.

Sr.No	Parameter	Value
1	Regression equation	y=0.0698x+0.002
2	Correlation coefficient (R^2)	0.9972
3	Slope	0.0698
4	Intercept	0.002

7.2.2 Standard calibration curve of Domperidone phosphate buffer (pH 6.8)

Domperidone showed maximum absorption at wavelength 272 nm in Phosphate buffer (pH 6.8). Standard curve was plotted by taking absorption of diluted stock solutions (4, 8, 12, 16, 20, 24, 28 µg/ml) at wavelength 272 nm.

Table No.14: Standard Calibration Curve of Domperidone in Phosphate Buffer (PH 6.8).

Sr.No.	Concentration in µg/ml	Absorbance at 272 nm
1	0	0.00
2	4	0.157
3	8	0.276
4	12	0.429
5	16	0.540
6	20	0.654
7	24	0.827
8	28	0.948

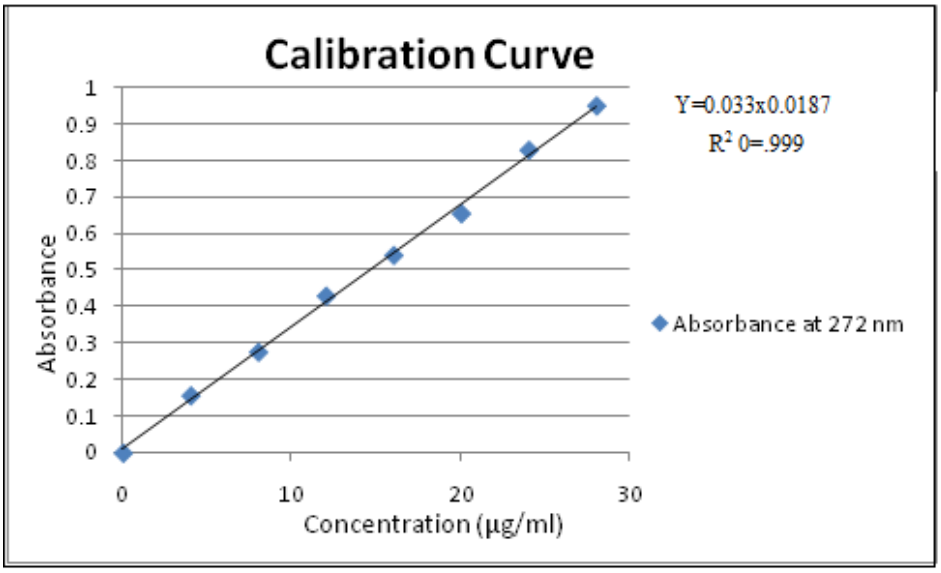


Figure No.07: Calibration Curve of Domperidone in 6.8 Phosphate Buffer

Table No.15: Standard Calibration Curve Parameters of Domperidone in Phosphate Buffer

Sr.No	Parameter	Value
1	Regression equation	Y=0.033x+0.0187
2	Correlation coefficient (R^2)	0.9975
3	Slope	0.033
4	Intercept	0.0187

7.2.3 Standard calibration curve of Domperidone in 0.1 N HCl

Domperidone showed maximum absorption at wavelength 272 nm in 0.1 N HCl. Standard curve was plotted by taking absorption of diluted stock solutions (2-26 µg/ml) at wavelength 272 nm.

Table No. 16: Standard Calibration Curve of Domperidone 0.1 N HCl.

Sr.no.	Concentration in µg/ml	Absorbance at 272 nm
1	0	0.00
2	2	0.078
3	4	0.150
4	6	0.232
5	8	0.296
6	10	0.374
7	12	0.440
8	14	0.525
9	16	0.589
10	18	0.661
11	20	0.731
12	22	0.811
13	24	0.874
14	26	0.941

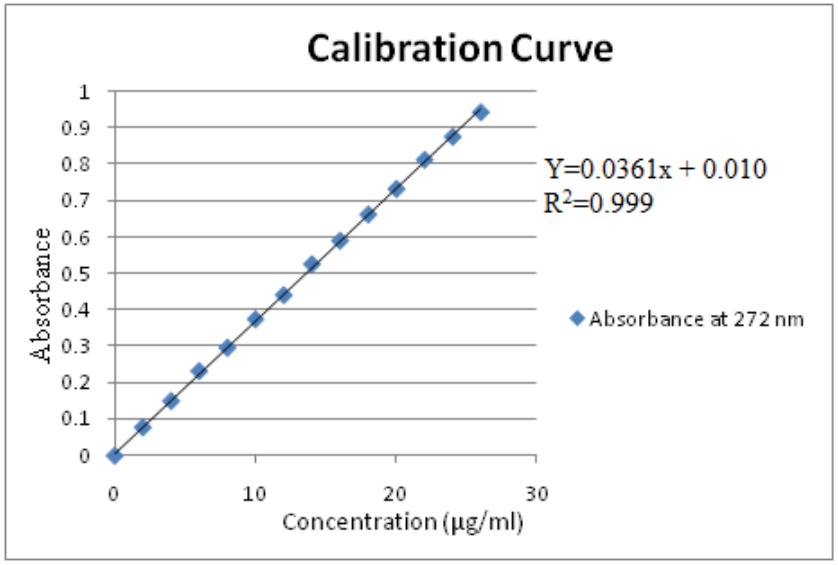


Figure No. 08: Calibration Curve of Domperidone in 0.1 N HCl.

Table no. 17: Standard calibration curve parameters in 0.1 N HCl

Sr.No	Parameter	Value
1	Regression equation	y=0.0361x + 0.010
2	Correlation coefficient (R^2)	0.9997
3	Slope	0.0361
4	Intercept	0.010

7.3 Drug excipients compatibility studies by IR spectroscopy

The infrared spectrum of Domperidone recorded in a KBr pellet on FTIR-4100, Jasco, Japan. From the Infrared frequencies and the respective assignments are given below.

Table No.18: IR Peaks of Various Functional Groups of Domperidone.

Functional group	Wave number (cm^{-1})
Aliphatic C-H stretch	2879 cm-1
Amide C=O stretch	1648 cm-1
Aromatic C=C stretch	1550 cm-1
Amine N-H stretch	3449 cm-1

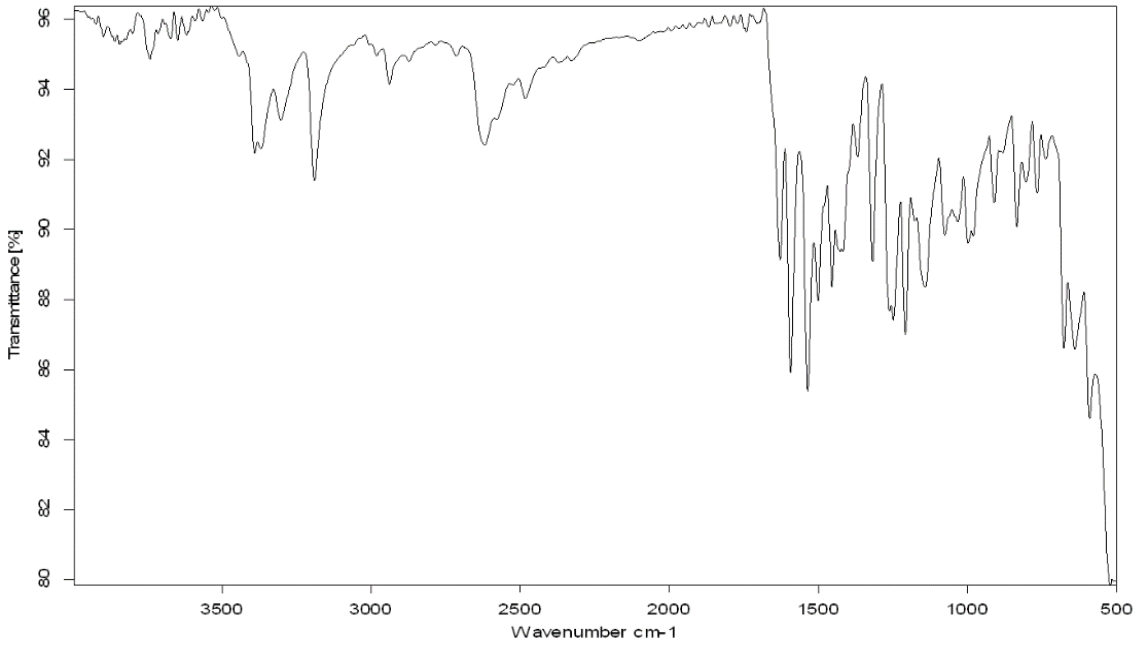


Figure no. 09: IR spectrum of Domperidone

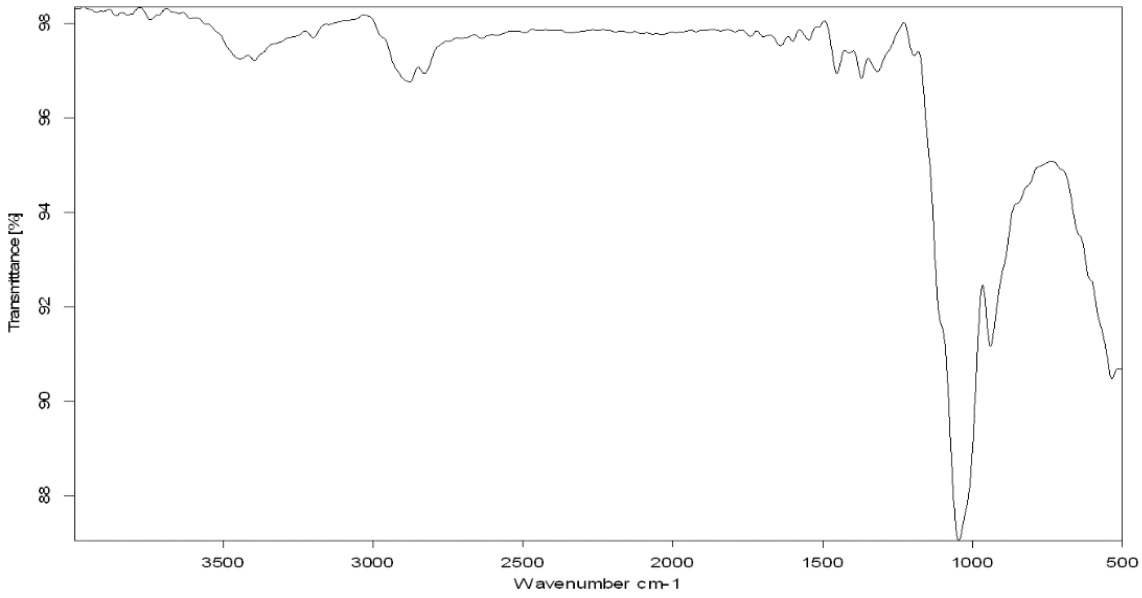


Figure No. 10: IR Spectra of HPMC E5

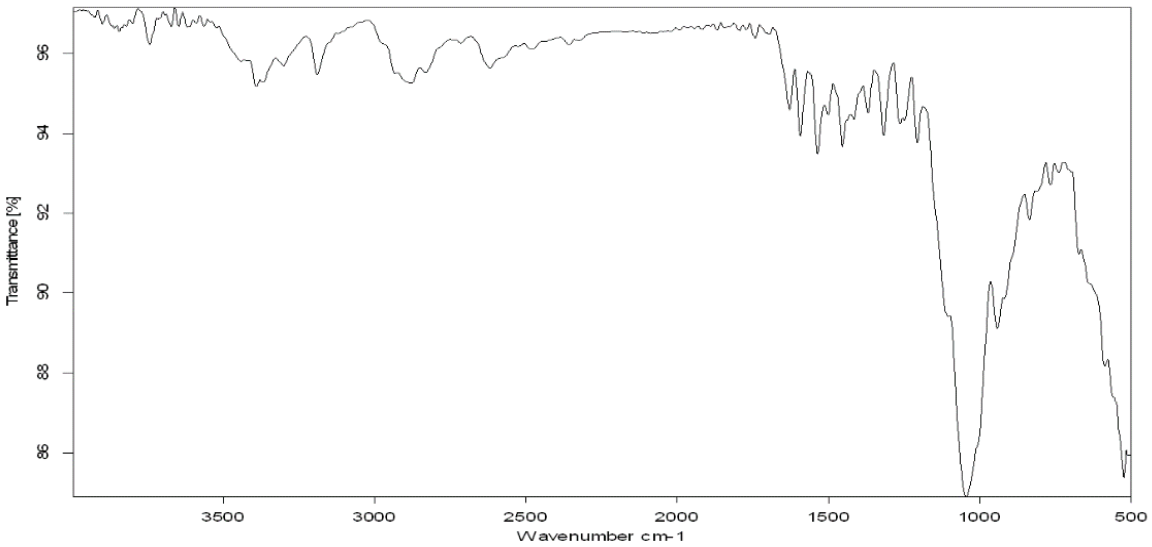


Figure No.11: IR Spectra of Domperidone With HPMC E5.

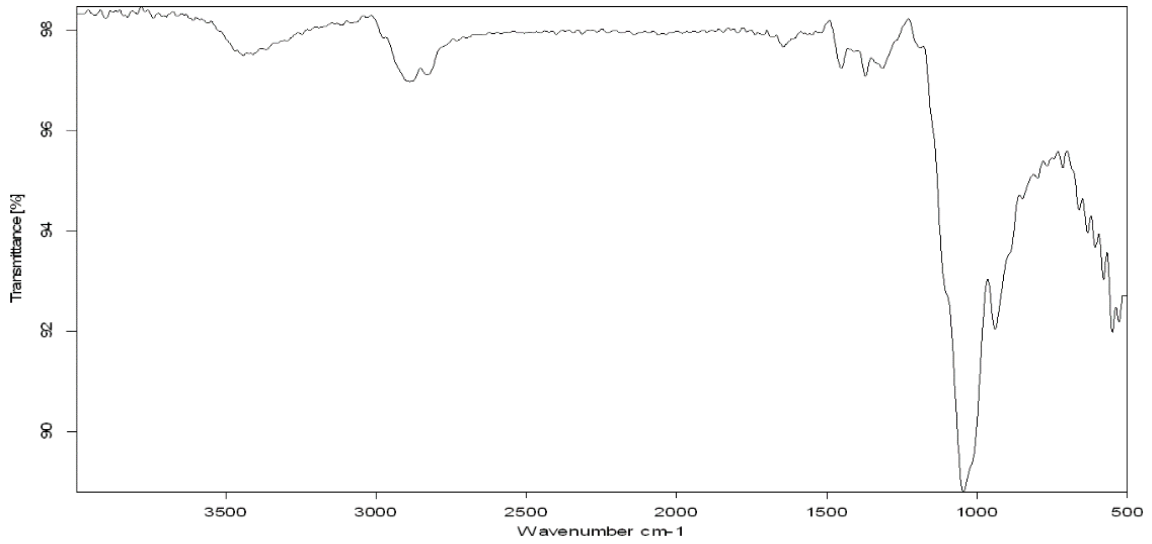


Figure No. 12: IR Spectra of HPMC E15.

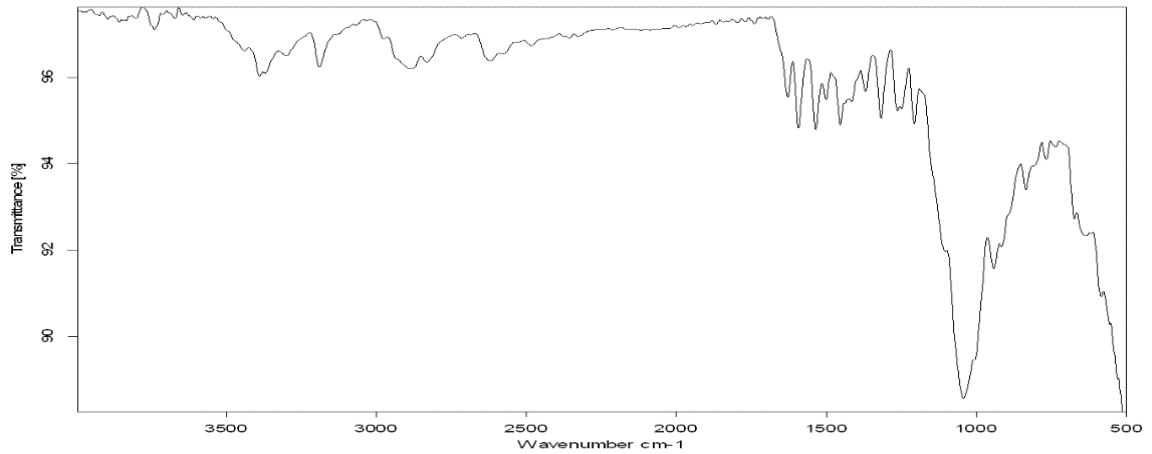


Figure No. 13: IR Spectra of Domperidone With HPMC E15.

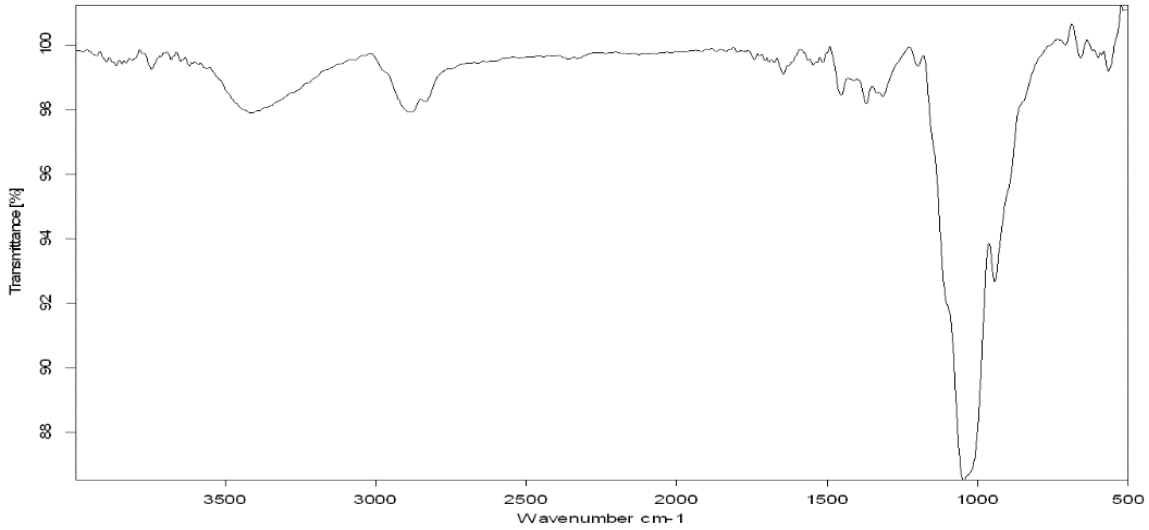


Figure No. 14: IR Spectra of HPMC K4M.

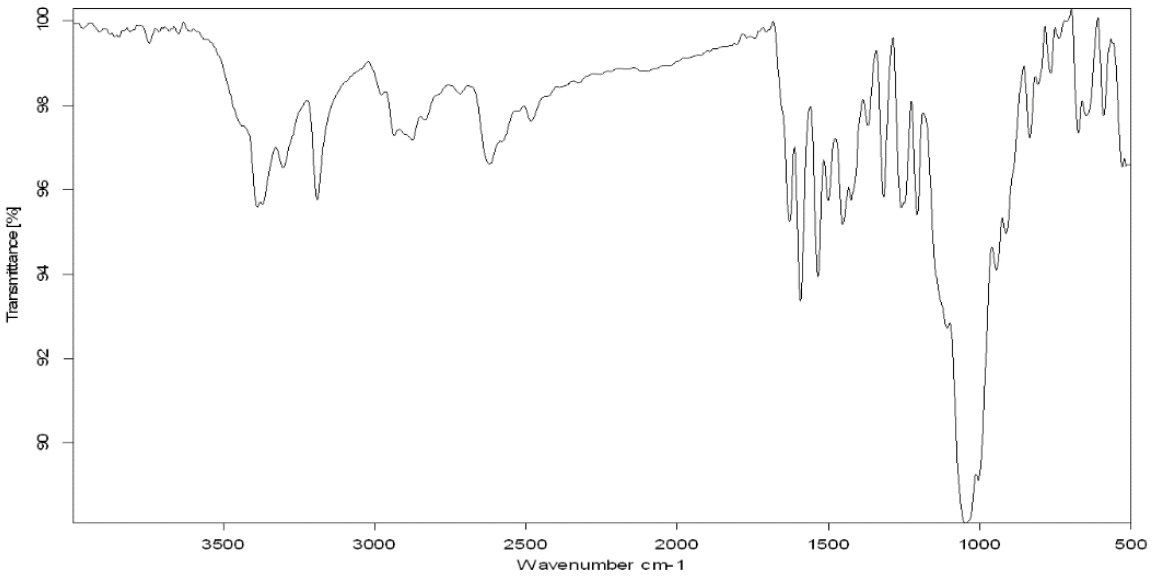


Figure No. 15: IR Spectra of Domperidone With HPMC K4M.

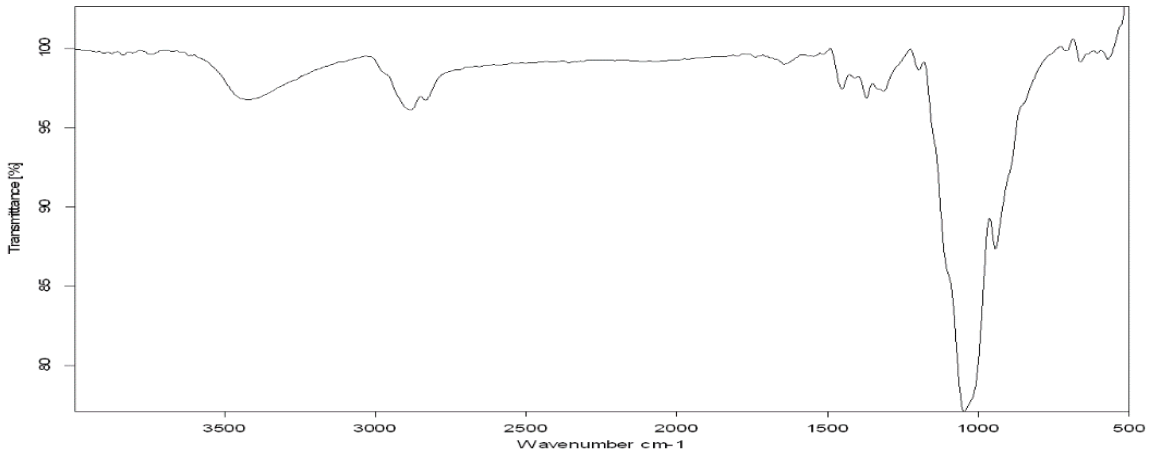


Figure No. 16: IR Spectra of HPMC K15.

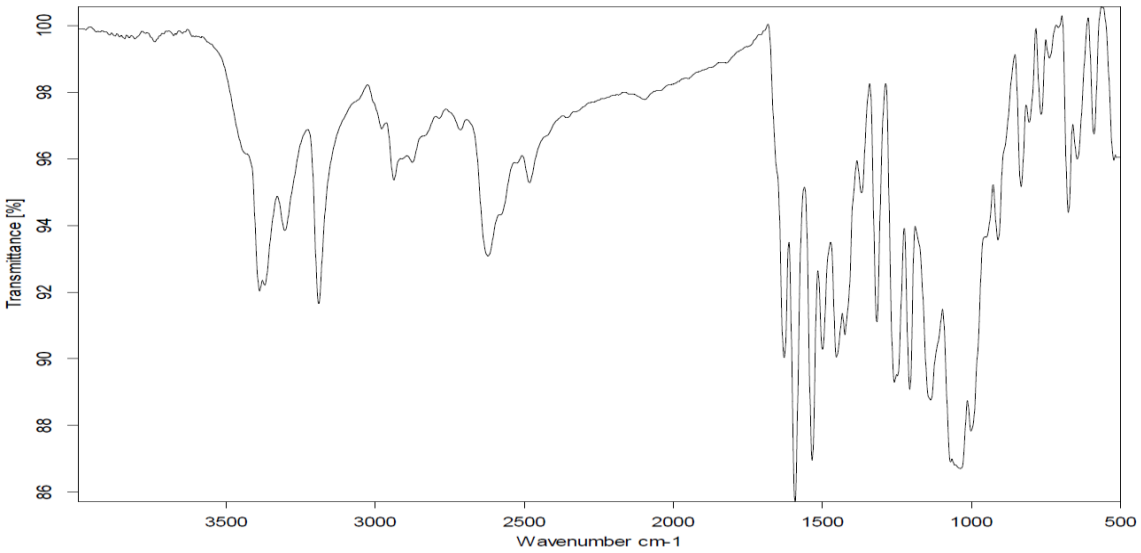


Figure No.17: IR Spectra of Domperidone With HPMC K15.

7.4 Formulation of fast dissolving oral film

7.4.1 Dose calculation

Diameter of the plate = 6 cm

Area of the plate = πr^2 =28.26 cm^2

No of 4 cm^2 films present in whole plate = 28.26/4 s = 7.065

Each film contains 10 mg of drug.

The amount of drug to be loaded in each plate was =7.065 x 10

=70.65 mg

7.4.2 Exploration of the polymers for formulation of oral fast dissolving film

Different polymers like HPMC E5, HPMC E15, HPMC K4M, HPMC K15M, Maltodextrin, Xanthum gum, Guar gum were used for preparation of FDF.

7.4.3 Selection of plasticizer for optimization of films

PEG 400, PG and Glycerol were used as a Plasticizer in films. All the films were transparent. As the concentration of plasticizer increases it also increases the flexibility of the films. All the trial Batches were formulated using various types and proportion of plasticizer. Plasticizer also affects the film separation property of the film. When the concentration of PEG 400 was increased, it also increases the flexibility of the film as compare to the Glycerol. The plasticizer affects the flexibility of the films hence folding endurance was also gets affected. The PEG 400 showed the good effect on folding endurance and Disintegration time. So it was selected as a plasticizer for further batches of the films.

7.5 Preparation of trial batches of fast dissolving oral films

Table No. 19: Trial Batches of Fast Dissolving Oral Films

Polymer	T1	T2	T3	T4	T5	T6	T7
HPMC E-5	✓						
HPMC E-15		✓					
HPMC K-4M			✓				
HPMC K-15				✓			
Maltodextrin					✓		
Xanthum gum						✓	
Guar gum							✓
Dist.water	✓	✓	✓	✓	✓	✓	✓

Table No. 20: Quantity of Polymer and Excipients Taken In Trial Batches.

Polymer	Drug	Polymer quantity	PEG-400	Saccharin	DW
HPMC	70	100	50	20	Qs
Xanthum gum	70	100	50	20	Qs
Guar gum	70	30	50	20	Qs
Maltodextrin	70	30	50	20	Qs

7.5.1 Preparation of film using HPMC grades polymers

Fast dissolving oral films using HPMC grades were formed. They were evaluated and screened for Appearance and dryness. Films formed were transparent, dry. Film forming capacity is high as compared to other polymers.

7.5.2 Preparation of film using xanthum gum as polymer

Film using xanthum gum doesn't form. Xanthum gum is largely used as binder, it forms clots in solution.s Film forming capacity of xanthum gum is very poor. Hence, this polymer was not used for further study.

7.5.3 Preparation of film using Guar gum as polymer

Film using guar gum doesn't form. Guar gum is largely used as binder, it forms clots in solution. Film forming capacity of guar gum is very poor. Hence, this polymer was not used for further study.

7.5.4 Preparation of film using Maltodextrin as polymer

Film using maltodextrin as polymer formed, but it cannot be removed from petri plate. It breaks down into pieces while removing from petri plate. Film forming capacity of maltodextrin is poor. Hence, this polymer was not used for further study.

Table No.21: Evaluation Parameters of Trial Batches.

Sr.no.	Polymer	Film forming capacity	Tack test	Appearance
1	HPMC	Good	Non tacky	Transparent
2	Xanthum gum	-------	-------	-------
3	Guar gum	-------	-------	-------
4	Maltodextrin	-------	-------	-------

7.6 Formulation design

Fast dissolving oral films are prepared using various grades of HPMC as polymer.

Table No. 22: Formulation Design.

Trial code	Domperidone	HPMC E-5	HPMC E-15	HPMC K-4M	HPMC K-15	PEG-400	Saccharin	DW
F1	70.65	100	----	----	----	50	20	Qs
F2	70.65	200	----	----	----	50	20	Qs
F3	70.65	300	----	----	----	50	20	Qs
F4	70.65	----	100	----	----	50	20	Qs
F5	70.65	----	200	----	----	50	20	Qs
F6	70.65	----	300	----	----	50	20	Qs
F7	70.65	----	----	100	----	50	20	Qs
F8	70.65	----	----	200	----	50	20	Qs
F9	70.65	----	----	300	----	50	20	Qs
F10	70.65	----	----	----	100	50	20	Qs
F11	70.65	-----	----	----	200	50	20	Qs
F12	70.65	----	----	----	300	50	20	Qs

*Area of the film- 2 X 2cm^2

** Dose of drug per film- 10 mg

7.7 Evaluation

Evaluation of Films prepared in Formulation design

In the following table, Film forming capacity, Tack test and Appearance were checked.

Table No. 23: Evaluation For Film Forming Capacity, Tack Test And Appearance of Film

Sr.no.	Formulation batch	Film forming capacity	Tack test	Appearance
1	F1	Good	Tacky	Transparent
2	F2	Best	Non tacky	Transparent
3	F3	Better	Non tacky	Transparent
4	F4	Good	Tacky	Transparent
5	F5	Best	Non tacky	Transparent
6	F6	Better	Non tacky	Transparent
7	F7	Good	Non tacky	Transparent
8	F8	Better	Non tacky	Transparent

9	F9	Better	Non tacky	Transparent
10	F10	Good	Non tacky	Transparent
11	F11	Better	Non tacky	Transparent
12	F12	Better	Non tacky	Transparent

Evaluation parameter of formulation batches

Table No.24: Evaluation Parameter of Formulation Batches.

Batch	Disintegration time(Sec)	Folding endurance	% drug content	Weight variation(mg)	Film thickness(mm)	pH
F1	16.6±0.57	15±1	2.49	12	0.7	6.26±0.011
F2	21.3±0.57	42.3±0.57	2.5	16	0.8	6.81±0.03
F3	30.3±0.57	51.6±0.57	2.51	22	1	6.73±0.06
F4	26±1	14.3±0.57	2.52	13	0.8	6.33±0.02
F5	30±1.73	41.3±0.57	2.48	16	0.9	6.38±0.015
F6	33.6±0.57	58.6±0.57	2.49	24	1	6.7±0.015
F7	27±1	15.3±1.15	2.52	13	0.8	6.32±0.11
F8	39±0	37.3±0.57	2.48	18	1	6.47±0.017
F9	47.3±0.57	56±0	2.49	27	1.1	6.75±0.02
F10	26.3±1.52	20±1	2.5	13	0.8	6.32±0.015
F11	36.6±0.57	47.6±1.15	2.52	18	1	6.55±0.015
F12	48.3±0.57	58.6±0.57	2.49	26	1.2	6.67±0.02

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

7.8 Evaluation parameters discussion

In the present research work, Preparation and evaluation of fast dissolving oral films, films were prepared Domperidone as drug and polymers like HPMC E5, E15, K4M and K 15 in different concentrations by solvent casting technique, the prepared fast dissolving film were evaluated for various parameters and the results of these parameters were given in Table no. 22 and they are discussed in detail in the following section of this chapter.

7.8.1 Physical appearance and surface texture of fast dissolving film

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

7.8.2 Thickness of fast dissolving film

The thickness of the fast dissolving films were measured using screw gauge and the average thickness of all Fast dissolving film was given in table no.24. The thickness of the Fast dissolving film prepared with HPMC E5, E15, K4M and K15 HPMC respectively.

Thickness of fast dissolving oral films were found between 0.7-1.2 mm (n=3).

7.8.3 Weight variation of fast dissolving film

The weight of Fast dissolving film was determined using digital balance and the average weight of all Fast dissolving film were given in table no.24.

7.8.4 Folding Endurance of Fast dissolving film

The folding endurance of the Fast dissolving film was determined by repeatedly folding a small strip of the Fast dissolving film at the same place till it broke and the average folding endurance of all Fast dissolving film was given in table no-24.

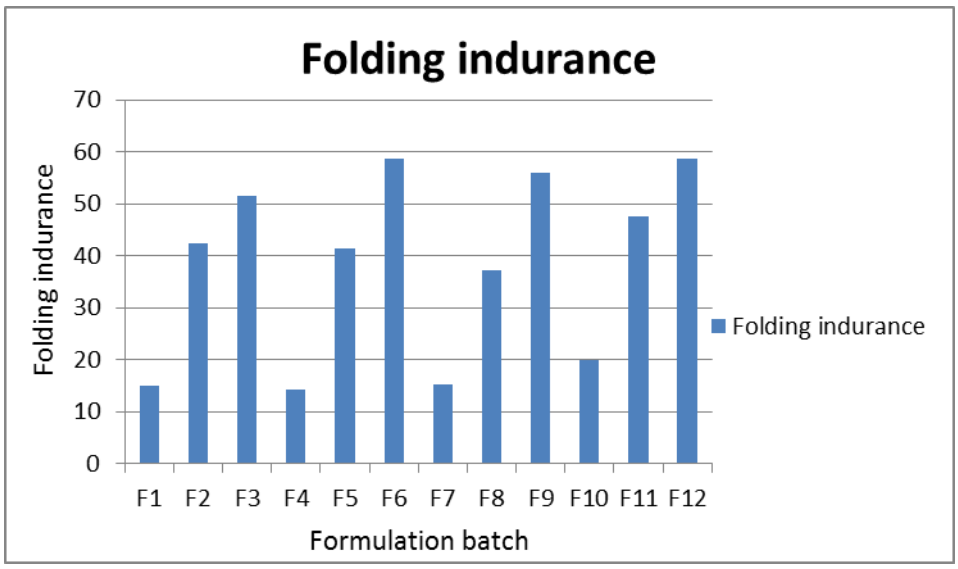


Figure No.18: Folding Endurance of Formulation Batch.

7.8.5 Surface pH of fast dissolving film

The surface pH was noted by pH meter near the surface of fast dissolving film and allowing to equilibrate for 1 min and the surface pH of all fast dissolving film was given in table no.24. The surface pH of the fast dissolving film was found to in-between 6.26-6.81 pH (n=3).

7.8.6 Tack test

All films were evaluated for tack test out of that only F1 and F4 batches were found to be tacky. The tack test of all fast dissolving oral films was given in table no.24.

7.8.7 Drug Content uniformity of fast dissolving film

In each case three fast dissolving films were used and the average drug content was calculated, the results were shown in table no.24. The drug was dispersed in the range of 2.48-2.52 (n=3). Suggesting that drug was uniformly dispersed in all fast dissolving film. The

S.D. value calculated for such formulation is very less which suggest that the results are reproducible and accuracy in the method used to prepare the fast dissolving film.

7.8.8 Disintegration time of fast dissolving film

Film of 2 x 2 cm^2 size taken and disintegration time checked visually. In each case three fast dissolving films were used and the average drug content was calculated, the results were shown in table no.24.

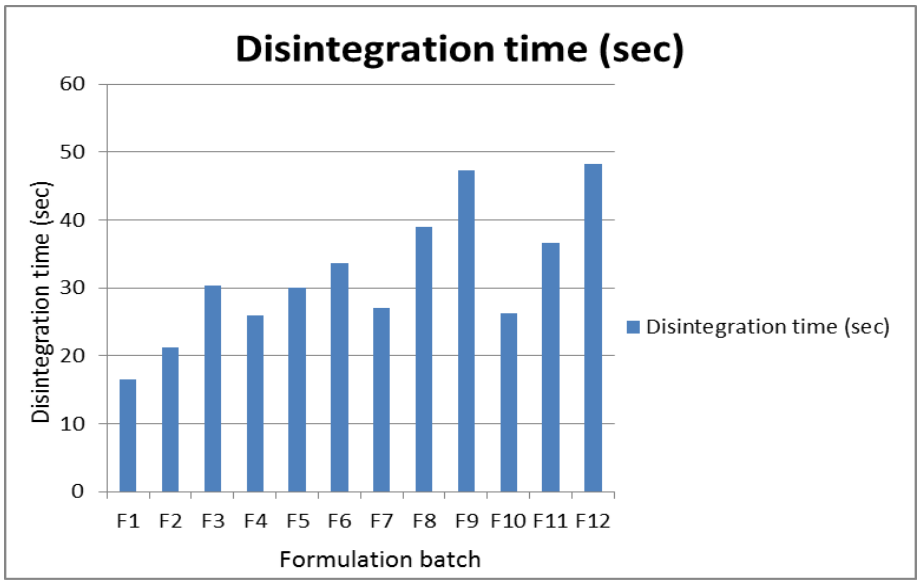


Figure No. 19: Disintegration Time of Formulation Batch.

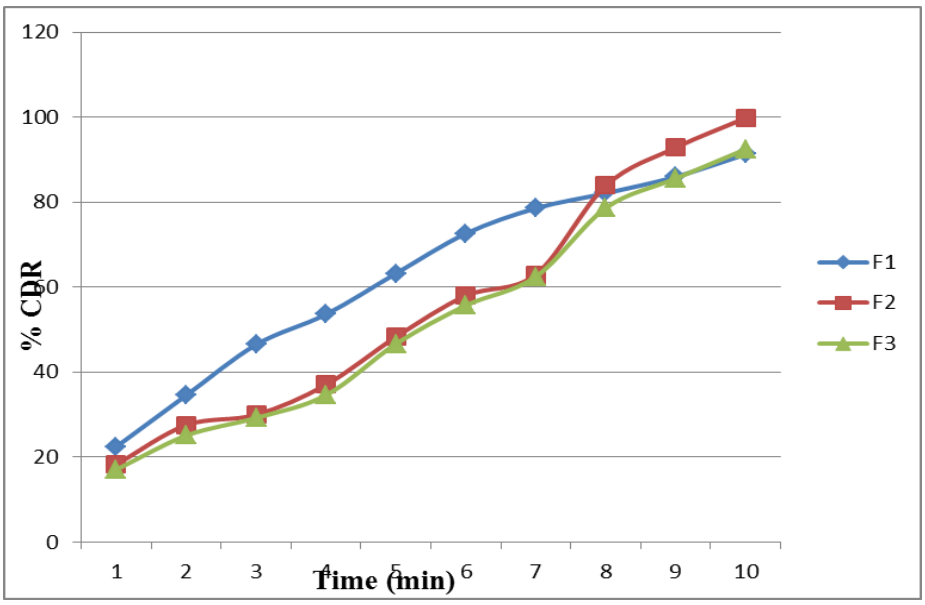


Figure No. 20: % Cumulative Drug Release From F1-F3.

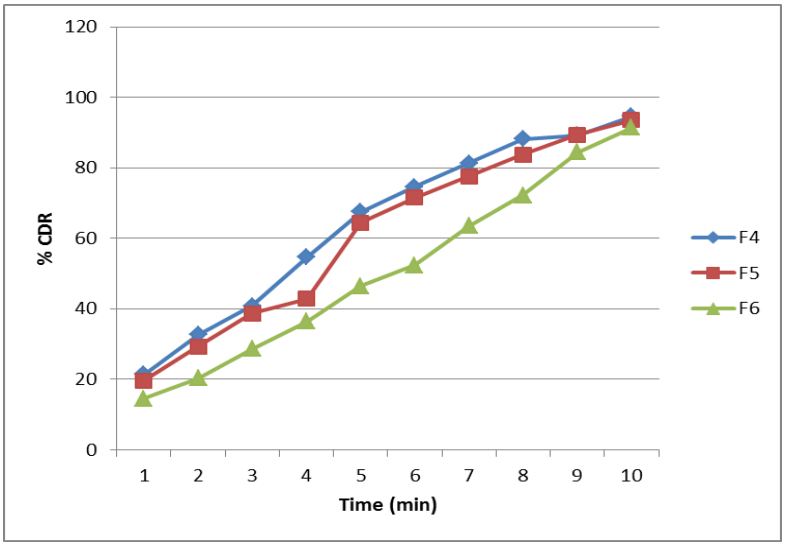


Figure No.21: % Cumulative Drug Release From F4-F6.

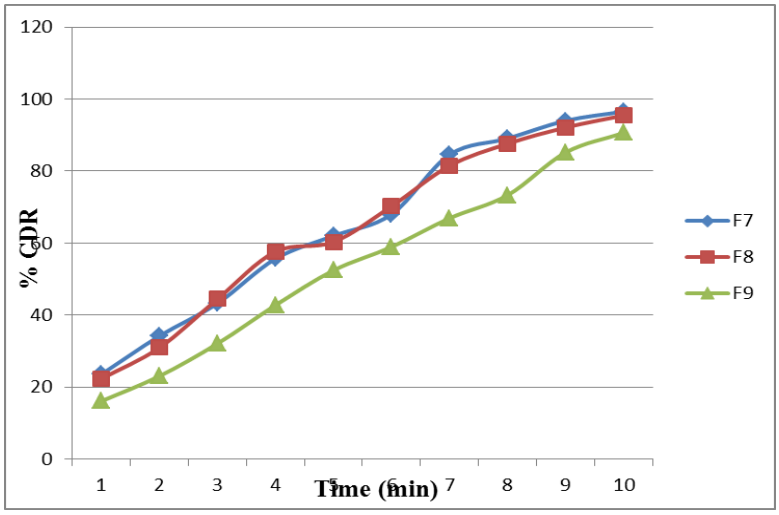


Figure No.22: % Cumulative Drug Release From F7-F9.

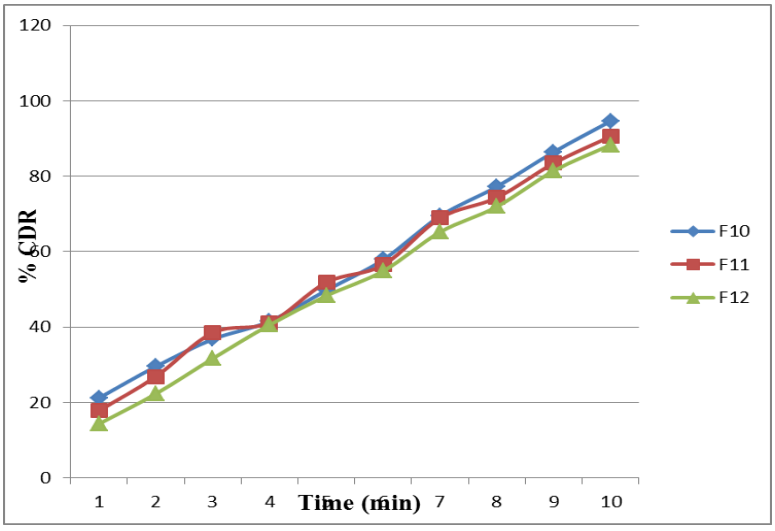


Figure No.23: % Cumulative Drug Release From F10-F12.

***In-Vitro* Dissolution Studies**

Table No.25: *In-Vitro* Dissolution Studies Of Domperidone From F1-F6.

Time (min)	% CDR					
	F1	F2	F3	F4	F5	F6
1	22.45±0.12	18.27±0.39	17.05±0.21	21.35±0.29	19.59±0.16	14.53±0.28
2	34.54±0.13	27.52±0.37	25.07±0.46	32.7±0.22	29.24±0.29	20.35±0.43
3	46.47±0.15	29.98±0.41	29.22±0.41	40.88±24	38.64±0.33	28.62±0.16
4	53.61±0.14	37.02±0.49	34.59±0.31	54.7±03	42.87±0.65	36.42±0.35
5	63.22±0.31	48.29±0.54	46.65±0.47	67.52±0.32	64.49±0.35	46.47±0.28
6	72.62±0.29	57.98±0.12	55.69±0.19	74.65±0.32	71.49±0.43	52.3±0.45
7	78.56±0.31	62.98±0.45	62.46±0.14	81.29±0.43	77.53±0.39	63.45±0.39
8	82.1±0.47	83.88±0.76	78.63±0.36	88.21±0.28	83.74±0.23	72.26±0.40
9	85.96±0.22	92.83±0.39	85.57±0.34	89.24±0.34	89.41±0.26	84.48±0.36
10	91.26±0.40	99.81±0.09	92.45±0.29	94.59±0.33	93.59±0.17	91.4±0.3

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

Table no.26: *In-Vitro* dissolution studies of Domperidone from F7-F12.

Time (min)	% CDR					
	F7	F8	F9	F10	F11	F12
1	23.53±0.23	22.32±0.55	16.08±0.79	21.21±0.74	17.84±0.64	14.37±0.41
2	34.18±0.56	30.94±0.49	23.04±0.22	29.56±0.18	26.91±0.32	22.33±0.08
3	43.27±0.04	44.46±0.98	32.08±0.46	36.78±0.07	38.53±0.41	31.67±0.44
4	55.65±0.79	57.65±0.12	42.75±0.89	41.55±0.28	41.18±0.62	40.61±0.66
5	62.02±0.67	60.32±0.36	52.43±0.07	49.78±0.66	51.88±0.77	48.33±0.33
6	68.02±0.34	70.27±0.49	58.95±0.71	57.89±0.34	56.49±0.86	54.89±0.07
7	84.58±0.92	81.50±0.86	66.92±0.38	69.45±0.67	68.93±0.43	65.21±0.71
8	59.08±0.88	87.63±0.35	73.34±0.96	77.27±0.33	74.36±0.11	71.96±0.61
9	94.02±0.07	92.15±0.73	85.20±0.21	86.45±0.41	83.47±0.18	81.45±0.37
10	96.55±0.39	95.47±0.08	90.64±0.77	94.63±0.55	90.58±0.32	88.33±0.18

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

CONCLUSION

Oral dosage forms remain the primary delivery route for pharmaceuticals because of ease of administration and beneficial release characteristics. A number of pharmaceutical dosage forms are available in the market. There are problem of tablets and painful parenteral dosage forms. Fast dissolving oral film has many advantages related to disintegration, dissolution and bioavailability over these existing dosage forms. In addition to this, film avoids first pass metabolism due to pre-gastric absorption and fast onset of action. Patient compliance is high in all age groups patients especially pediatrics and geriatrics. However, the pharmaceutical industry's interest has increased in this delivery forms that administer medicines directly through vehicles, like transdermal patches, and drug-impregnated medical devices, like intravaginal rings. The rapidly dissolving film drug delivery vehicle bridges the gap between

the two ideas, incorporating positive elements from both solid and liquid dosage forms into an elegant, stable, and effective delivery vehicle. But, this film dosage form has come across some obstacles during its formulation and development. So, there is need to address such challenges which may help in future to explore the particular area in research and that may help in overall formulation and development and large scale manufacturing.

For the present study, Domperidone was selected as a model drug candidate as no marketed film of Domperidone is available in India. Moreover, the conventional tablet leading to patient noncompliance. The developed formulation which disintegrates in oral cavity in less than 60 seconds without the need of drinking water; and improved patient compliance particularly for those who have difficulty in swallowing. A Preformulation study was carried out during the early stages of this work. It has found that Domperidone is having maximum absorption at wavelength 272 nm. The drug-polymer compatibility study was carried out to determine the interactions between the drug and the polymers used in the study. The FTIR study revealed that, polymers and excipients used were compatible with drug. The Fast dissolving films were formulated by solvent casting technique. Different polymers were screened for the preparation of Fast dissolving films. Amongst all the formulations, formulation containing HPMC E5 combine with PEG-400 as plasticizer has shown excellent *in vitro* disintegration time and *in vitro* cumulative percent dissolution, compared to other formulations.

Formulation F2 (HPMC E5: PEG-400, 200:50) disintegrated in 23 seconds and released 99.8% of drug within 10 minutes and was considered as the best formulation. As the concentration of film forming polymers gets increased it also increases the film forming capacity of the films.

From above discussion, it can be concluded that the successful formation and optimization of fast dissolving films of Domperidone using HPMC E5 as film forming polymer and PEG-400 as a plasticizer Hence Domperidone can be conveniently administered orally in the form of films.

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