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FORMULATION AND CHARACTERIZATION OF ORALLY DISINTEGRATING FILM OF INDOMETHACIN

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ABSTRACT

Technology advancements in recent years have made effective dose alternatives to the oral route for patients who are young, old, immobile, queasy, or unable to comply. Orally disintegrating film is a solid dosage form, which disintegrates or dissolves within 1 minute when placed in the mouth without drinking water or chewing. The oral film includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, film stabilizing agents, sweeteners, flavors, colors, saliva stimulating agents, preservatives, surfactants, etc but the first and far most a very essential ingredient that helps in film formationis a Polymer.

Orally disintegrating Film is prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. For quickly disintegrating films, wafter-soluble polymers are utilized as film formers, water-soluble polymers give the films quick disintegration, a pleasant mouthfeel, and mechanical qualities.

Oral films of Indomethacin were prepared by Solvent Casting method by using polymers like HPMC, propylene glycol, polyethylene glycol, citric acid, and saccharin sodium, total 9 formulations were done in which F3 was the most effective one and showed best results. Even Evaluations as thickness, weight variation, folding endurance, percentage elongation, tensile strength, drug content, SEM analysis, etc were done.

F3 has shown less disintegration time of 20 seconds and 99% drug released within 3 minutes therefore, rapid drug release was achieved for immediate onset of action which is beneficial when compared to conventional tablet dosage form.

KEYWORDS

1) Oral disintegrating film
2) Oral dissolving film
3) Indomethacin
4) NSAID (Non-steroidal anti-inflammatory drugs)
5) Water-soluble polymers
6) Fast dissolving
7) Folding endurance
8) Tensile strength
9) SEM analysis
10) FTIR

INTRODUCTION

1.1 Oral Disintegrating Film

Due to its simplicity, ability to reduce pain, adaptability (to accommodate a variety of drug candidates) and most importantly, patient compliance, oral administration is the most widely used route. Solid oral delivery systems also do not require sterile conditions, making them less expensive to produce. Recently, a number of innovative oral administration methods have been made available to address the physicochemical and pharmacokinetic properties of medications while enhancing patient compliance. Additionally, recently developed technologies include computer-assisted three-dimensional printing (3DP) tablet production and electrostatic drug deposition and coating.

For paediatric and elderly patients who have trouble swallowing standard oral solid dosage forms, such as pills, capsules and syrups, oral-dissolving drug delivery devices were initially created in the late 1970s. Oral dissolve, rapid dissolve, rapid melt, and quick disintegrating tablets are examples of revolutionary oral dispersing dosage forms technology. However, all of these dosage forms share a similar principle and function.

An oral-dispersing dosage form is, by definition, a solid that quickly dissolves or disintegrates in the mouth to produce a solution or suspension without the need for water to be administered. Dysphagia, or trouble swallowing, affects people of all ages, but it's more prevalent among the elderly. It can also make it difficult to take regular tablets and capsules. Numerous medical illnesses, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck thyroid treatment, and other neurological conditions, such as cerebral palsy, are linked to dysphagia.

Tablet size was the most often mentioned issue, followed by surface, form, and flavour. Patients with elderly and paediatric conditions, as well as those who were travelling and might not have easy access to water, had more difficulty taking tablets.

❖ Salient Features of Orally Dissolving Drug Delivery System

1. Convenience of administration for mentally ill, impaired, and uncooperative patients.
2. Don't need water.
3. Overcomes the medicine's unpleasant flavour.
4. May be created to leave little to no aftertaste in the mouth and to provide the user a satisfyingmouthfeel.
5. The ability to offer liquid medicinal benefits in the form of a solid formulation.
6. Budget friendly.

❖ Need for Orally Dissolving Drug Delivery System

Dysphasia or trouble swallowing, affects people of all ages frequently. Dysphasia affects roughly 35% of the general population, as well as an additional 30–40% of the elderly and 18–20% of all people living in long-term care institutions, according to research. There are frequent complaints regarding the size, surface, form, and flavour of tablets making them difficult to swallow. Patients in the elderly, children, and on the go who might not have easy access to water require dosage forms that are simple to ingest. These findings highlight the critical need for a dose form, such as FDDDS, that causes tablets to dissolve in the mouth without chewing or additional water consumption, improving patient compliance.

❖ Market Review

Due to low patient compliance with current administration regimens, a small market for pharmaceutical companies and medication users, as well as significant disease treatment expenses, the demand for non-invasive delivery systems is still present. One factor contributing to the rise in oral-dissolving/disintegrating products is pharmaceutical marketing. Pharmaceutical companies frequently create a specific therapeutic entity in a new and enhanced dosage form as a drug entity approaches the end of its patent life. A dosage form enables the producer to increase market exclusivity while providing a more practical dosage form or dosing schedule to its patient population. Oral dissolving/disintegrating formulations are comparable to several prolonged-release formulations that are now widely accessible in this regard. An oral-dissolving or disintegrating dosage form can extend market exclusivity, which boosts sales while also focusing on the underserved and under-treated patient

population.

❖ **These oral-dissolving films provide a number of benefits, including**

1. Films provide quick disintegration and dissolving in the oral cavity due to the huge surfacearea present.
2. Dosing convenience.
3. Quick effects that follow rapid breakdown are advantageous in some circumstances, such as when there is pain.
4. Oral dissolving films can be used anytime, anywhere, and without water.
5. Suitability for elderly and young patients, those who have trouble swallowing, those who are mentally ill, those who are developmentally disabled, and patients who are uncooperativeor on reduced liquid intake programs.
6. No chance of choking.
7. Because oral dissolving films are flexible and portable, they are simple to travel, handle byconsumers, store, and have improved stability.
8. Beneficial in circumstances such as motion sickness, acute discomfort, allergic reaction orcoughing, when an extra quick beginning of action is required.
9. When compared to liquid formulations, dosage accuracy is from each film strip, it is guaranteed.
10. Due to the highly vascularized oral or buccal mucosa, medicines can be absorbed immediately and can enter the systemic circulation without first going through hepatic first pass metabolism. This benefit can be used to create products that have better oral bioavailability of compounds that experience the first-pass effect.
11. Thin-film sublingual and buccal drug delivery has the potential to speed up the beginning of action, reduce dosage, and improve the drug's efficacy and safety profile.
12. Greater patient adherence.
13. Life cycle administration.
14. Tablet swallowing difficulties are avoided, which is beneficial for both paediatric and geriatric patients with disorders that induce nausea or vomiting.[14]

1.2 Oral Dissolving Films

The more recent technology used in the production of oral disintegrating dose forms are oral films. They are thin, attractive films made of ingestible, water-soluble polymers that might be square, rectangular, or disc-shaped. The stripes could be clear or opaque, flexible or brittle.

They are created to break down quickly on the tongue without the aid of water. The specific surface area for disintegration in Oral disintegrating films (ODFs) is considerable. The films overcome the shortfalls of oral rapid-dissolving pills by reducing the risk or worry of choking, making them simple to handle and administer and easy to make. This dosage form low medication loading capacity and limited flavour masking possibilities are significant drawbacks.

A thin film with a surface area of 1–20 cm^2 and a thickness of 1–10 mm is referred to as a Oral dissolving film. Approximately 15 mg of medication can be ingested in a single dose. Due to a specific matrix constructed of water-soluble polymers, which typically has minimal tack for easy handling and application, products dissolve instantly in saliva. However, the wet tack and mucoadhesive characteristics of the system are intended to fix the film at the application location upon wetting. Films are chosen for their strength and flexibility to make production processes such as rewinding, die cutting, and packing easier. On the patient's tongue are mucosal tissue, which is quickly evaporating film, which is immediately moistened by saliva. The film quickly hydrates and sticks to the application place. The medicine is then quickly released for either gastric absorption when swallowed or for oral mucosal absorption.[12]

Table 1: Comparison between Oral disintegrating film and Oral disintegrating tablet.

Oral dissolving films	Oral disintegrating tablets
It is a film	It is a tablet
Greater dissolution due to larg surface area	Lesser dissolution due to less surfaceare
Better durable than ora disintegratingtablets	Less durable as compared with oralfilms
More patient compliance	Less patient compliance than films
Low dose can only be incorporated	High dose can be incorporated
No risk of chocking	It has a fear of chocking

1.3 Formulation Consideration

- Active Pharmaceutical Ingredient
- Film-forming polymer
- Plasticizer
- Sweetening agent
- Saliva stimulating agent
- Flavouring agent
- Colouring agent

❖ **Active Pharmaceutical Ingredient**

A typical film composition has 1-25% weight/weight of the medication. Oral dissolving films can provide a variety of APIs. The most suitable options for incorporation into ODFs are small dosage compounds. Multivitamins up to 10% by weight of the dry film were added to the films with a dissolving time of under 60 seconds. Having micronized API is usually beneficial as it will enhance the texture of the film and also promote improved dissolving and uniformity in the ODF. Many APIs, which could be used with ODF technology, have an unpleasant aftertaste. The formulation becomes unpleasant as a result, especially for paediatric preparations. Thus, the flavour must be covered up before the API is added to the ODF. The formulation can be made more palatable using a variety of techniques.

❖ **Film Forming Polymers**

All thin film oral dose forms rely primarily on the disintegration in the oral cavity's saliva, hence the final film utilised must unavoidably be water soluble. Excipients or polymers must be water soluble, have a low molecular weight, and have an excellent ability for film formation in order to create a thin film formulation that is water soluble. It must be non-toxic, non-irritating, and free of contaminates that can be washed away. It should have good spreading and wetting properties. It should be reasonably priced and easily accessible. Additionally, microcrystalline cellulose was employed to speed up the drug's dissolution from the films and shorten their time of disintegration. Examples of polymers are:

- Guar gum
- Xanthum gum
- Acacia
- Tragacanth
- Polyethylene oxide
- Sodium carboxy methyl cellulose
- Hydroxyl propyl methyl cellulose
- Polyvinyl alcohol

❖ **Plasticizers**

Plasticizer lessens the brittleness of the films and aids in improving the strip's flexibility. The choice of plasticizer will depend on both the solvent type used in the casting film and how well it works with the polymer. Several plasticizers include

- Glycerol

- Propylene glycol
- Polyethylene glycol
- Dimethyl phthalate
- Diethyl phthalate
- Dibutyl phthalate
- Triacetin
- Castor oil

❖ **Sweeteners / Sweetening agents**

Sweeteners now play a crucial role in formulations intended to dissolve or disintegrate in the oral cavity. In most cases, sweeteners are utilised at a concentration of 3-6% weight/weight. These oral dissolving films are made using both natural and artificial sweeteners. Because they also have a pleasant mouthfeel and a cooling effect, polyhydric alcohols like sorbitol, manitol, and isomalt can be utilised in combination. However, it should be emphasised that persons who are on a diet or those who have diabetes should limit their use of natural sugarsin such preparations. Artificial sweeteners have grown in popularity in culinary and pharmaceutical preparations as a result. Examples of artificial/natural sweeteners are:

- Glucose
- Fructose
- Maltose
- Saccharin
- Cyclamate
- Aspartame

❖ **Saliva stimulating agents**

The goal of using saliva stimulating compounds is to boost saliva production, which will help the formulations for rapid dissolving stripes dissolve more quickly. Generally speaking, salivary stimulants can be made from acids that are used in meal preparation. Examples are:

- Citric acid
- Malic acid
- Lactic acid
- Ascorbic acid
- Tartaric acid

These agents are used along are in combination between 2-6 % w/w of the stripes.

Flavouring Agent

In the ODF formulations, flavours should ideally be added up to 10% by weight. The initial flavour quality, which is noticed in the first few seconds after the product has been ingested, and the after taste of the formulation, which lasts for at least roughly 10 minutes, are the two main factors that determine a person's willingness to accept an oral disintegrating or dissolving formulation. The elderly prefer flavours like fruit punch, raspberry, or mint or orange. It can be chosen from synthetic flavour oils, oleoresins, and fruity flavours like vanilla, cocoa, coffee, chocolate, and citrus. Examples of flavour oils are peppermint oil, cinnamon oil, spearmint oil, and oil of nutmeg. Some examples of the fruit essence category are apple, raspberry, cherry, and pineapple.

❖ **Colouring agent**

Orally dissolving films are made with FD&C-approved colouring additives, with concentration levels not to exceed 1% (w/w). Think of titanium dioxide.

Table 2: Properties of the Oral Film.[4]

PROPERTY	FLASH RELEASE	MUCOADHESIVE MELT RELEASE	MUCOADHESIVE SUSTAINED RELEASE
Area (cm^2)	2-8	2-7	2-4
Thickness (µm)	20-70	50-500	50-250
Structure	Film singlelayer	Single or multilayer system	Multilayer system
Excipients	Soluble, highl hydrophilic polymer	Soluble, hydrophili polymer	Low/non-solublepolyme
Drug phase	Solid solution	Solid solution/suspends drug particle	Suspension or solid solution
Application	Tongue (upperplate)	Gingival or buccalregion	Gingival (or other region of oral cavity)
Dissolution	Maximum sixty second	Disintegration in few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic orlocal	Systemic or local	Systemic or local

1.4 Overview of Oral Mucosa

An outer layer of stratified squamous epithelium makes up the oral mucosa. A basement membrane, a lamina propria, and the sub mucosa make up the layers below this. The epithelium has a mitotically active basal cell layer that progresses through a number of developing intermediate layers to the superficial layers, where cells are shed from the epithelium's surface, similar to stratified squamous epethelia present in the rest of the body.[5]

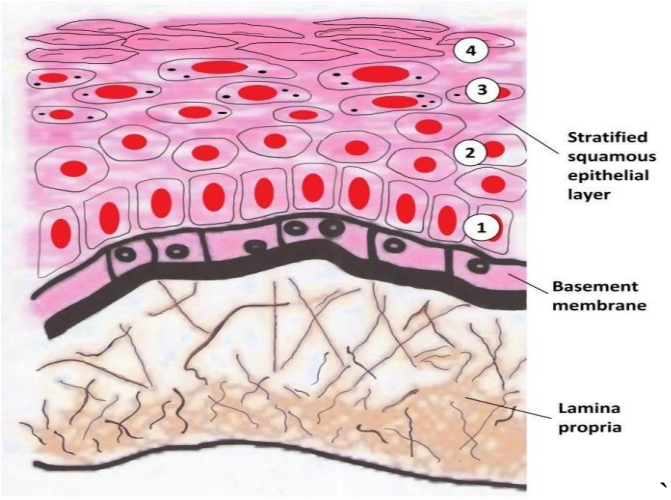

Fig. 1: Overview of Oral Mucosa.

1.5 METHODS OF PREPARATION OF ORAL DISSOLVING FILMS

One or a combination of the following processes can be used to manufacture the mouth dissolving films.

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

1. Solvent Casting Method

Water-soluble substances and the medicine are both dissolved in water when using the solvent casting procedure. Excipients are dissolved in an appropriate solvent, and both solutions are then combined and agitated before being cast into a petri dish and dried.

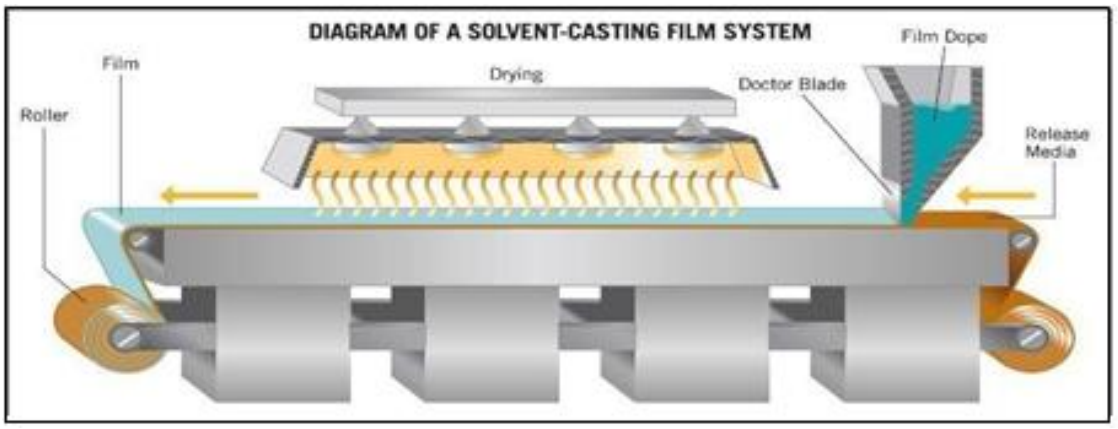

Fig. 2: A Solvent Casting Film System.

2. Semisolid Casting

In the semisolid casting procedure, a solution of a film-forming polymer that is water soluble is first made. A solution of an acid-insoluble polymer (such as cellulose acetate phthalate or cellulose acetate butyrate), produced in ammonium or sodium hydroxide, is added to the resultant solution.

After that, the correct quantity of plasticizer is added to create a gel mass. Finally, using heat-controlled drums, the gel mass is cast into the films or ribbons. The film is between 0.15 and 0.5 inches thick. The ratio of film-forming polymer to acid-insoluble polymer should be 1:4. Each component is combined to create a homogeneous, viscous solution that is then drained under vacuum. The non-treated casting film is coated with a bubble-free solution before being delivered to an oven for aeration drying. The film is sliced into the proper size and shape.

3. Hot Melt Extrusion

In the hot melt extrusion procedure, the medication and carriers are first combined in solid form. The mixture is then melted by a heater-equipped extruder.

Finally, the dies form the melt into films. The hot melt extrusion has some advantages.

- A decrease in operation units
- More uniform content
- A process that is anhydrous

4. Solid Dispersion Extrusion

In this technique, drug-immiscible components are extruded together to create solid dispersions. Finally, using dies, the solid dispersions are formed into films.

5. Rolling Method

The rolling method involves rolling a drug-containing solution or suspension on a carrier. Water and an alcohol-water mixture make up the majority of the solvent. The film is cut into the desired shapes and sizes after it has dried on the rollers.[6]

Table 3: Examples of Marketed Oral Films.

Brand name	Manufacturer/ distributor	API (strength)	Uses
Anti-Emetic film	Delvin formulation pvtltd	Ondansetron 4 mg	Nausea&vomiting
Listerine cool min pocket packs	Pfizer	Mint crystals	Mouth freshener
Niquistin stripes	Omega pharma ltd	Nicotine 2.5 mg	Anti-smoking
Zupelnz stripes	Monosol Rx	Ondansetron 8 mg	Ondansetron
Spiromont	Monosol Rx	Montelukast 10 mg	Asthma& allergy
Sildenafil citratefilm	Alpha pharma healt care	Sildenafil 50 mg	Erectile function
Tadalafil stripes	Alpha pharma healt care	Sildenafil 20 mg	Erectile function
Vitamin D3	Zim laboratories	Calciferol 2,000I. U	Calcium supplement
Benadryl	MC Neil consume health care	Diphenhydramine 2 mg	Antihistamine
Tri aminic	Novartis	12.5 mg	Antiallergic

Table 4: Excipients Generally Used in Preparation of Oral Film List of Excipients.

Ingredients/purpose	Examples	% (W/W)
Water soluble polymers	Cellulose ethers (HPMC, HEC,HPC, and MC), PVC, PVA, gelatin, pullulan, kollicoat IR, tragacanth gum, guar gum, chitin, etc.,	40-50
Plasticizers	Glycerol, PG, PEG	0-20
Disintegrants	Pre gelatinised starch, MCC, crosspovidone, soluble starch	0-40
Preservatives	Salts of edetate (di sodium EDTA)	0.01-1
Saliva stimulating agent	Citric acid, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acid.	2.5-6
Cooling agents	Mono methyl succinate	0.2-0.4
Surfactants	Mono & di glycerides of FA, poly oxy ethylene sorbitol esters	0.5-15
Stabilizing agents	Xanthan gum, locust bean gum and carrageenan	0.1-2
Emulsifying agents	Triethanolamine stearate, Qt.ammonium compounds, acacia, gelatin	0.01-0.7
Thickening gents	MC, CMC	0.01-5
Binding agents	Starch	0.01-2
Sweetening agents	Sucralose, aspartame, acesulfame K,eotame	0-2

1.6 EVALUATION OF THE FILMS

a) Thickness

The film thickness was measured using a micrometer screw gauge at five pointson the film to ensure the uniformity of the film thickness. The mean thickness wascalculated from the five points.

b) Folding endurance test

Folding endurance values reflect the strength of the film prepared.

c) Weight variation

Ten films were randomly selected and their average was obtained. Individually films were weighed and compared with the average weight for the deviation.

d) Drug content

Drug content determination of the films is to ascertain whether the requiredamount of drug loaded in the polymer or not.

e) Disintegration test

To find out actual time required for disintegration of the film.

f) Fourier transform infrared spectroscopy studies (FT-IR)

FTIR spectral measurements are useful to find out the interaction between the polymer, excipients and drug if any.

g) Differential scanning calorimeter studies (DSC)

DSC studies are useful to know the thermal stability of the drug and loaded film.

h) *In-vitro* dissolution test

Dissolution study was carried out by using a UV spectrophotometer.

i) *In-vitro* disintegration test

2ml of water was placed in a petriplates with a film on the surface of water. The time taken for the disintegration of the film was measured.

j) SEM Analysis

The morphological study of oral film was done by the scanning electronmicroscopy at definite magnification (SEM).

k) Taste Masking Techniques

On the tongue, roof of the mouth, cheeks, and throat, there are thought to be roughly 10,000 taste buds, each of which has 60–100 receptor cells. These receptor cells engage with chemicals dissolved in saliva to create a flavour, either good or bad. In their natural state, many medications are unpleasant to taste and look at. Drug interactions with taste receptors

have been avoided or minimised through the use of physiological and physicochemical strategies. Because H+- receptors exist in the taste bud, acids induce sourness.

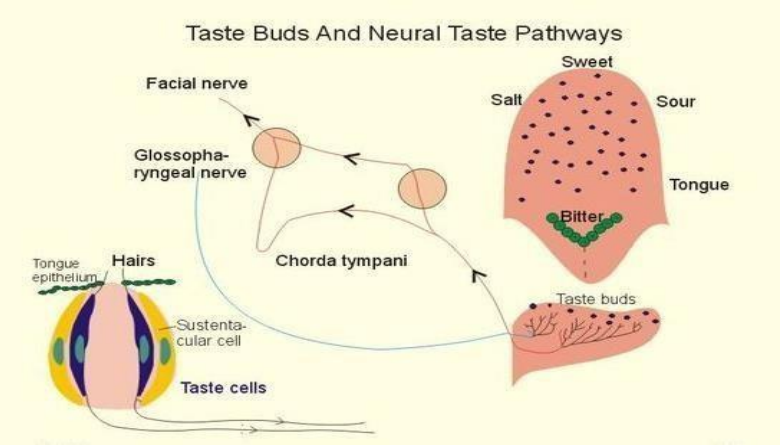

Fig. 3: Taste buds and Neural taste pathways.

The anions of inorganic salts are what give them their saltiness. The cl- receptor is especially good at detecting salty. A large number of long chain chemical molecules excite the bitter taste receptors located at the base of our tongue. In addition to tasting bitter, alkaloids include quinine, caffeine, and nicotine. Sucrose, glucose, lactose, maltose, glycerol, alcohol, aldehydes, ketones, and organic compounds all trigger the sweet receptors.

The medicine included in FDDFs dissolves in the saliva and remains in the oral cavity until it is ingested. Therefore, in order to maximise patient tolerance of a medicine with a bitter taste, taste creation becomes critically important in the formulation. Since it is anticipated that the dosage form will not dissolve until it has passed through the oral cavity, traditional tablet formulations typically do not address the problem of taste masking.

In the relevant literature, oral films, sometimes known as oral wafers, are a collection of flat films that are placed within the mouth.

❖ Application of Oral Strip in Drug Delivery

For therapies that call for quick absorption, such as those used to treat pain, allergies, difficulty sleeping, and central neurological diseases, oral mucosal delivery via buccal, sublingual, and mucosal routes by the use of OTFs may become the preferred delivery strategy.

Dissolvable oral thin films (OTFs), once used to distribute confections and oral care products in the shape of breath stripes, have quickly developed into an innovative and well-liked

delivery method for vitamins and personal care items.

a) Topical applications

The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care other applications.

b) Gastroretentive dosage systems

Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could be potentially used to treat gastrointestinal disorders.

c) Diagnostic devices

Dissolvable films may be loaded with sensitive reagents to allow control release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction with a diagnostic device.[7]

1.7 Pain as a symptom

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It motivates the subject to evade and withdraw from potentially damaging situations, protect a damaged body part while it heals, and avoid harmful situations in the future. Usually, pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body, and sometimes pain arises in the absence of any detectable stimulus, damage or pathology.

The classification system used by the International Association for the Study of Pain (IASP) describes pain according to five categories: duration and severity, anatomical location, body system involved, cause, and temporal characteristics (intermittent, constant, etc). In addition, some years ago the “neurochemical mechanism” category was proposed to the IASP in order to treat the symptom in a correct way, based on its molecular mechanism.8 In terms of duration, pain can be classified as acute or chronic. Acute pain occurs while the painful stimulus is present, and when it is removed it tends to disappear. When pain does not disappear within 6- 12 months after the painful stimulus has been removed, it becomes chronic. Migraine and fibromyalgia are two illnesses where pain shows itself in a discontinuous way, making it

difficult to classify it as acute or chronic. The IASP recognizes 11 levels of pain going from 0 (no pain) to 10, being 10 the worst possible pain that can be imagined.[8]

1.8 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the second most prescribed class of drugs in Sweden today, after antibiotics. While antibiotics are only sold in pharmacies as prescription drugs, NSAIDs can be bought either with a prescription or over-the-counter (OTC) in pharmacies and retail shops. In 2016 NSAIDs were prescribed to more than 1 million patients in Sweden1 and more than 300 million defined daily doses (DDD) were dispensed ina population of 10 million.

Composed by a large number of families, with a non-common chemical scaffold, these products are also known as minor analgesics or aspirin-like analgesics. Along with aspirin, ibuprofen, acetaminophen (paracetamol) and naproxen are the most used over the counter analgesics. These products act as analgesics, antipyretics, antithermics and some of them as antirheumatics.

NSAIDs act in a non-selective way on different cyclooxygenase isozymes. These enzymes catalyse the formation of prostanoids (prostaglandins and thromboxanes) from arachidonic acid. Prostaglandins (PGs) are mediators and have a variety of strong physiological effects, such as regulating the contraction and relaxation of smooth muscle tissue, aggregation or disaggregation of platelets or sensitization of spinal neurons to pain.[9]

METHODOLOGY

MATERIALS AND METHODS

Table 5: List of materials.

Sl. No.	Ingredients	Manufacturer
1.	Indomethacin	Yarrow chemicals, Mumbai
2.	HPMC	Otto Chemica-Biochemika reagent, Mumbai
3.	Propylene Glycol	Karnataka fine chemicals, Bangalore
4.	Polyethylene glycol	Karnataka fine chemicals, Bangalore
5.	Citric acid	Sisco Research Laboratories Pvt Ltd,Mumbai
6.	Ethanol	Karnataka fine chemicals, Bangalore
7.	Saccharin sodium	Sigma Aldrich, Bangalore

Table 6: List of instruments.

Sl. No	Name of Instrument	Model and Manufacturer
1.	Electronic balance	Sartorius, Germany
2.	Hot air oven	Hicon, New Delhi
3.	UV Spectrometer	UV-2450 Shimadzu, Mumbai
4.	Dissolution test Apparatus	Electro lab Mumbai
5.	Micrometer screw gauge	Mitutoyo, China
6.	Disintegration test apparatus USP	Electro Lab
7.	pH meter	Digisun Electronics, Hyderabad
8.	Stability chamber	Thermo lab Pvt ltd

4.3 PRE-FORMULATION STUDIES

Pre-formulation may be described as the stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequent stages of development. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the pre-formulation phase of product development followed by studying the properties of the excipients on their compatibility.[26-30]

a) Solubility

Solubility is expressed in terms of parts per million of solvent in which 1g of solidis soluble. Solubility of the powder in different solvents like ethanol was determined at 20°c.[31,32]

b) Heavy metal content

The part of Lead per million parts of powder was examined by comparing sample solution with 10 ppm lead standard solution for 2 gm material.[33,34]

c) Melting point

The melting point was carried out by using capillary tube method.[35]

d) Compatibility Studies

FTIR study was carried out to check the compatibility of drug with polymers. Infrared spectrum of Indomethacin was determined on Fourier transform Infrared spectrophotometer using KBr dispersion method. The baseline correlationwas done using dried potassium bromide. Then the spectrum of dried mixture of drug and Potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption

maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.[36,37]

4.4 Formulation Development of Indomethacin Oral Film

Table 7: Formulation trials.[38,39,40]

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indomethacin (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
HPMC E15 (g)	1.0	1.25	1.5	-	-	-	1.25	-	1.25
HPMC E50 (g)	-	-	-	1.0	1.25	1.5	-	1.25	1.25
PEG 400 (g)	1.5	1.25.	1.0	-	-	-	-	1.25	-
Propylene glycol (ml)	-	-	-	1.5	1.25	1.0	1.25	-	-
Citric acid(g)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Sodium saccharin (g)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Ethanol (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

4.5 PROCEDURE

The water-soluble polymers and plasticizers were dissolved in water. The solution is stirred up for 2 hrs in the magnetic stirrer and kept aside to remove all air bubbles entrapped. Meanwhile, the excipients and drug were dissolved and stirred well for 30 min, after the completion of stirring both the solutions are mixed together. Finally, the solution is casted on a suitable petriplate to form a film. The plates were kept in a hot air oven at 60° C+ for 1 hour. The dried film was gently separated from the glass plate and cut into desired sizes.[41,44]

Dose calculations

Length of glass plate =10 cm.Width of glass plate =10 cm. Area of the plate =100 cm^2.

No. of 4 cm^2 films present whole plate =100/4 =25 films.Each films contains 25 mg of drug. 25 films contain 625 mg drug (25×25).Labelled claim= 25 mg

Standard Graph of Indomethacin

Stock solution was prepared by using 50 mg of Indomethacin in 100 ml of Ethanol. From this stock solution 10 ml was withdrawn and diluted upto 100 ml using water. Calibration curve was prepared by using different concentration (20µg/ml-100 µg/ml) by appropriate dilution of stock solution. The absorbance was measured at 267 nm.[45- 47]

4.6 EVALUATION OF ORAL FILM

a) Thickness

A micrometer screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness is measured at 5 different locations. The thickness of the film should be less than 5 %.[48]

b) Weight variation

Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation.[49]

c) Folding endurance

To determine folding endurance, a film is cut and rapidly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Topical folding endurance for film was between100-150.[50]

d) Percentage elongation

It was calculated by[51]

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

e) Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula:[52]

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 10}{\text{Strip thickness} \times \text{strip width}}$$

f) *In-vitro* disintegration

Disintegrating time is defined as the time (sec) at which a film breaks when brought in contact with water or saliva.[53-54]

g) Petri dish method

2 ml of distilled water was placed in the petri dish and one film was added on the surface of water and the time measured until the oral film was dissolved completely.

h) *In-vitro* dissolution

900 ml of o.1 N HCL was used as a media, at was maintained at 37 +0.5 °c while the basket was set at 100 rpm. A film sample of 4 cm2 (2×2 cm) was cut and takeninto the basket. 5 ml of the sample were taken every 2 minutes and the same amount was replaced with fresh 0.1 N HCL. The withdrawn samples were filtered and analyzed using a UV spectrometer at a wavelength of 267 nm.[55]

i) Drug content

This test was performed by dissolving a 4 cm2 area of film in 50 ml of 0.1 N HCL with stirring. This solution was filtered using a Whatman filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using UV spectrometer.[56]

j) Assay

This test was performed by dissolving a 4 cm area of thin film in 50 ml of pH 6.8 phosphate buffer with stirring. This solution was filtered using a Whatmann filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using UV spectrophotometer.

k) SEM analysis

Scanning Electron Microscopy (SEM) is a test process that scans a sample with an electron beam to produce a magnified image for analysis. The method is also known as SEM analysis and SEM microscopy and is used very effectively in microanalysis and failure analysis of solid inorganic materials.[57]

The morphological study of the oral strip was done by scanning electron microscopy (SEM) at a definite magnification. The study refers to the difference between the upper and lower sides of the films. It also helps in the determination of the distribution of API.

5.1 RESULTS AND DISCUSSIONPREFORMULATION STUDIES Solubility

Solubility is expressed in terms of parts per million of solvent in which 1g of solid is soluble.Solubility of the powder in different solvents like ethanol was determined at 20°c.

Heavy metal content

The part of Lead per million parts of powder was examined by comparing sample solution with 10 ppm lead standard solution for 2 gm material.

Melting point

The melting point was carried out by using capillary tube method.

Table 8: API characterization- Indomethacin.

S.no	Test	Specification	Result
1	Description	White powder	White powder
2	Solubility	Soluble in organic solvents	Complies
3	Taste	Bitter	Complies
4	Odour	Odourless	Complies
5	Heavy metals (ppm)	Should not be more than20 ppm	Less
6	Melting point	Range: 155° c to 162° c	157° c

CALIBRATION CURVE OF INDOMETHACIN

Stock solution was prepared by 50 mg of Indomethacin in 100 ml of water. From this stock solution 10 ml was withdrawn and diluted upto 100 ml using water. Calibration curve was prepared by using different concentration (20 µg/ml-100 µg/ml) by appropriate dilution of stock solution. The absorbance was measured at 267 nm. The absorbance of various concentration measured at 267 nm is as follows in table 5.2

Table 9: Standard graph of Indomethacin.

S.no	Concentration µg/ml	Absorbance (267nm)
1	0	0
2	20	0.226
3	40	0.434
4	60	0.638
5	80	0.742
6	100	0.801

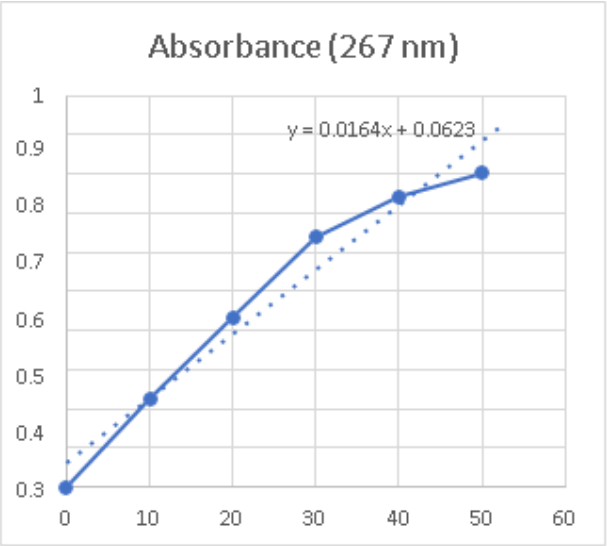

Fig. 4: Standard graph of Indomethacin.

FT-IR Studies

FTIR study was carried out to check the compatibility of drug with polymers. Infrared spectrum of Indomethacin was determined on Fourier transform Infrared spectrophotometer using KBr dispersion method. The baseline correlation was done using dried potassium bromide. Then the spectrum of dried mixture of drug and Potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximum in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

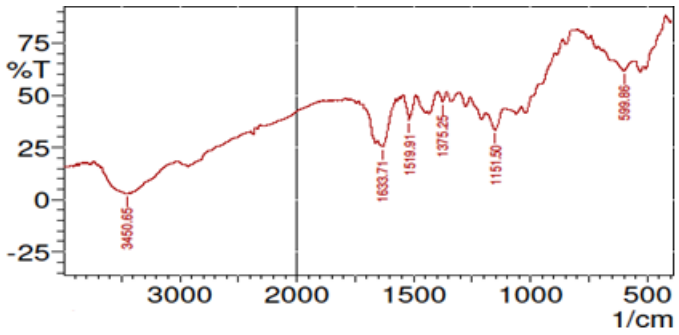

Fig. 5: IR Spectra of Indomethacin.

Table 10: IR Spectra of Indomethacin.

No.	Peak	Intensity	Corr. Intensity	Base(H)	Base(L)	Area	Corr.Area
1	599.86	61.564	5.035	561.29	561.29	15.901	1.269
2	1151.5	33.276	9.285	1109.07	1109.07	33.648	3.623
3	1375.25	46.849	4.9	1394.53	1357.07	11.258	0.773
4	1519.91	38.144	12.121	1543.05	1490.97	18.539	2.975
5	1633.71	25.357	7.832	1653	1575.84	36.913	3.504
6	3450.65	2.846	0.383	3473.8	3433.29	61.349	0.947

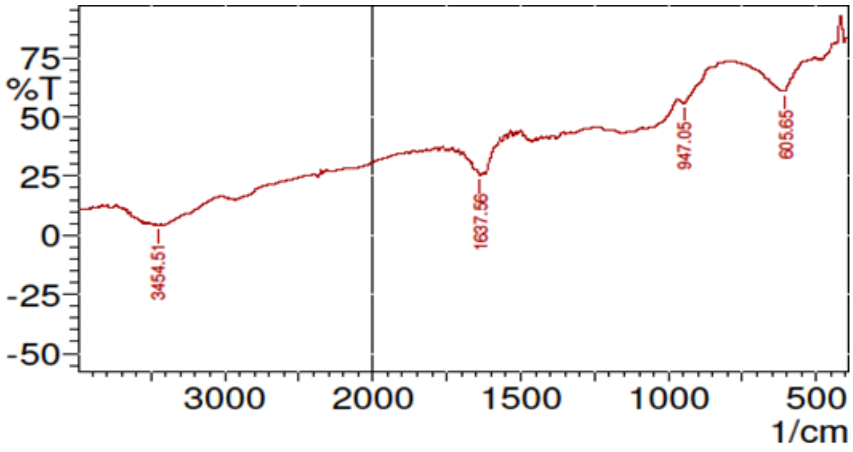

Fig. 6: IR Spectra of HPMC E15.

Table 11: IR Spectra of HPMC E15.

No.	Peak	Intensity	Corr. Intensity	Base(H)	Base(L)	Area	Corr.Area
1	605.909	60.909	1.441	6.11	543.93	11.593	-0.046
2	947.05	55.948	4.051	966.34	860.25	22.036	1.415
3	1637.56	25.336	0.552	1651.07	1651.07	8.863	0.019
4	3454.51	4.455	0.023	3462.22	3452.58	13.003	0.013

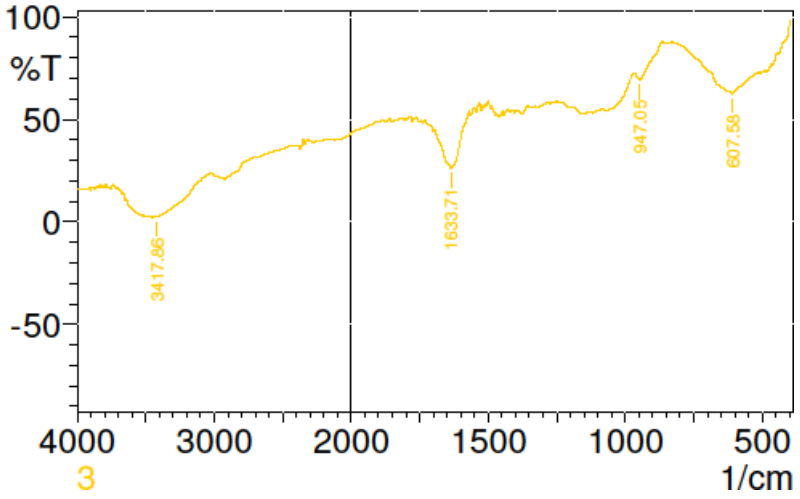

Fig. 7: IR Spectra of HPMC E50.

Table 12: Spectra of HPMC E50.

No.	Peak	Intensity	Corr. Intensity	Base(H)	Base(L)	Area	Corr.Area
1	607.58	62.6036	1.6909	617.22	580.57	7.0633	0.1823
2	947.05	69.2787	6.4461	968.27	864.11	11.9589	1.7804
3	1633.71	26.4988	0.5196	1635.64	1627.92	4.3949	0.052
4	3417.86	2.4373	0.4349	3431.36	3394.72	57.4735	1.3563

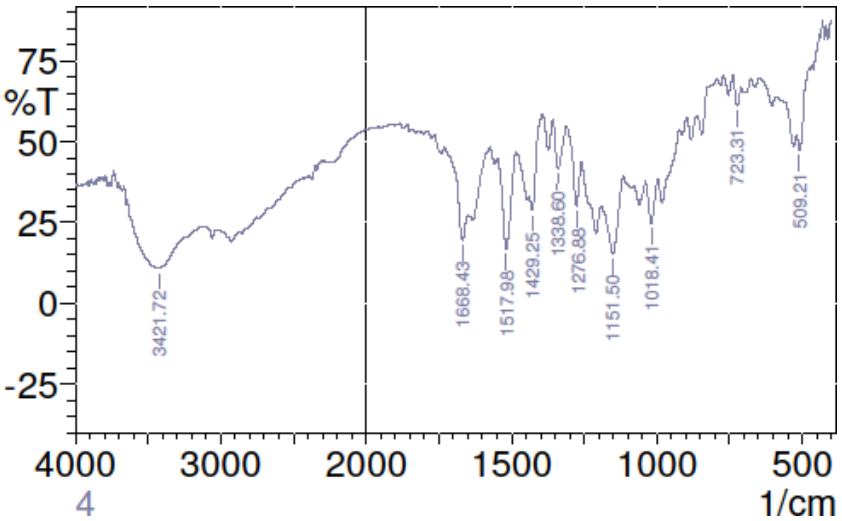

Fig. 8: IR Spectra of Indomethacin + HPMC E15.

Table 13: IR Spectra of Indomethacin + HPMC E15.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr.Area
1	509.21	47.35	9.618	518.85	478.35	9.733	1.195
2	723.31	61.02	7.496	738.74	711.73	5.127	0.733
3	1018.41	24.65	13.381	1037.7	997.2	20.677	3.675
4	1151.5	15.266	19.575	1192.01	1114.86	47.294	11.445
5	1276.88	30.095	17.342	1311.59	1259.52	19.707	3.575
6	1338.6	41.608	14.362	1357.89	1311.59	14.661	2.943
7	1429.25	28.691	9.694	1438.9	1392.61	17.337	0.844
8	1517.98	16.845	28.864	1546.91	1487.12	31.57	11.253
9	1668.43	19.401	13.906	1697.36	1649.14	27.051	4.454
10	3421.72	10.728	0.854	3433.29	3143.97	222.048	-7.282

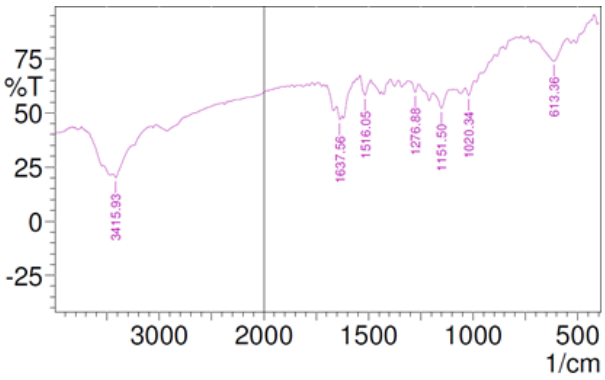

Fig. 9: IR Spectra of Indomethacin + HPMC E50.

Table 14: IR Spectra of Indomethacin + HPMC E50.

No.	Peak	Intensity	Corr. Intensity	Base(H)	Base (L)	Area	Corr.Area
1	613.36	73.909	10.211	713.66	549.71	16.616	4.239
2	723.31	58.154	4.755	1037.7	993.34	9.521	0.696
3	1151.5	52.214	7.835	1192.01	1112.93	19.454	1.923
4	1276.88	59.615	4.263	1311.59	1259.52	10.545	0.494
5	1516.05	58.215	8.182	1541.12	1489.05	10.788	1.51
6	1637.56	46.897	3.47	1653	1627.92	7.72	0.349
7	3415.93	20.069	3.568	3442.94	3248.13	109.507	0.838

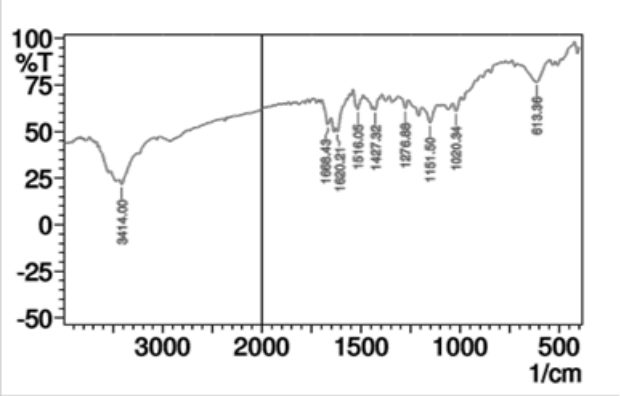

Fig. 10: IR Spectra of Indomethacin + HPMC E15 + HPMC E 50.

Table 15: IR Spectra of Indomethacin Phosphate + HPMC E15 + HPMC E 50.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	613.36	76.445	10.358	680.87	549.71	11.719	3.618
2	1020.34	60.974	5.393	1037.7	995.27	8.238	0.762
3	1151.5	54.71	8.866	1192.01	1114.86	17.204	2.007
4	1276.88	62.386	4.943	1311.59	1261.45	9.048	0.564
5	1427.32	61.595	3.497	1438.9	1411.89	5.287	0.302
6	1516.05	61.92	7.385	1539.2	1500.62	7.169	1.133
7	1620.21	50.03	4.028	1627.92	1571.99	12.983	0.281
8	1668.43	53.824	6.898	1699.29	1651.07	11.082	1.039
9	3414	21.642	4.53	3442.94	3250.05	101.18	1.264

EVALUATION PARAMETERS

Thickness

A micrometer screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness is measured at 5 different locations. The thickness of the film should be less than 5%. The thickness of fast dissolving films of all formulations given in table and figure.

Folding endurance

To determine folding endurance, a film is cut and rapidly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Topical folding endurance for film was between100-150. The folding endurance of fast dissolving films of all formulations given in table and figure.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the stripspecimen breaks. It is calculated by the formula.

Tensile strength = $\frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{Strip width}}$

The tensile strength of fast dissolving films of all formulations given in table and figure.

Percentage elongation

It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

The percentage elongation of fast dissolving films of all formulations given intable and

figure.

***In-Vitro* disintegrationPetri dish method**

2 ml of distilled water was placed in the petri dish and one film was added on the surface of water and the time measured until the oral film was dissolved completely.

The in-vitro disintegration time of fast dissolving films of all formulations givenin table and figure.

Table 16: Evaluation Parameters.

Formulations	Thickness (mm)	Folding endurance	Tensile strength	% elongation	In-Vitro Disintegration Time(sec)
F1	0.58	9	48.41	8	25
F2	0.55	10	51.18	9	28
F3	0.59	13	62.04	11	20
F4	0.51	9	54.25	9	31
F5	0.53	11	53.68	10	35
F6	0.52	11	52.33	8	27
F7	0.55	12	56.45	7	36
F8	0.57	10	57.62	9	32
F9	0.53	9	48.63	10	35

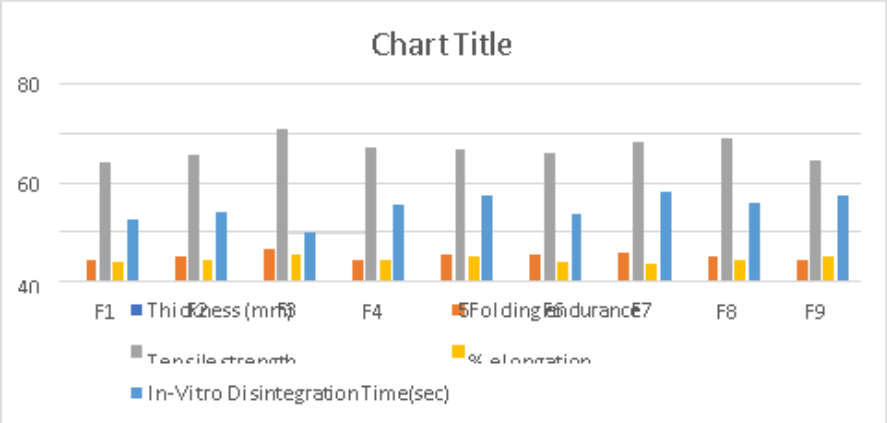

Fig. 11: Bar chart of evaluation parameters.

WEIGHT VARIATION

Weight variation

Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation. The weight variation of fast dissolving films of all formulations givenin table and figure.

Table 17: Weight variation.

Formulations	Weight variation (mg)
F1	69
F2	68
F3	68.2
F4	69.4
F5	70.2
F6	69.4
F7	68.3
F8	70.6
F9	69.2

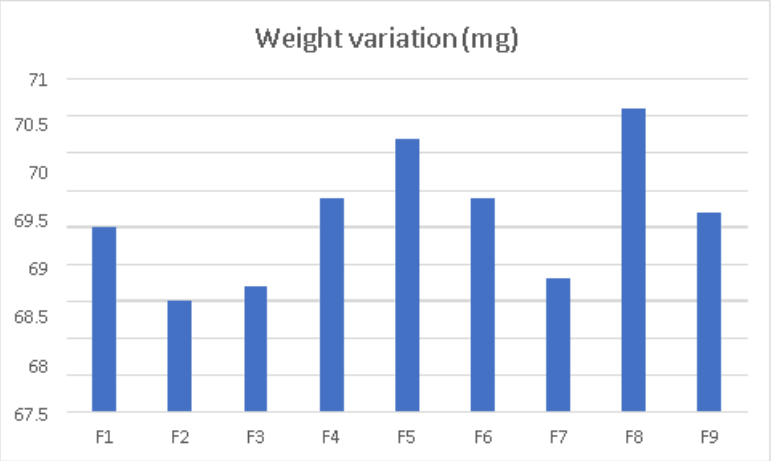

Fig. 12: Bar chart of weight variation.

DRUG CONTENT AND ASSAY

Drug content

This test was performed by dissolving a 4 cm^2 area of film in 50 ml of 0.1 N HCL with stirring. This solution was filtered using a whatmann filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analysed using UV spectrometer. The drug content result of all the formulations shown in table 19 and the values depicted as graphical representation infigure.

ASSAY

This test was performed by dissolving a 4 cm area of thin film in 50 ml of pH 6.8 phosphate buffer with stirring. This solution was filtered using a Whatmann filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using UV spectrophotometer. The assay result of all the formulations shown in table 19 and the values depicted as graphical representation in figure.

Table 18: Drug content and Assay.

Formulation	Drug content (mg)	Assay (%)
F1	24.86	97.25
F2	23.25	98.14
F3	25.01	99.87
F4	22.91	98.34
F5	24.55	98.45
F6	23.88	97.22
F7	24.78	98.33
F8	24.63	97.87
F9	23.52	98.12

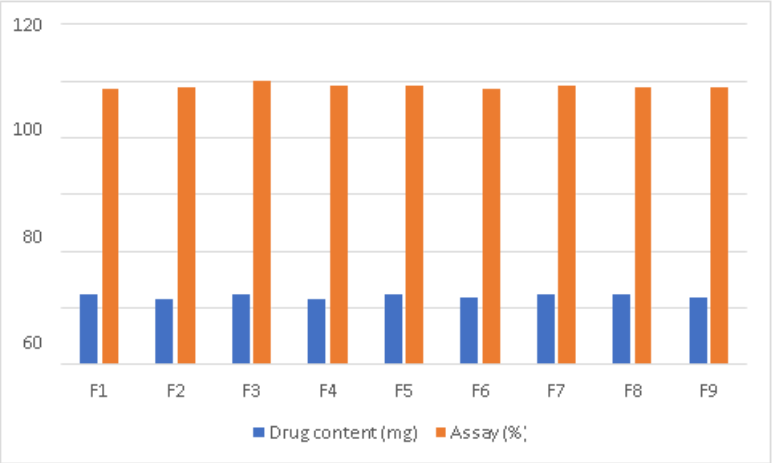

Fig. 13: Bar chart of drug content and assay.

IN-VITRO DISSOLUTION

In-vitro dissolution

900 ml of o.1 N HCL was used as a media, at was maintained at 37 +0.5 °c while the basket was set at 100 rpm. A film sample of 4 cm^2 (2×2 cm) was cut and takeninto the basket. 5 ml of the sample were taken every 2 minutes and the same amount was replaced with fresh 0.1 N HCL. The withdrawn samples were filtered and analyzed using a UV spectrometer at a wavelength of 267 nm. In-vitrodissolution profile data of all formulations given the table and figure. The Percentage Cumulative Drug Release of F1 - F9 shown in table Figure. The in-vitro dissolution profile data of marketed formulation depicted in table and figure. The comparison of in-vitro release data of marketed formulation and formulation 3 shown in table and figure.

Table 19: *In-Vitro* dissolution of F1.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amountrelease mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.043	4.134	18.60	18.6	19
1.0	0.073	7.019	31.58	31.6	32
1.5	0.121	11.63	52.35	52.4	52
2.0	0.164	15.76	70.96	71.0	71
2.5	0.193	18.65	83.94	84.0	84
3.0	0.214	20.57	92.59	93.0	93

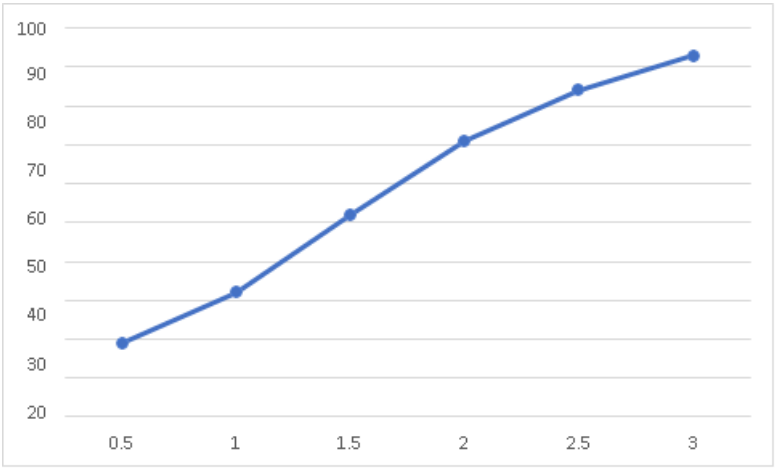

Fig. 14: *In-Vitro* dissolution of F1.

Table 20: *In-Vitro* dissolution of F2.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.049	4.71	21.20	21.2	21
1.0	0.083	7.98	35.91	36.0	36
1.5	0.135	12.98	58.41	58.4	58
2.0	0.156	15.1	67.5	68.0	68
2.5	0.198	19.03	85.67	86.0	86
3.0	0.225	21.63	97.36	97.3	97

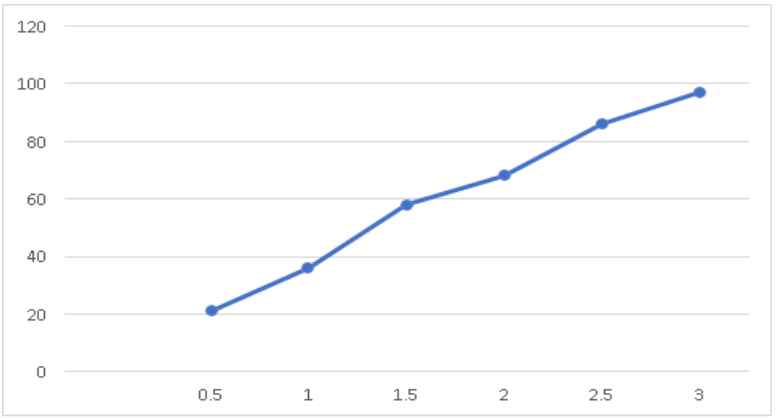

Fig. 15: *In-Vitro* dissolution of F2.

Table 21: *In-Vitro* dissolution of F3.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.050	4.807	17.30	17.3	17
1.0	0.086	8.260	37.21	37.2	37
1.5	0.100	9.611	43.26	43.3	43
2.0	0.181	17.40	78.31	78.3	78
2.5	0.220	21.15	82.21	82.2	82
3.0	0.228	23.36	98.63	98.6	99

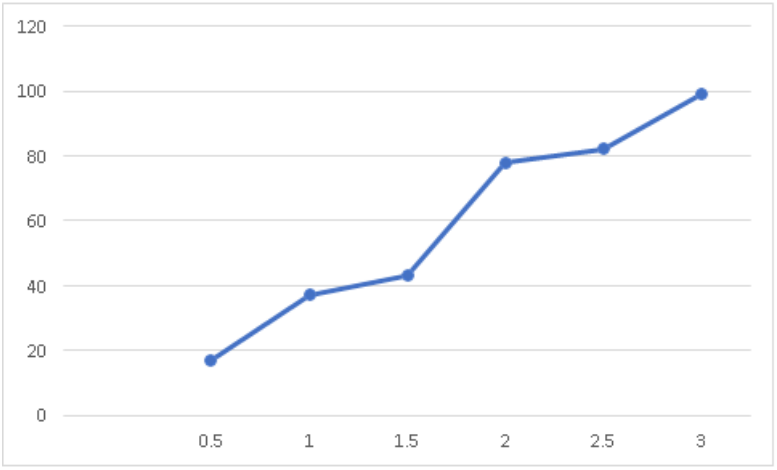

Fig. 16: In-vitro dissolution of F3.

Table 22: *In-Vitro* dissolution of F4.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amountrelease mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.052	5.01	22.54	23.0	23
1.0	0.098	9.42	42.40	42.4	42
1.5	0.134	12.88	58.10	58.1	58
2.0	0.169	16.25	73.13	73.1	73
2.5	0.188	18.07	81.35	81.3	81
3.0	0.220	21.15	95.20	95.2	95

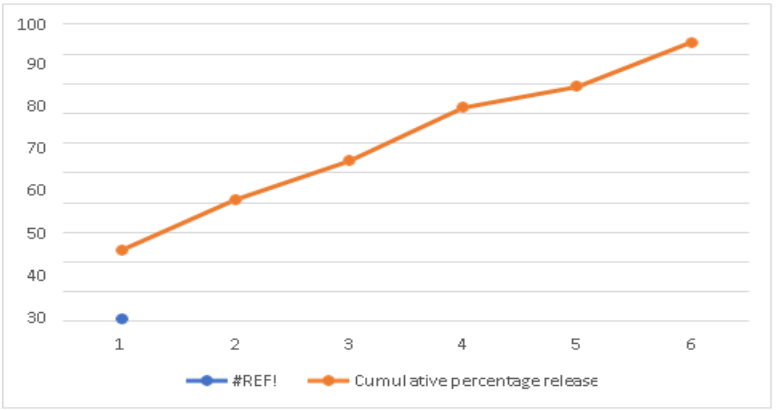

Fig. 17: In-vitro dissolution of F4.

Table 23: *In-Vitro* dissolution of F5.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amountrelease mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.053	5.09	22.93	23.0	23
1.0	0.095	9.13	41.10	41.1	41
1.5	0.124	11.9	53.65	54.0	54
2.0	0.166	15.9	71.82	72.0	72
2.5	0.182	17.5	78.85	79.0	79
3.0	0.218	20.9	94.32	94.3	94

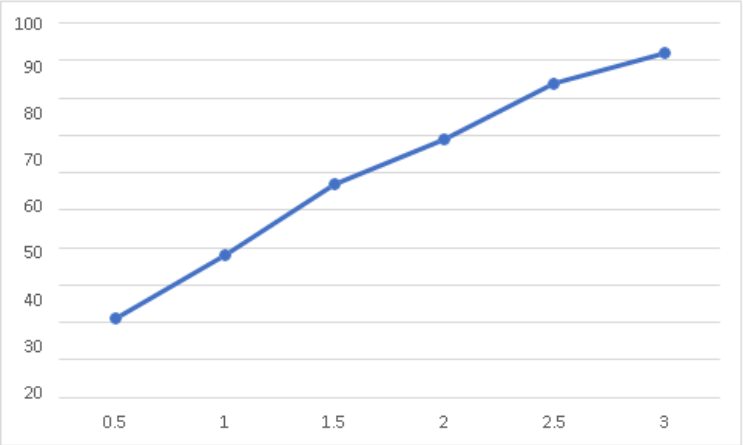

Fig. 18: *In-Vitro* dissolution of F5.

Table 24: *In-Vitro* dissolution of F6.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.049	4.71	21.20	21.2	21
1.0	0.088	8.46	38.08	38.0	38
1.5	0.132	12.7	57.16	57.2	57
2.0	0.059	15.3	68.8	69.0	69
2.5	0.194	18.7	83.9	84.0	84
3.0	0.213	20.5	92.16	92.2	92

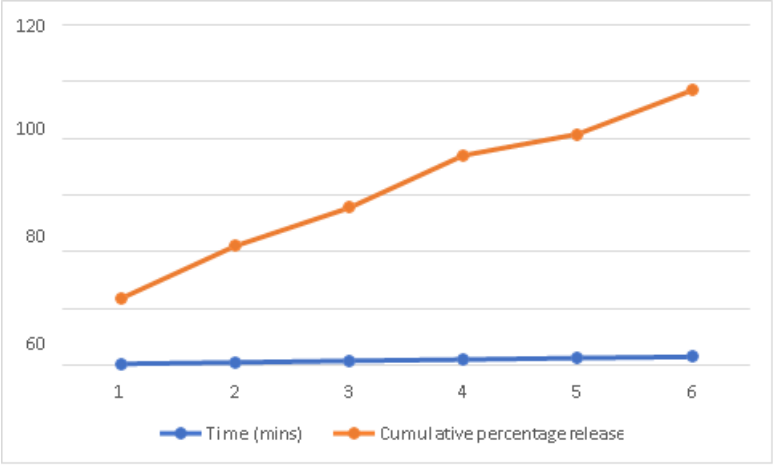

Fig. 19: *In-Vitro* dissolution of F6.

Table 25: *In-Vitro* dissolution of F7.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amountrelease mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.048	4.62	20.76	20.8	21
1.0	0.088	8.46	38.07	38.1	38
1.5	0.128	12.31	55.39	55.4	55
2.0	0.159	15.29	68.80	69.0	69
2.5	0.189	18.17	81.77	82.0	82
3.0	0.223	21.44	96.49	96.5	97

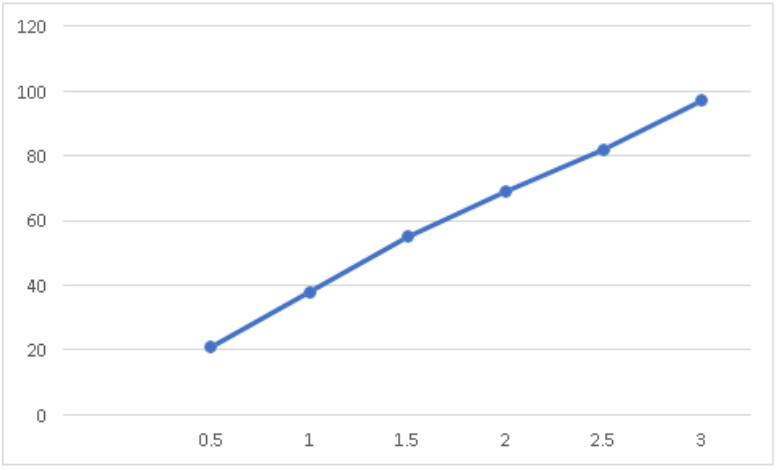

Fig. 20: *In- Vitro* dissolution of F6.

Table 26: *In-Vitro* dissolution of F8.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.039	3.75	16.88	16.9	17
1.0	0.078	7.52	33.75	33.8	34
1.5	0.134	12.88	57.98	58.0	58
2.0	0.164	15.76	70.96	71.0	71
2.5	0.190	18.27	82.21	82.2	82
3.0	0.224	21.54	96.92	97.0	97

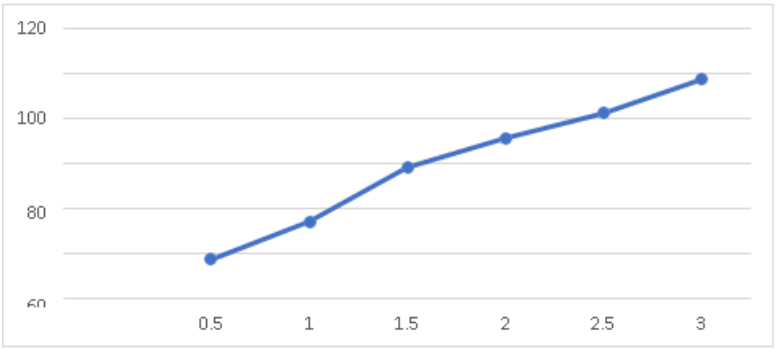

Fig. 21: *In-Vitro* dissolution of F8.

Table 27: *In-Vitro* dissolution of F9.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amountrelease mg/ml	Cumulative amount release	Cumulative percentage release
0.5	0.046	4.42	19.90	19.9	20
1.0	0.082	7.88	35.48	35.5	36
1.5	0.140	13.46	60.58	60.6	61
2.0	0.162	15.58	70.1	70.1	70
2.5	0.186	17.88	80.5	81.0	81
3.0	0.221	21.25	95.6	96.0	96

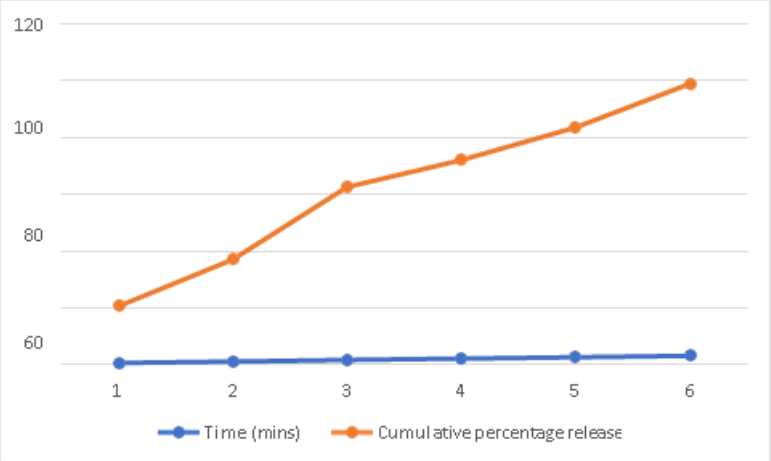

Fig. 22: In-vitro dissolution of F9.

Table 28: In-vitro dissolution of F1-F9.

Percentage drug release									
Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	19	21	17	23	23	21	21	17	20
1.0	32	36	37	42	41	38	38	34	36
1.5	52	58	43	58	54	57	55	58	61
2.0	71	68	78	73	72	69	69	71	70
2.5	84	86	82	81	79	84	82	82	81
3.0	93	97	99	95	94	92	97	97	96

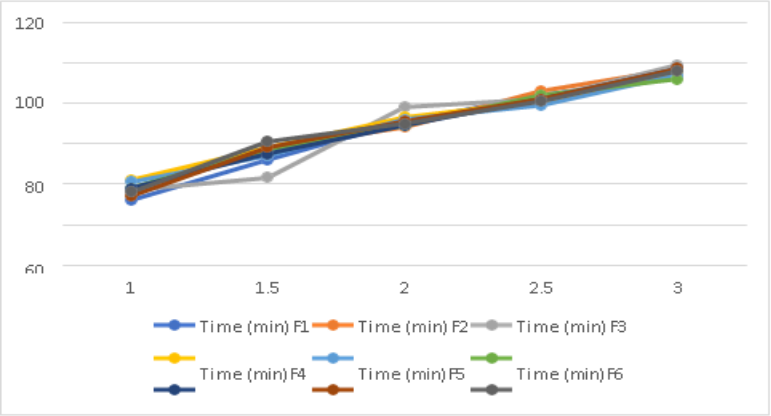

Fig. 23: In-vitro dissolution of F1-F9.

IN-Vitro Drug Release Profile Data Of Marketed Formulation

Table 29: *In-Vitro* drug release profile data of marketed formulation.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release
10	0.038	3.65	16.44	16.4	16
20	0.079	7.59	34.2	34.2	34
30	0.110	10.58	47.6	48.0	48
40	0.147	14.13	63.61	64.0	64
50	0.178	17.16	77.02	77.0	77
60	0.218	20.46	94.33	94.3	94

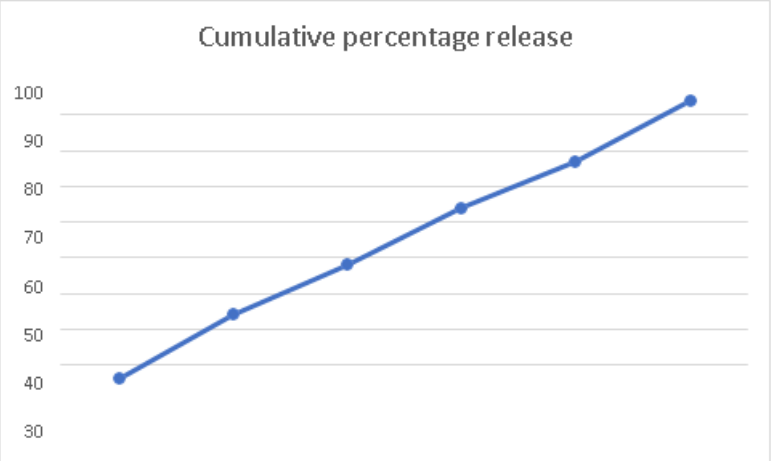

Fig. 24: *In-Vitro* drug release profile data of marketed formulation.

Comparison of in-vitro drug release data of marketed formulation and formulationand formulation 3

Table 30: Comparison of in-vitro drug release data of marketed formulation and formulation and formulation 3.

Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	Cumulative percentage release	Cumulative percentage release of formulation3
10	0.038	3.65	16.44	16.4	16	17
20	0.079	7.59	34.2	34.2	34	37
30	0.110	10.58	47.6	48.0	48	43
40	0.147	14.13	63.61	64.0	64	78
50	0.178	17.16	77.02	77.0	77	82
60	0.218	20.46	94.33	94.3	94	99

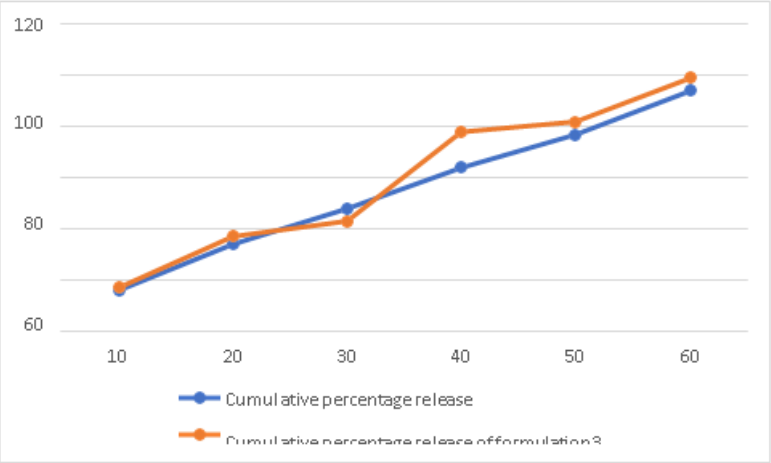

Fig. 25: Comparison *in-Vitro* release data of marketed formulation.

SEM ANALYSIS

The morphological study of oral strip was done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the difference between upper and lower side of the films. It also helps in determination of the distribution of API.

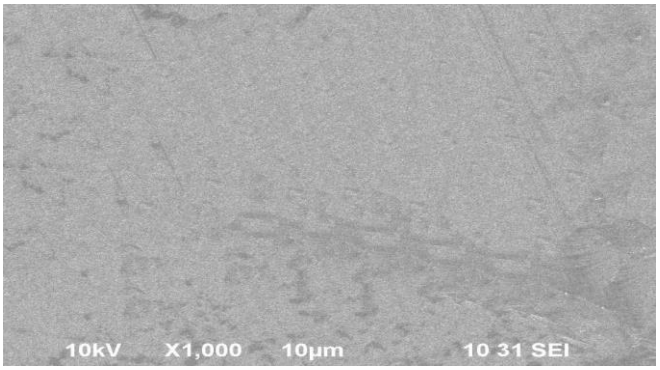

Fig. 26: SEM image 1.

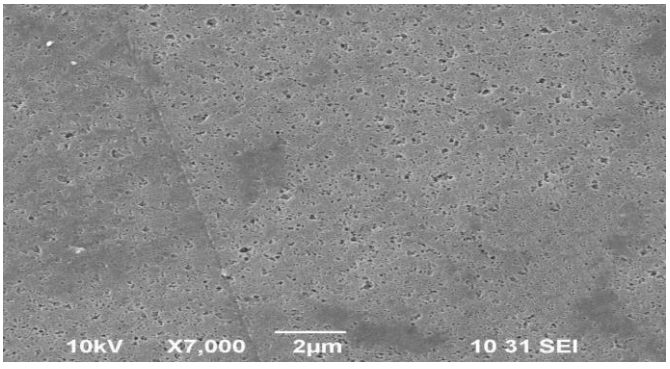

Fig. 27: SEM Image 2.

The present investigation was undertaken to formulate Indomethacin oral films which are used as NSAID's.

F1-F3 were carried out with HPMC E15 cps, PEG 400, sodium saccharin, citric acid and flavor. The films were clear and transparent. The thickness also uniform. The flexibility also good. The films shown good mechanical properties. Accordingto the assay result the drug was properly loaded in the film.

F4-F6 were carried out with HPMC E50, propylene glycol, sodium saccharin, citric acid and flavor. The films shows good appearance. The thickness also not uniform. The flexibility of the film was not good. The percentage drug release wasfound to be.

F7 was formulated with HPMC E15, propylene glycol, sodium saccharin, citric acid and flavor. The appearance of the film was also good but the thickness and disintegration time was more.

F8 was formulated with HPMC E50, PEG 400, sodium saccharin, citric acid and flavor.
F9 was formulated with HPMC E15 & E50 without the addition of plasticizers. The formulatedfilms were more brittleness.

Among all the formulations F3 shown good mechanical properties and less disintegration time of 20 seconds. All the parameters of film were found to be satisfactory. And the dissolution profile was found to be desirable andreproducible.

The morphological study (SEM) of F3 shows more porous. Therefore rapid drug release was achieved for the immediate onset of action.

The film (F3) samples evaluated gave maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament. Therefore the oral films have considerable advantage over the conventional dosage forms.

SUMMARY AND CONCLUSION

The primary objective of this work was to develop a mouth dissolving film with Indomethacin along with basic ingredients like polymers, plasticizers, sweetener, saliva stimulating agent and flavor.

The films were prepared by solvent casting method.

HPMC E50 cps, which was not able to impart thickness to the film. HPMC E15 shown good flexibility.

The plasticizer propylene glycol which was not able to impart flexibility and folding endurance to the film. PEG 400 produced good folding endurance, tensile strength and percent elongation.

The optimized formulation (F3) was shown good mouth feel, folding endurance, instant drug release as well as good mechanical properties.

The F3, shown less disintegration time of 20 seconds and 99% drug released within 3 minutes while the marketed formulation took 1 hour.

Therefore, rapid drug release was achieved for immediate onset of action which is beneficial when compared to conventional tablet dosage form.

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