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"Formulation and optimization of Pantoprazole Sodium oral film"

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Abstract

Oral films are a novel drug delivery system that consists of oral strips (solid dosage form) that dissolve or disintegrate in the oral cavity within seconds. This dosage form is readily administered by placing the strip or film on the patient's tongue.

Pantoprazole is a Proton-pump inhibitor used in the management of ulcers and gastroesophageal reflux disease (GERD); Pantoprazole is a lipophilic drug with a weak base and poor aqueous solubility at acidic ph. It is unstable in a low pH medium and undergoes rapid acid-catalyzed degradation. The study aims to overcome the degradation of Pantoprazole in an acidic environment and enzymatic degradation through first-pass metabolism along with the formulation of an oral film based on a polymeric matrix of Polyvinyl alcohol, Polyvinyl pyrrolidinone, and pullulan for the delivery of Pantoprazole through the oral mucosa. The Oral films were commonly manufactured via solvent casting method in an aqueous or hydro-alcoholic mixture of excipient with active pharmaceutical ingredients being cast into a surface, dried, and cut into the desired size. the prepared film exhibited acceptable folding endurance value; The time required for the film to disintegrate was found to be within few seconds 44-55 seconds, due to the water-soluble polymers used in the formulation.

Key words: Oral film, polymer, pantoprazole, plasticizer, solvent casting

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الملخص

الأفلام الفموية هي نظام جديد لتوصيل الدواء يتكون من شرائط فموية (شكل جرعات صلبة) تذوب أو تتفكك في تجويف الفم خلال ثوانٍ. يتم إعطاء هذا الشكل الصيدلاني بسهولة عن طريق وضع الشريط أو الفيلم على لسان المريض.

بانتوبرازول هو مثبط لمضخة البروتون يستخدم في علاج القرحة ومرض الجزر المعدي المريئي (GERD)؛ بانتوبرازول هو دواء محب للدهون مع قاعدة ضعيفة وذوبان مائي ضعيف عند درجة الحموضة الحمضية. إنه غير مستقر في وسط منخفض الأس الهيدروجيني ويخضع لتدهور سريع محفز بالحمض. تهدف الدراسة إلى التغلب على تحلل البانتوبرازول في بيئة حمضية والتحلل الأنزيمي من خلال استقلاب المرور الأول إلى جانب تكوين فيلم فموي يعتمد على مصفوفة بوليمرية من كحول البولي فينيل، والبولي فينيل بيروليدينون، والبولولان لتوصيل البانتوبرازول من خلال. الغشاء المخاطي للفم. يتم تصنيع الأغشية الفموية عادةً عبر طريقة الصب بالمذيبات في خليط مائي أو كحولي مائي من السواغ مع المكونات الصيدلانية الفعالة التي يتم صبها على السطح، وتجفيفها، وتقطيعها إلى الحجم المطلوب. أظهر الفيلم المُجهز قيمة تحمل قابلة للطي مقبولة؛ وجد أن الوقت اللازم لتفكك الفيلم هو خلال ثوان قليلة 44-55 ثانية، وذلك بسبب البوليمرات القابلة للذوبان في الماء المستخدمة في التركيبة.

الكلمات المفتاحية: الغشاء الفموي، البوليمر، البانتوبرازول، الملدنات، صب المذيبات.

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Introduction

Oral films are a novel drug delivery system that consists of oral strips (solid dosage form) that dissolve or disintegrate in the oral cavity within seconds. This dosage form is readily administered by placing the strip or film on the patient's tongue. The film disintegrates rapidly when come in contact with the saliva without water, then absorbs the medication through sublingual mucosa to the gastrointestinal tract; this film can be applied for local and systematic drug delivery. (Muhammed and Omer,2020)

The oral route is preferred for most patients to administer the therapeutic agent due to its ease of administration, the accuracy of dose, and noninvasive property.

Even though many patients (both pediatric and geriatric) are struggled to swallow tablets and hard gelatin capsules and fail to take their prescriptions as directed (RÉDAI, Emőke-Margit, et al., 2021)

In order to increase patient acceptance and compliance, pharmaceutical scientists have developed a new approach to the oral release of active pharmaceutical ingredients (APIs) in the form of an oral film.

These oral film dosage forms provide several advantages: no need for water for disintegration, precise dosing, rapid onset of action, the convenience of transport and handling, and increased patient compliance. In some situations, the drug's bioavailability is much higher than the traditional formulations.

An oral film can be developed and obtained using a variety of procedures, including solvent casting, semisolid casting, hot-melt extrusion, and rolling. The solvent casting method is the most often used method for obtaining an oral film. It involves the following steps: (1) preparing the casting solution by dissolving or suspending the API in the polymer along with the plasticizer solution and volatile solvents (water and alcohol); (2) degassing and removing air bubbles from the resulting mixture; (3) casting the resulting solution in a dried Petri dish; (4) solvent evaporation from the poured dispersion to form a film by drying it in a controlled temperature oven. (RÉDAI, Emőke-Margit, et al., 2021)

Polymers, plasticizers, sweetening agents, saliva-stimulating agents, coloring agents, and flavoring agents are the essential excipients in the oral film formulation. These excipients must be safe and non-toxic. (Muhammed and Omer, 2020)

Pantoprazole is a Proton Pump Inhibitors (PPIs) that bind to the proton pump;

Thereby reducing the gastric acid production in the parietal cells.

The PPIs have been used to treat ulcers; gastroesophageal reflux disease (GERD), a disease that is susceptible to recurrence acid from the stomach

and cause heartburn and hurt the esophagus; and in conditions of producing too much acid, such as in Zollinger-Ellison syndrome. Proton pump inhibitors can be used to prevent the effects of ulcers caused by NSAIDs and to heal ulcers triggered by these drugs. (KORHONEN, 2017)

Pantoprazole is hepatically metabolized via cytochrome P2C19 to inactive metabolite (hydroxy-pantoprazole) that subsequently undergoes sulfate conjugation.

Pantoprazole is a lipophilic drug, a weak base and poor aqueous solubility at acidic pH. pantoprazole is unstable in a low PH medium and undergoes rapid acid-catalyzed degradation, though relatively stable at neutral or high pH. Effective drug delivery is difficult due to Pantoprazole Sodium's pH sensitivity. The majority of PPIs were available as an enteric-coated solid dosage form (such as a delayed release capsule or tablet) or as an intravenous solution. (Ratnaparkhi, et al., 2013)

In order to enhance the stability of pantoprazole in a low PH environment, Along (Kaza, Raju and Nagaraju, 2014) with overcome the degradation of pantoprazole in an acidic environment (stomach PH), as well as enzymatic degradation through first-pass metabolism. Therefore, this study exists to formulate an oral film based on polymeric matrix of Polyvinyl alcohol and Polyvinyl pyrrolidinone for the delivery of pantoprazole through the oral mucosa. furthermore, to Develop and evaluate oral film containing Pantoprazole Sodium as an active pharmaceutical ingredient, suitable for pediatric, geriatric, and uncooperative patient.

Problem Statement:

Pantoprazole Sodium, a proton pump inhibitor (PPI), is widely used to treat conditions like gastroesophageal reflux disease (GERD) and Zollinger-Ellison syndrome, which require the reduction of gastric acid production. Despite its therapeutic efficacy, Pantoprazole Sodium faces significant challenges in drug delivery due to its instability in acidic environments, poor aqueous solubility, and susceptibility to rapid acid-catalyzed degradation in low pH. Traditional formulations, such as enteric-coated tablets and intravenous solutions, present difficulties for pediatric, geriatric, and uncooperative patients who struggle with swallowing or have issues with compliance.

To address these challenges, this research aims to develop and optimize an oral film formulation for Pantoprazole Sodium, utilizing a polymeric matrix composed of Polyvinyl alcohol (PVA) and Polyvinyl pyrrolidone (PVP). The goal is to create a novel drug delivery system that enhances the stability and bioavailability of Pantoprazole Sodium, while providing a patient-friendly administration route that dissolves rapidly in the oral cavity without the need for water. This study will focus on formulating the oral film, optimizing its properties, and evaluating its effectiveness in delivering Pantoprazole Sodium through the oral mucosa, particularly targeting pediatric, geriatric, and uncooperative patient populations.

Objectives of Research:

1. **Formulation Development**:
    - To develop an oral film formulation for Pantoprazole Sodium using a polymeric matrix of Polyvinyl alcohol (PVA) and Polyvinyl pyrrolidone (PVP).
    - To optimize the formulation process using the solvent casting method to ensure uniformity, stability, and appropriate mechanical properties of the oral film.
2. **Optimization**:
    - To determine the optimal concentration of polymers, plasticizers, and other excipients that contribute to the film's disintegration time, mechanical strength, and drug release profile.
    - To optimize the conditions for solvent evaporation and film drying to achieve consistent and reproducible film characteristics.

3. **Characterization**:
    - To evaluate the physical and chemical properties of the formulated oral film, including thickness, weight uniformity, tensile strength, folding endurance, and surface pH.
    - To assess the drug content uniformity and in vitro dissolution profile of the Pantoprazole Sodium oral film.
4. **Stability Assessment**:
    - To conduct stability studies under various environmental conditions (temperature, humidity) to ensure the formulated film maintains its integrity and drug stability over time.
    - To investigate the stability of Pantoprazole Sodium in the film matrix in the presence of saliva and under different pH conditions simulating the oral cavity.

By achieving these objectives, the research aims to provide an innovative and effective drug delivery system that enhances patient compliance, improves therapeutic outcomes, and addresses the limitations associated with current Pantoprazole Sodium formulations.

Aim of Research:

The aim of this research is to develop and optimize a novel oral film formulation for Pantoprazole Sodium that enhances its stability, bioavailability, and patient compliance. By utilizing a polymeric matrix composed of Polyvinyl alcohol (PVA) and Polyvinyl pyrrolidone (PVP), the study seeks to create a rapidly disintegrating oral film suitable for pediatric, geriatric, and uncooperative patients who face challenges with traditional solid dosage forms. This innovative drug delivery system aims to improve therapeutic outcomes for conditions requiring reduced gastric acid production by ensuring effective and convenient administration of Pantoprazole Sodium.

Research terminologies:

Oral Film: Oral films are a type of solid dosage form that rapidly dissolves or disintegrates when placed in the mouth. They deliver the active pharmaceutical ingredient through the oral mucosa to the systemic circulation or for local action (Muhammed, 2020).

Polymer: Polymers are large molecules composed of repeating structural units (monomers) connected by covalent chemical bonds. In pharmaceuticals, they are used to formulate drug delivery systems, providing structural integrity and controlled release properties (Remington, 2012).

Pantoprazole: Pantoprazole is a proton pump inhibitor (PPI) that reduces gastric acid production by binding to the H+/K+ ATPase enzyme in the

stomach's parietal cells. It is used to treat conditions like GERD, peptic ulcers, and Zollinger-Ellison syndrome (Korhonen, 2017).

Plasticizer: Plasticizers are additives used in the formulation of films and polymers to enhance their flexibility, workability, and pliability. They reduce the brittleness of the polymer matrix by increasing its plasticity (Rowe, 2009).

Solvent Casting: Solvent casting is a technique used to produce films by dissolving a polymer and active pharmaceutical ingredient in a suitable solvent, followed by casting the solution onto a substrate and evaporating the solvent to form a solid film (Redai, 2021).

Literature Review:

Overview of Oral Films in Drug Delivery

Oral films represent an advanced drug delivery system that has garnered significant attention due to their rapid disintegration, ease of administration, and enhanced patient compliance. These films are particularly advantageous for pediatric and geriatric populations, as well as for patients with swallowing difficulties (dysphagia) . Oral films are designed to dissolve quickly in the oral cavity, delivering the active pharmaceutical ingredient (API) directly through the mucosal tissues or allowing it to be swallowed and absorbed via the gastrointestinal tract (Ratnaparkhi, 2013) .

Advantages and Development of Oral Films

Oral films offer several benefits over traditional solid dosage forms such as tablets and capsules. They do not require water for administration, provide accurate dosing, have a rapid onset of action, and are convenient for transportation and handling . The development of oral films involves various techniques, with solvent casting being the most widely used method. This technique allows for the uniform distribution of the drug within the polymer matrix, leading to consistent film properties .

Polymers in Oral Film Formulations

Polymers play a critical role in the formulation of oral films, providing the necessary structural integrity and flexibility. Commonly used polymers include Polyvinyl alcohol (PVA) and Polyvinyl pyrrolidone (PVP), which are chosen for their film-forming properties, safety, and biocompatibility . The choice of polymer affects the film's mechanical strength, disintegration time, and drug release profile (Korhonen, 2017).

Plasticizers in Oral Films

Plasticizers are essential components in oral film formulations, enhancing the flexibility and reducing the brittleness of the films. They work by inserting themselves between polymer chains, increasing the mobility of

the polymer matrix . Common plasticizers include glycerin, propylene glycol, and polyethylene glycol.

Pantoprazole and Its Challenges

Pantoprazole, a proton pump inhibitor (PPI), is widely used to treat conditions like gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome . However, Pantoprazole presents significant formulation challenges due to its instability in acidic environments and poor aqueous solubility at low pH . These characteristics necessitate the development of specialized delivery systems to protect the drug from degradation and enhance its bioavailability (Rowe, 2009).

Solvent Casting Method for Oral Films

The solvent casting method is the preferred technique for preparing oral films due to its simplicity and effectiveness in producing uniform films . The process involves dissolving the polymer and API in a volatile solvent, casting the solution onto a substrate, and evaporating the solvent under controlled conditions. This method ensures the uniform distribution of the drug within the film and allows for precise control over the film's thickness and drug loading.

Recent Advances and Studies

Recent studies have explored various aspects of oral film formulations, including the optimization of polymer and plasticizer concentrations, the development of taste-masking strategies, and the evaluation of in vitro and in vivo drug release profiles . For instance, research by Muhammed and Omer (2020) highlighted the potential of oral films for delivering APIs with improved patient compliance and rapid onset of action . Another study by Redai et al. (2021) focused on the solvent casting technique and its application in developing effective oral film formulations .

Pantoprazole Oral Films

The formulation of Pantoprazole as an oral film aims to overcome its stability issues and enhance its bioavailability. Incorporating Pantoprazole into an oral film using PVA and PVP as polymers can protect the drug from acidic degradation and ensure its controlled release through the oral mucosa. Studies have shown that such formulations can effectively deliver Pantoprazole with improved stability and patient acceptability (Remington, 2012).

Methodology:

Formulation consideration:

A standard formula contains the following: (Siddiqui, Garg and Sharma, 2011)

Table 1: the compositions of oral film

Active pharmaceutical ingredient

Class: proton pump inhibitor

Drug: pantoprazole sodium

Film forming polymers (water soluble polymers)

1. In this study the PVA, PVP were used and tested to obtain oral films for pantoprazole as drug delivery system

Cellulose, cellulose derivatives and starches, and modified starches, such as carboxymethyl cellulose (CMC) is the most commonly used natural polymers in the fabrication of oral films.

Furthermore, the synthetic polymers have been also intensively studied as film-formers, but the majority converge to PVA, PVP, and methacrylate polymers.

There are various polymers that are continuously being studied to improve this matrix for drug delivery. The several types of polymers, the different polymer rate, and the various polymer-polymer blend ratios result in an exponential number of achievable formulations and a broad range of final product characteristics.

Active pharmaceutical ingredient	5 to 30% w/w
Water soluble polymer	40 to 50% w/w
Plasticizer	0 to 20 % w/w
Sweetening agent	3 to 6% w/w
Saliva stimulating agent	2 to 6% w/w

- Polyvinyl alcohol

PVA is a biocompatible, water-soluble polymer generated from polyvinyl acetate through partial or complete alkaline hydrolysis and has been successfully used as the primary film-forming polymer. Regarding the fabricating process, it is important to remember that PVA is only fully dissolved in hot water and the increase in PVA hydrolysis is proportional to the temperature required for PVA to fully dissolve.

- Polyvinyl pyrrolidione K- 30

PVP or povidone is a polymer with linear 1-vinyl-2-pyrrolidinone groups of varying molecular weights. Generally, PVP is described as a good film forming agent or a polymer with very poor film forming ability, which can be enhanced to a general film former polymer when mixed with other polymer as PVA or HPMC, resulting in clear and rapidly disintegrating

films, PVP Widely studied as a film former because it is a palatable polymer that dissolves rapidly in the mouth

PVP has sufficient solubility in both water and organic solvents, so the most suitable solvent can be used in the process and manufacturing process according to the drug constituent.

Although polymers are the major constituent of the oral film, extra excipients may be essential to modify the target product profile. These excipients include plasticizer, sweeteners, flavors, colorants, stabilizers, fillers, salivary stimulants, buffering systems, and others. (borges, 2015)

Plasticizer

In addition to the film-forming polymer, the plasticizer is the major component in the oral film. Plasticizers increase flexibility, improve polymer processability, and improve mechanical strength, Plasticizers can cause internal plasticization through chemical interactions or external plasticization without affecting the chemical interactions between the components. Glycerol, dibutyl phthalate, PEG, and glycerin are the most Widely used plasticizers. Glycerol has a low molecular weight, , low volatility, and good compatibility with the polyvinyl alcohol. (KORHONEN, 2017)

Sweetening agent

Sweeteners are an essential component in formulations designed to be disintegrated or dissolved in the oral cavity. Sweeteners are typically employed in concentrations ranging from 3 to 6 % w/w, alone or even in combination. Natural and artificial sweeteners are used in the manufacture of the oral films. (Pallavi et al.,2014).The following sweeteners are appropriate for oral film:

(a) Stevioside, glucose, maltose, and fructose are natural sweeteners.

(b) Artificial sweetener: sodium or calcium saccharin salts. (Lodhi, et al., 2021)

Saliva stimulating agent

Saliva stimulating agents are used to increase the rate of saliva secretion (Agents that stimulate saliva), which aids in the disintegration of the oral film formulation. Salivary stimulants include citric acid, malic acid, ascorbic acid, and tartaric acid. (Juluru, 2013)

Manufacturing methods

The following processes are utilized in the manufacture of oral film formulations:

To make the oral films, one or more of the following processes can be employed.

1.solvent casting

2. Semisolid casting

3. Hot melt extrusion from

4. Rolling (Jain, Ahirwar, et al., 2018)
the solvent casting and hot-melt extrusion techniques are the most commonly used for manufacturing oral films, (Patel, Prajapati and Raval, 2010)

Materials and preparation method Materials :
Table 2: materials and its applications

	Properties	Applications
Sodium phosphate monobasic	Powder	Bioreagent Used for buffer
Disodium hydrogen phosphate	Powder	Bioreagent Used for buffer
DL-Malic acid	Clear colorless to fainty yellow powder	Saliva Stimulating agent
Polyvinyl pyrrolidione K- 30	Powder	Water soluble polymer
Poly(vinyl alcohol)	Powder	Water soluble polymer
Glycerol	Colorles, odorless and viscous liquid	Plasticizer agent
Pullulan	White powder	Synthetic polysaccharide polymer
Ethanol	Colorless liquid	Solvent
Pantoprazole sodium	Powder	Active ingredient

Table 3: equipment

Weighing balance
Overhead mixer
Hot plate magnetic stirrer
Controlled temperature oven

Table 4: instrumentations:

Fourier-transform infrared (FTIR)	Absorption spectra by using infrared Bruker Tensor 37 spectrometer and OPUS-65 software.
X-Ray Diffraction (XRD	Data collected at 22θ° from 20 to 60°, by using Unisantis XRD-300 operator and XQ Suite software.
Differential scanning calorimetry (DSC)	Data collected by using DSC-60 operator and TA acquisition software.
The Ultraviolet-Visible (UV.VIS)	CARY 60 UV-VIS spectrometer with UV. Region of electromagnetic spectrum is 200-400 nm and The VIS. Is 400-800 nm. Single beam.

Preparation method :

Preparation of drug-loaded oral films and blank oral films

Oral films were commonly manufactured via solvent casting method in an aqueous or hydro-alcoholic mixture of excipient with active

pharmaceutical ingredients being cast into a surface, dried, and cut into the desired size. (Pechováetal. Et al., 2018)

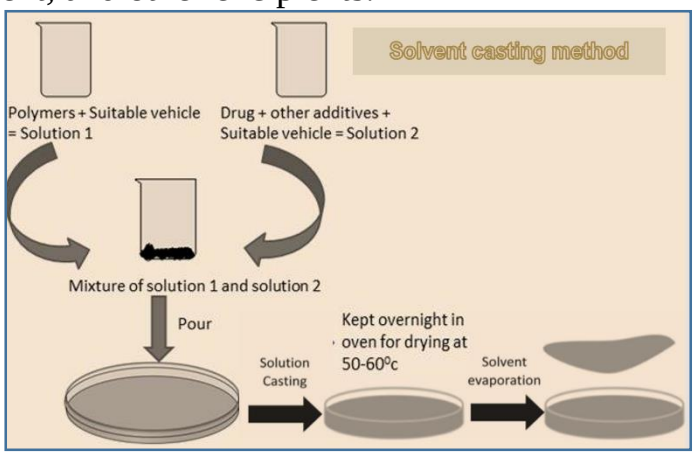
Film-forming agents such as PVA and PVP were prepared in the form of an aqueous solution individually in 100 ml beaker, (Balakrishna, T.,etal., 2018). The solution is continuously stirred on a magnetic stirrer or overhead mixer (Pallavi et al.,2014),

To attain clear solutions and kept for 1 hour to remove all air bubbles entrapped. After an hour has passed, mix any of the solutions used in the experiment, then keep them aside.

Meanwhile, in the separate container remaining water-soluble excipients, i.e., Pantoprazole, sweetening agent, and saliva stimulating agent, is dissolved in a suitable solvent with a constant magnetic stirrer (Balakrishna, T., etal., 2018), then add a defined quantity of the plasticizer (glycerol) and keep stirring to attain homogenous solutions. Both the solutions were mixed with stirring for another 1 hour on the overhead mixer when the stirring was over. Then kept the solution stationary for 1 hour to let the foams and air bubbles settle down. (Pallavi et al.,2014)

The resulting formulations were cast on dried Petri dishes and kept in the controlled temperature oven overnight to evaporate the solvent and dry the solutions, (Muhammed and Omer, 2020). Dried films are then carefully removed and wrapped in aluminum foil and kept at ambient conditions for further characterizations. (Pallavi et al.,2014)

In the same conditions, 9 formulations of oral films were prepared, (RÉDAI, Emőke-Margit, et al., 2021) with different concentration ratios of the film-forming agents and different concentrations of the plasticizer, active ingredient, and other excipients.



Fiqure 1: prepration method (Joshi, Akram, Chauhan and Garud, 2022)

Development of preliminary trial batches for oral film

Development of preliminary trial batches for the selection of film-forming materials. Different concentrations from all ingredients are added to the formulation to check their effect on film properties (Modi, Kamble and Chauha, 2013). PVA, PVP, glycerol, and malic acid were evaluated by the general

preliminary trial batches NO:	1	1	2	3	4	4	4	5	5
Materials/formula no. :	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pantoprazole Sodium	150	--	10	--	--	--	--	10	--
Polyvinyl Alcohol	300	300	30	15	15	15	15	30	30
Polyvinyl Pyrrolidione	250	250	15	7.5	7.5	5	2	15	15
Malic acid	20	20	2	2	2	2	2	2	2
Stevia sweetener	20	20	2.5	2.5	2.5	2.5	2.5	2.5	2,5
Glycerol	100	100	35	7	5	7	5	20	20
Distilled water	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.
Ethanol	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.
Blank/drug loaded	Drug loaded	blank	Drug loaded	blank	blank	blank	blank	Drug loaded	blank

appearance, such as the identity and overall "elegance", size, shape, color, and presence or absence of an odor surface texture, and dryness test/tack test. The best one was selected for further optimization. (Poojan, et al., 2013)

The various compositions and schematic representations of oral films are given in table 5

Table 5 : preliminary trial batches for oral film

Development of preliminary trial batches for oral film

- Preliminary trial batch NO.1 : containing four formulae (F1, and F2)

1- F1 and F2, was prepared by different concentration of PVA and PVP
2- PVA is the primary polymer and in higher concentration than PVP
3- Glycerol 100 ml was added to get a drug and plasticized solution
4- F1 is a drug loaded film, F2 is a blank film (without drug)
5- Other additives are with fixed concentrations of all formulae.

6- These films were subjected for further evaluation of physical characterizations

- Preliminary trial batch NO.2 : containing one formula (F3)

1- F3 is a drug loaded film with different concentrations of PVA (highest concentration) and PVP (lowest concentration).
2- The quantity of glycerol compared with patch no. 1 was decreased to 35 ml to improve the elasticity of the films.
3- This film was subjected for further evaluation of the physical characterizations

- Preliminary trial batch NO.3 : containing one formula (F4)

1- This film is a blank film
2- From the optimization of the previous formula F3, this film F4 was produced
3- PVA is the primary polymer and in higher concentration than PVP
4- The quantity of glycerol compared with patch NO. 2 (F3) was decreased from 35 ml to 7 ml to improve the elasticity of the films.
5- This film was subjected for further evaluation of the physical characterizations

- Preliminary trial batch NO.4 : containing three formulae (F5, F6, and F 7)

1- F4 was prepared in the previous trial batch but for further optimization and enhancement F5, F6, and F7 were produced.
2- In comparison of F4, F5 was prepared same as F4 but the glycerol quantity was decreased from 7 ml to 5 ml.
3- In addition, F6 was same as F4 but the PVP concentration was decreased from 7.5 gm to 5 gm.
4- F7 was prepared as F4 but the PVP concentration was decreased from 7.5 gm to 2 gm and the glycerol quantity was decreased from 7 ml to 5 ml.
5- Polyvinyl alcohol in constant concentration 15 gm in all formulae and higher than the PVP, The PVP concentration varies according to the glycerol quantity.
6- These films were subjected for further evaluation of the physical characterizations

- Preliminary trial batch NO.5 : containing two formulae (F8, and F9)

1- From the optimization of the previous trial batches NO.2 (F3) and NO.3(F4), these films were produced.
2- The PVA and PVP were prepared as on F3 , 30ml and 15ml respectively.
3- The glycerol quantity is 20 ml which is less than 35 ml as on F3, and more than 7ml as on F4.
4- F8 is drug loaded films while F9 is the blank film of F8.

5- These films were subjected for further evaluation of the physical characterizations

Evaluation tests:

The prepared drug loaded\blank oral films is evaluated by the following tests

Physical characterizations:

Physical characterizations can be carried out by hands for the appearance and texture, surface smoothness, stiffness, stickiness, and the presence of air bubbles. Also color, odor, brittleness, and peeling ability

The physical characterizations were performed for all formulae starting from F1 until F9.

Thickness test

The thickness can be measured by a micrometer screw gauge (at least) at three different strategic locations, concerned with the drug content uniformity The ideal film thickness ranging between 5-200 µm.

(Bhupinder, et al., 2011), then mean thickness was calculated by using Microsoft excel (Muhammed and Omer, 2020).This test was performed to F8 & F9.

Medium	Composition	Quantity	Ph value
Artificial saliva	Disodium hydrogen phosphate	2.07 gm	Ph 7.2
	Sodium di hydrogen phosphate monohydrate	1.0 gm	
	Distilled water	To 1000 ml	

Table 6: Disintegration time

Dryness/tack test

Tack or dryness test is obstinacy with which film adheres to the accessory (a piece of paper or aluminum foil, F3, F8, and F9 were taken, and the dryness/tack test were checked with the help of paper. (Mushtaque et al., 2020)

Disintegration time

Disintegration time can be performed for the drug loaded film F8 in stimulated saliva solution (Juluru, 2013). The film of (2x2cm^2) was immersed on a beaker containing 100 ml of stimulated artificial saliva.

stimulated artificial saliva was prepared as the following formula:

Dryness/tack test

Tack or dryness test is obstinacy with which film adheres to the accessory (a piece of paper or aluminum foil, F3, F8, and F9 were taken, and the dryness/tack test were checked with the help of paper. (Mushtaque et al., 2020)

Disintegration time

Disintegration time can be performed for the drug loaded film F8 in stimulated saliva solution (Juluru, 2013). The film of (2x2cm²) was immersed on a beaker containing 100 ml of stimulated artificial saliva.

stimulated artificial saliva was prepared as the following formula:

drug content

Preparation of standard calibration curve of pantoprazole sodium:

A stock solution of 0.001% (10 µg/ml) of pantoprazole sodium was prepared using a volumetric flask in distilled water. The stock solution was diluted(1:10) as follow 2:10, 3:10, 4:10, 5:10, 6:10, 7:10, 9:10, and 10:10 corresponding to 2, 3, 4, 5, 6, 7, 9, and 10 µg/ml pantoprazole sodium. The resulting solutions were analyzed at 291.0 nm, spectrophotometrically, using CARY 60 UV-VIS. Spectrophotometer on eight samples, the result of the calibration curve was to evaluate pantoprazole sodium oral film content (RÉDAI, Emőke-Margit, et al., 2021), and the statistical result was analyzed by the SPSS program to determine the correlation between the concentrations (2 to 10 µg/ml). (MS, C, Kumar and J, 2016)

folding endurance

Folding endurance was determined by repeated folding of the films at the same place till the film breaks or cracks. The number of frequent films folded without breaking was computed as the folding endurance value. (Siddiqui, Garg and Sharma, 2011).

The folding endurance determination will help to determine the mechanical strength like brittleness and flexibility of the film. The increment folding endurance value will directly be proportional to its mechanical strength (Raghavendra and Kumar, 2017).

X-Ray Diffraction (XRD)- crystallinity analysis

XRD was carried out to evaluate the effect of the film formulation process on the crystallinity of the drug (Rashid et al., 2021). The XRD was performed on the F8, F9, PVA, PVP, and on Pantoprazole sodium -pure drug-

The analysis data were collected at two theta (angle) from 20 to 60 °, by using Unisantis XRD-300 operator and XQ Suite software; Setup the measurement setting of the software such as measuring time, sample ID, sample spinner, start and stop angle then save the setting and start a new measurement

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed using the DSC-60 operator and TA acquisition software, with the initial and final temperature at 0 ºC and 300 ºC, respectively, allowing a rise in temperature to the tune of 20 Cº/1 min.

Fourier-transform infrared (FTIR)

FT-IR spectroscopy can inspect and predict the physicochemical relations between a component in a formulation (Jawahar, Sood, Jain and Barath, 2012).

FT-IR spectroscopy was employed on the pantoprazole sodium, drug-loaded film F8, and blank film F9, PVA, and PVP.

Results

Physical characterizations:

Preliminary trial batch NO.1

- The prepared films of F1 and F2, as in the (Appendices I, Figure 3) are not completely dried and are still sticky even though these films were kept in the oven at 50 ºc for one week and under an infrared lamp for 24 hours.
- These films are not considered for further characterization.

Preliminary trial batch NO.2

- This film F3 (Appendices I, Figure 4) is a drug-loaded film; the brown color indicates the presence of pantoprazole due to its photosensitive property.
- The general appearance evaluated the obtained films; The tack test failed to meet the required attributes in terms of tackiness due to the high quantity of glycerol as a plasticizer.
- This film is subjected to further optimization.

Preliminary trial batch NO.3

- The prepared film F4 (Appendices I, Figure 6) the general appearance for this film was almost good; non-tacky surface, easy to peel, smooth surface texture.
- The small quantity of the glycerol 7 ml as a plasticizer leads to poor flexibility and plasticity of the film
- This film is for further optimization

Preliminary trial batch NO.4

- The obtained films F5, F6, and F7 (Appendices I, Figure 8) were not considered for further characterization due to the non-smooth surface texture (sponge-like), full of air bubbles.

Preliminary trial batch NO.5

- The prepared films of F8 and F9 (Appendices I, Figure 9, 10) were evaluated by the general appearance; the films successfully meet the basic standards and specifications for the fabrication of an oral film.
- These films are for further characterization and evaluation.
- The following tests evaluated the F17 and F18:

Thickness test

The mean of the thickness test for drug loaded films F8 was 93,116 µm, whereas the blank
films F9 was 189,653 µm. Therefore, F8 and F9 were exhibited uniform thickness(Mushtaque et al., 2020).

Dryness/tack test

the F8 and F9 formulations having 20 ml glycerol passed the tack test(Mushtaque et al., 2020). The result of the tacking was correlated with the concentration of the plasticizer (glycerol).

Disintegration time

The time required for the film to disintegrate ranges from 44 to 55 seconds.

Drug content:

Calibration curve of pantoprazole sodium

.

Concentration µg/ml	Absorbance (Abs.)	Statistical parameter Regressed
0	0	Correlation co-efficient R^2=0.99707 Line equation Abs.=0.11836xconc-0.0305
2	0.1980	
3	0.3241	
4	0.4316	
5	0.5493	
6	0.6790	
7	0.7616	
9	1.0477	
10	1.1804	

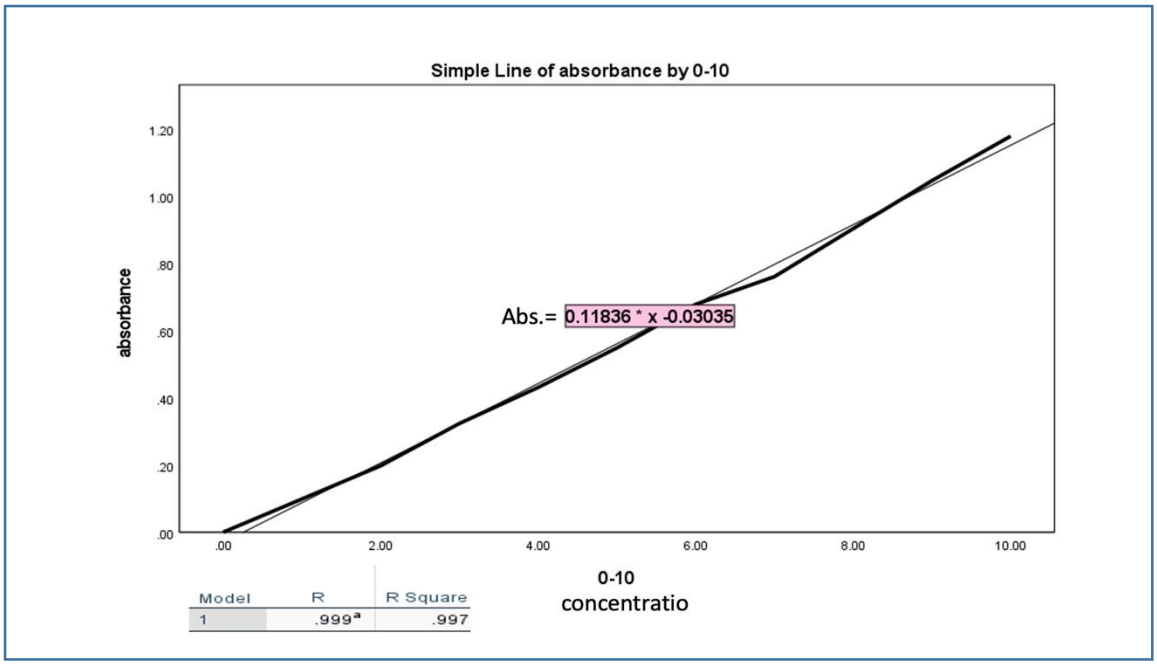


Table 7: drug content

Correlation coefficient for standard curves was found to be very near to one (0.997), which indicates the good co-liner correlation between concentrations 2-10 µg/ml (Choursiya and Pandit, 2021)

The F8 drug-loaded film was found to contain an almost uniform quantity of the drug, drug content in the film was evaluated, and the value was 98.6%. As per the USP requirements, the F8 film was found to meet the criteria for content uniformity(Rao and Reddy, 2018).

Folding endurance

The folding endurance of (2 x 2cm²) (Bala, Pawar, Khanna and Arora, 2013), Of the drug-loaded film F8 and the blank film F9 was estimated and found to be more than 1000 which indicate its flexibility and mechanical strength as necessitated in a drug delivery system (Raghavendra and Kumar, 2017).

XRD

- The pantoprazole sodium showed characteristic peaks ranging from 13.8 to 26.5θ°

- the main characteristic peak exists around 22 θ. (Appendices II, Figure 11)

-the PXRD data (2θ° values) of the prepared film revealed sharp broad peaks related to the pantoprazole sodium (pure drug). Appendices II, Figures 11, 12, 13 and 16)

-The sharp peaks indicates that the pantoprazole and the drug loaded film f8 and the blank film f9 are in a crystalline nature form. The crystallinity of the compound is detected by the presence of sharp peaks, which are not found in amorphous compounds.

DSC

• The pantoprazole exhibited an endothermic peak at 148.6 Cº, corresponding to its melting point. (Appendices III, Figure 17)

• The prepared film exhibited the characteristic endothermic peak of pantoprazole at 153.168 Cº. (Appendices III, Figure 18, 22)

• The DSC thermograms indicated no interaction between the drug and polymers used in the film formulations.

FT-IR

There was no appearance or disappearance of peaks in drug-loaded film F8 (Appendices IV, Figure 24) and blank film F9 (Appendices IV, Figure 25) compared with the common spectra of pantoprazole sodium (Appendices IV, Figure 23), which confirmed the absence of any chemical interaction between the drug and the polymers (Jawahar, Sood, Jain and Barath, 2012).

Discussion

For the pantoprazole formulation as an oral film, three types of polymers and various concentrations were used for each, as shown in Table 5. The best blank film (F9) was selected to formulate pantoprazole according to its physical properties. Films (F8, F9) prepared with 35% PVA and 15% PVP had a good appearance and were not sticky with a homogenous, smooth texture. They were easily removed from the Petri dish. Evaluation tests were performed for the prepared film (F8). The film had good folding endurance, which indicates its acceptable mechanical stability. Different studies showed that PVA has an excellent film-forming capacity. The selected polymers are all suitable film former depending on the plasticizer type.

The films (F8, F9) were thin with the mean of the thickness test for drug-loaded films F8 was 93,116 µm, whereas the blank films F9 was 189,653 µm. The thickness of the film is directly concerned with drug content uniformity; it is necessary to ascertain uniformity in the thickness of the films. Since there is a change in polymer concentrations, the prepared oral films need to have acceptable folding endurance. Hence, they can withstand handling during packaging, and they could be removed from the unit dose easily without breaking.

While in our study, Glycerol is used as a plasticizer to get better folding endurance. The type of plasticizer had a great effect on the elasticity and peel-ability of the oral strip. Regarding disintegration time, all prepared films were broken in <1 min due to the use of the water-soluble polymer. The films containing PVA-PVP disintegrated within 40–55 seconds when Glycerol was used as a plasticizer. The results of the FTIR spectra did not show any interaction between the drug and the excipients of the formulation (Muhammed and Omer, 2020).

The DSC thermal analysis of pantoprazole (pure drug) exhibited an endothermic peak at 148.6 Cº, corresponding to its melting point.

The prepared film (F8, F9) exhibited the characteristic endothermic peak of pantoprazole at 153.168 ºc Thermograms of the prepared films confirmed that there was no specific interaction
Between the drug and excipients used in the film formulation (20moh) The prepared film's XRD data (2q° values) revealed sharp broad peaks related
To the pantoprazole sodium (pure drug).
The XRD and DSC results indicated the compatibility between the drug and polymers used for the preparation of an oral film.

Conclusion:

In conclusion, the Oral film containing pantoprazole sodium can be prepared by solvent casting method using a polymer-polymer ratio of PVA and PVP, Regarding the results of this study, among the 9 formulations, 30% PVA and 15% PVP were the best polymer concentration to be used in the formulation of pantoprazole as an oral film. The prepared film exhibited acceptable folding endurance value; the time required for the film to disintegrate was found to be within few seconds 44-55 seconds, due to the water-soluble polymers used in the formulation. The XRD and DSC results indicated the compatibility between the drug and polymers used to prepare the oral film. film formulation can be a potential novel drug delivery system that overcomes the instability of pantoprazole in the acidic medium.

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Appendices

Figure NO.:	Formula	**I-Prepared films**
3	F1, 4	
4	F3	

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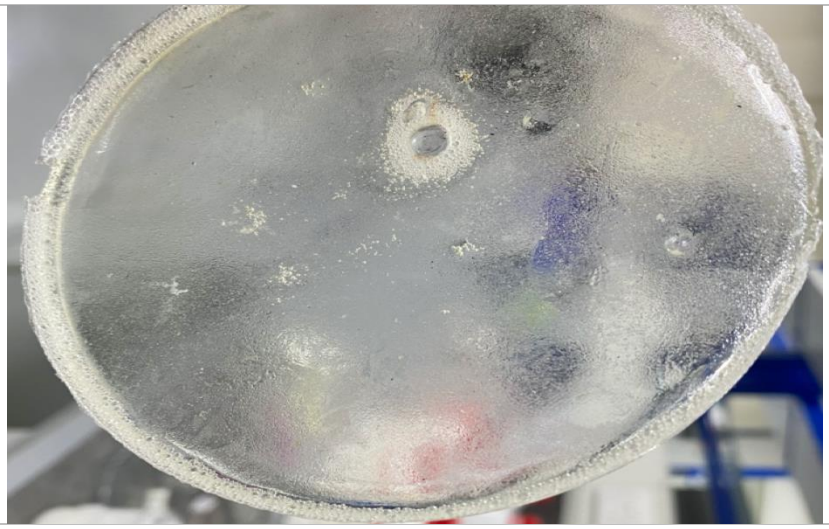
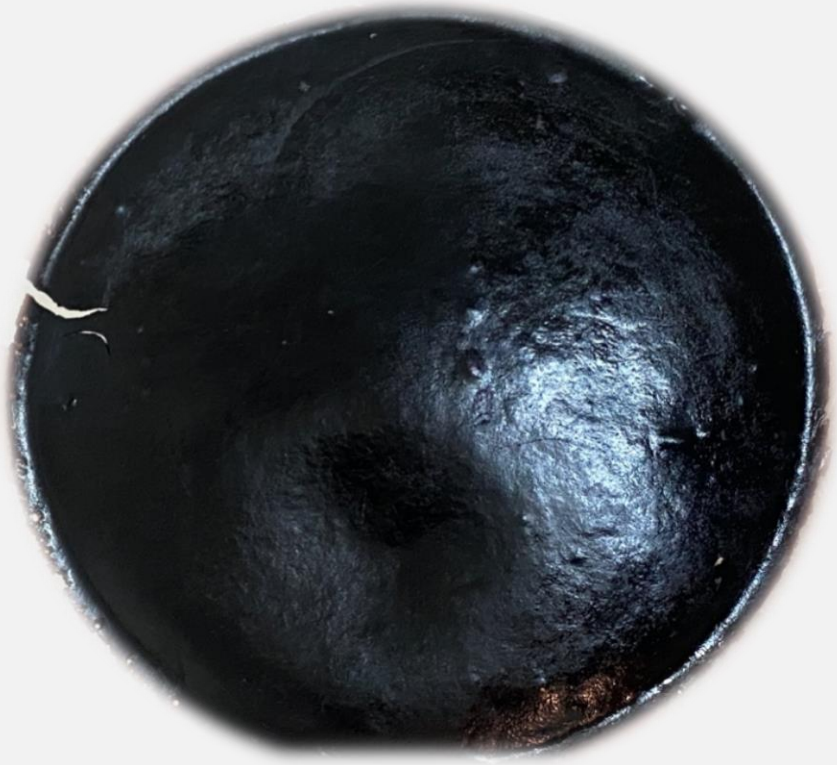
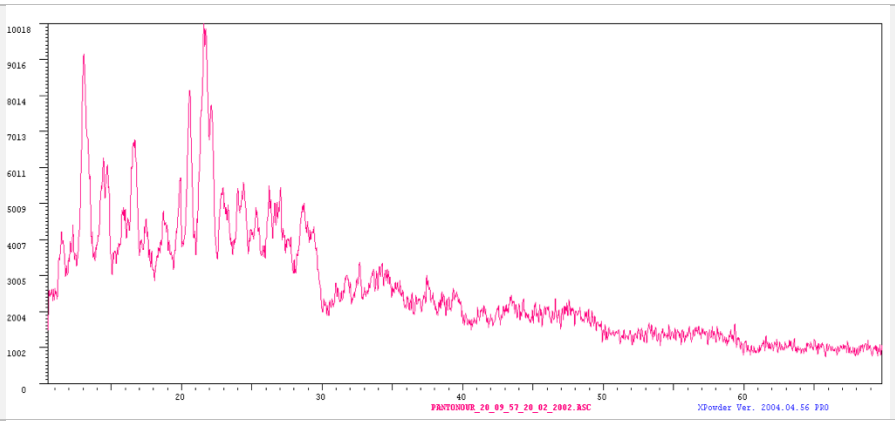
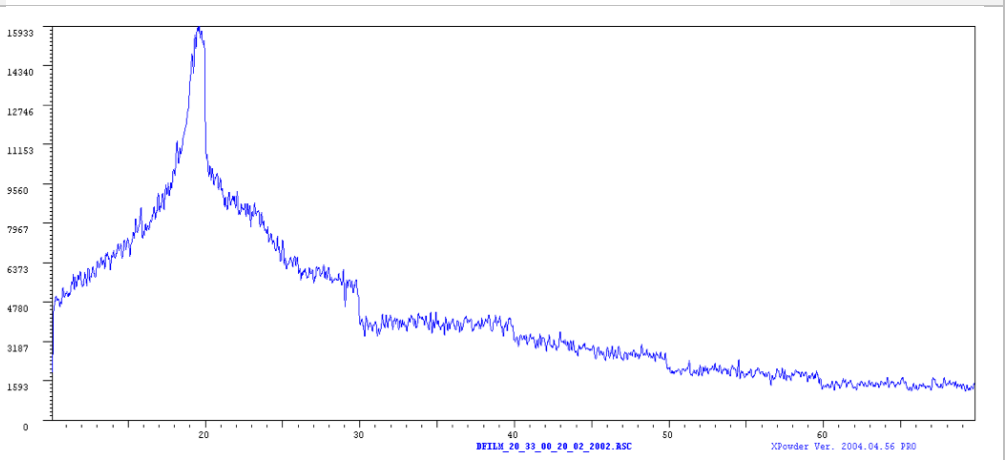
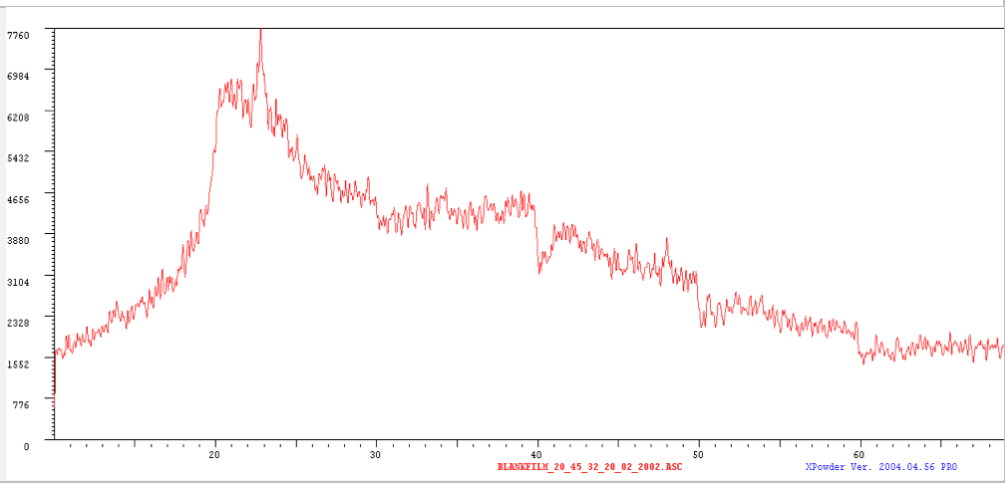
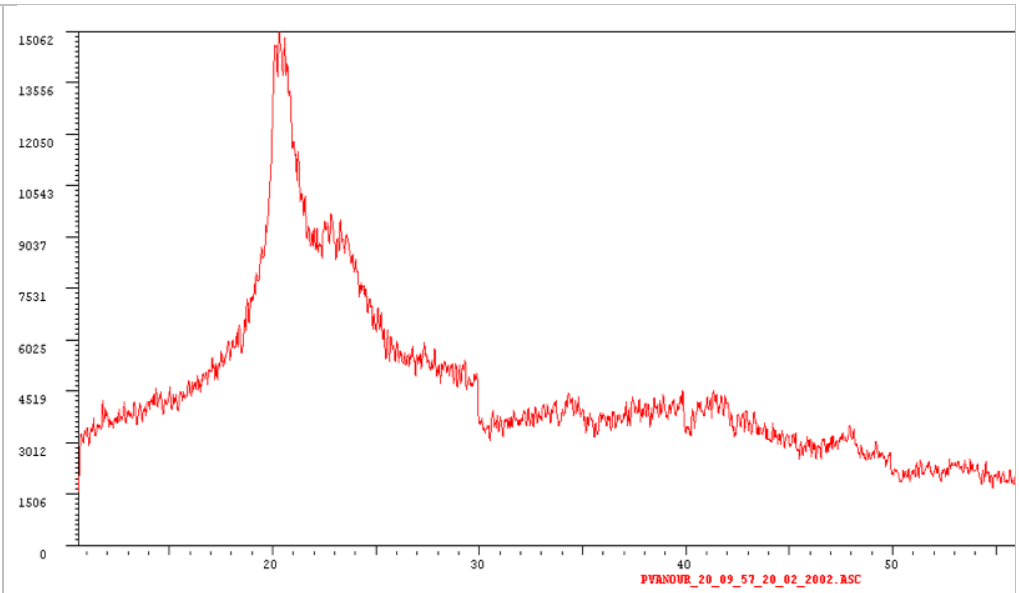
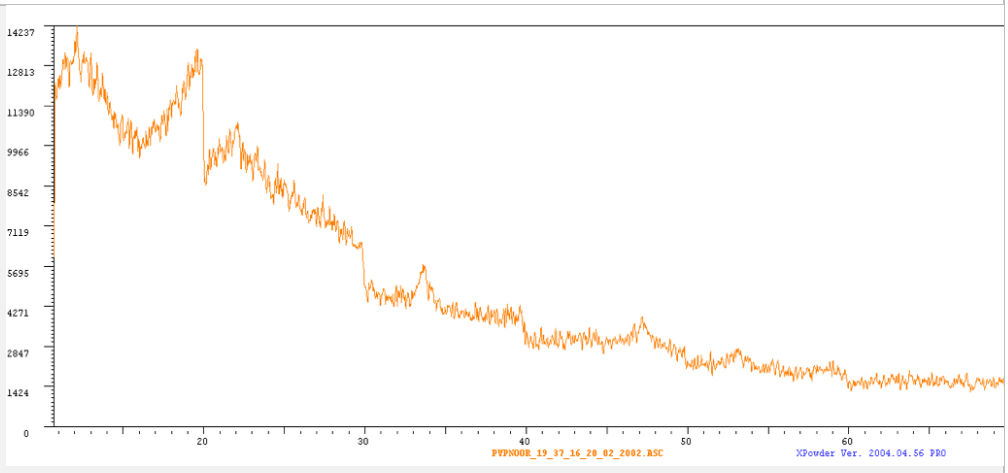
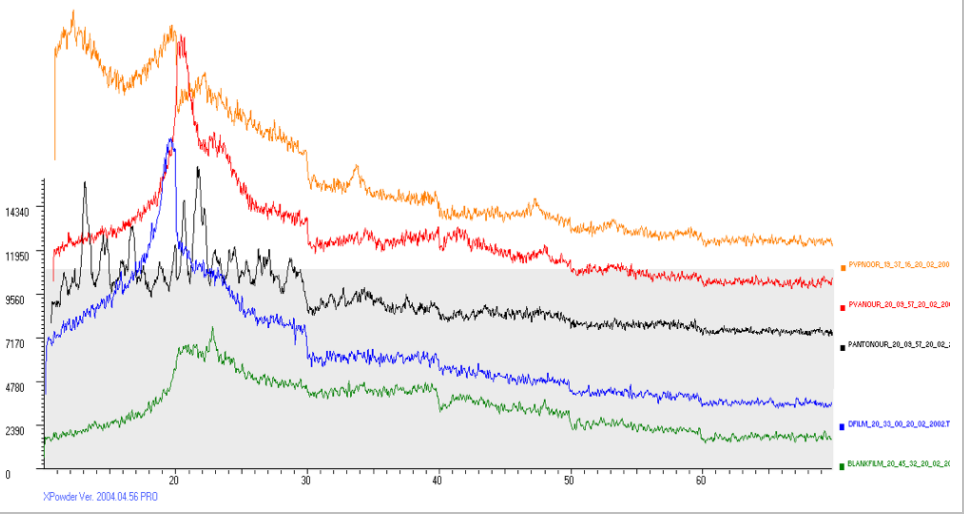
6	F4		

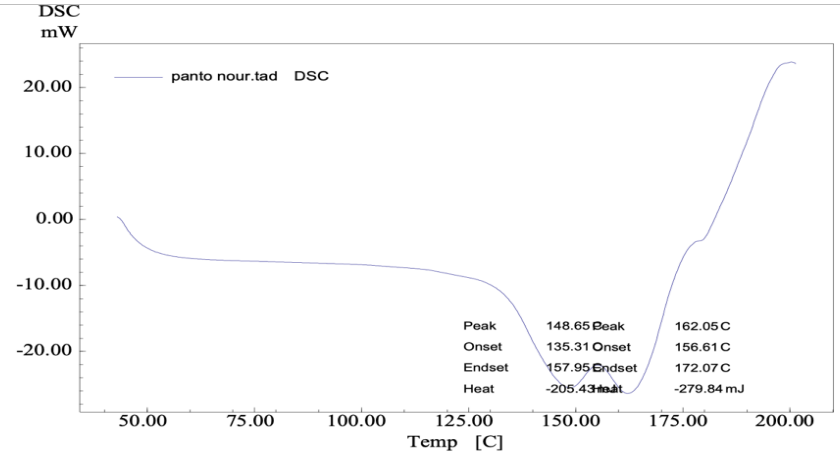
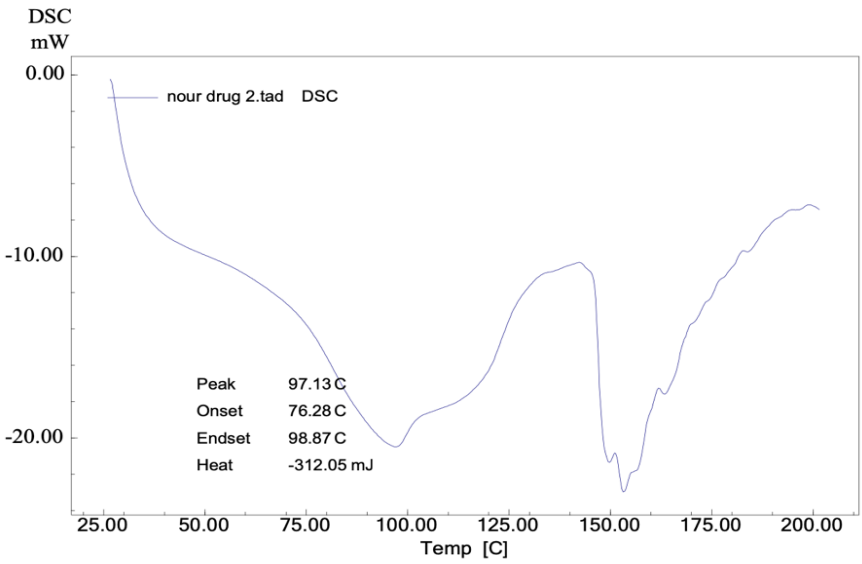
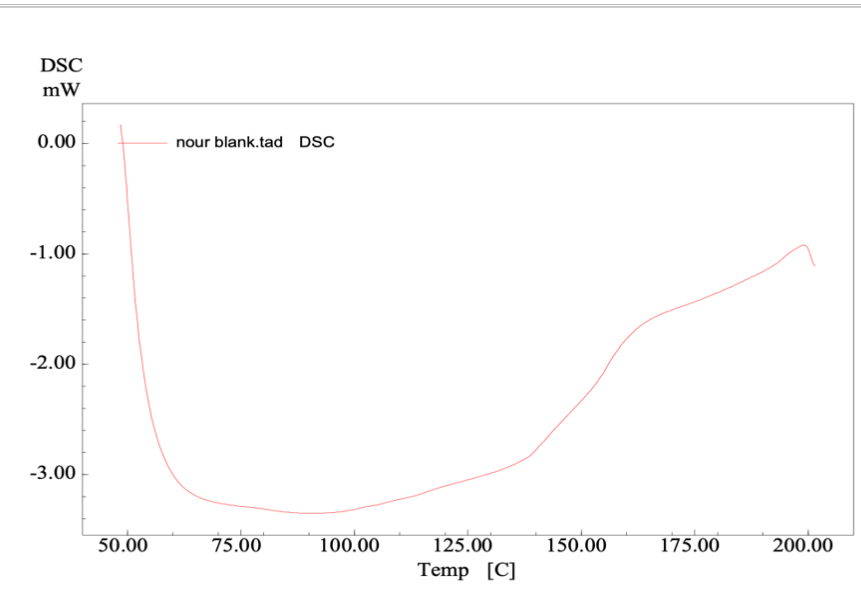
8	F5, F6, F7	

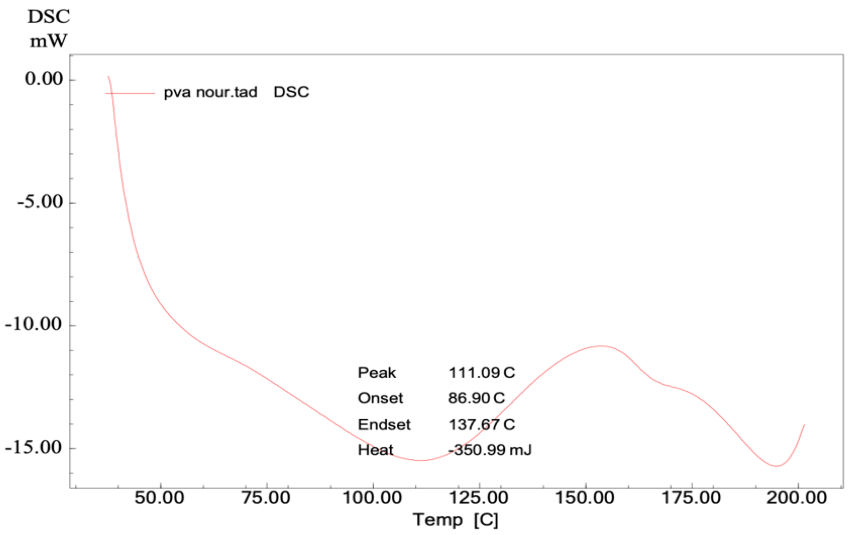
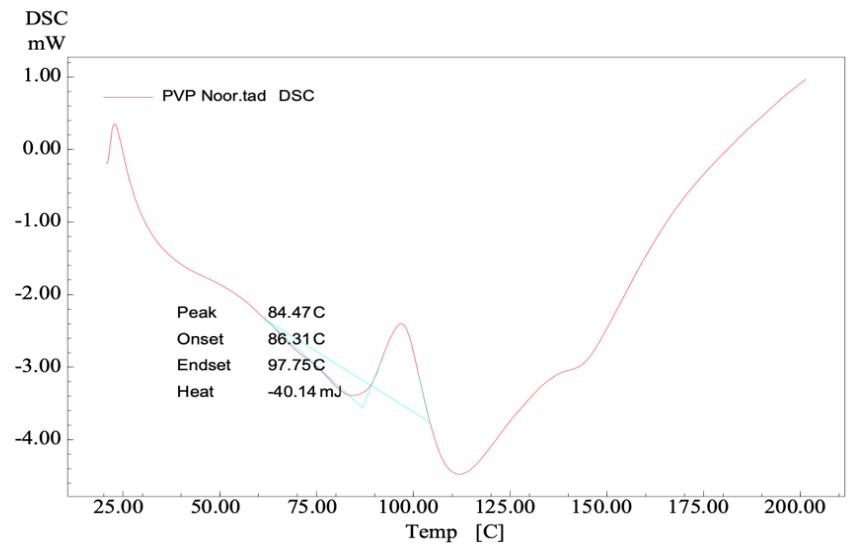
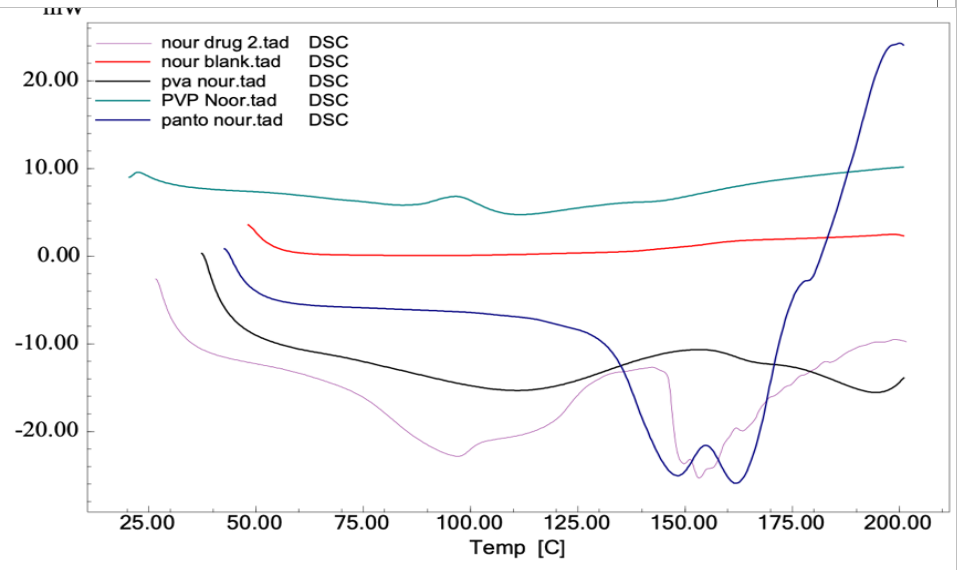
9	F8	
10	F9	
II- XRD - PATTERN		

11	XRD-Pantoprazole	
12	XRD-drug loaded film F8	
13	XRD-blank film F9	

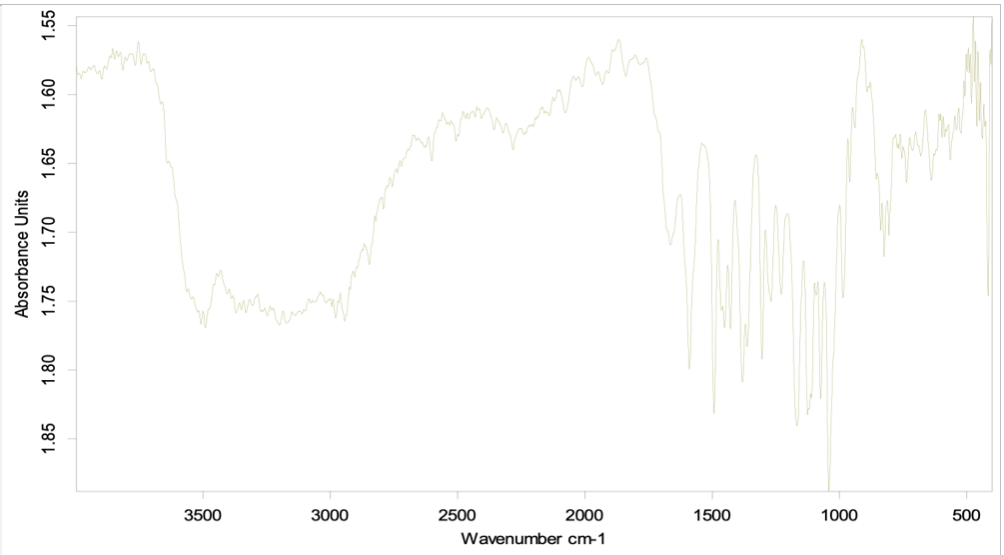
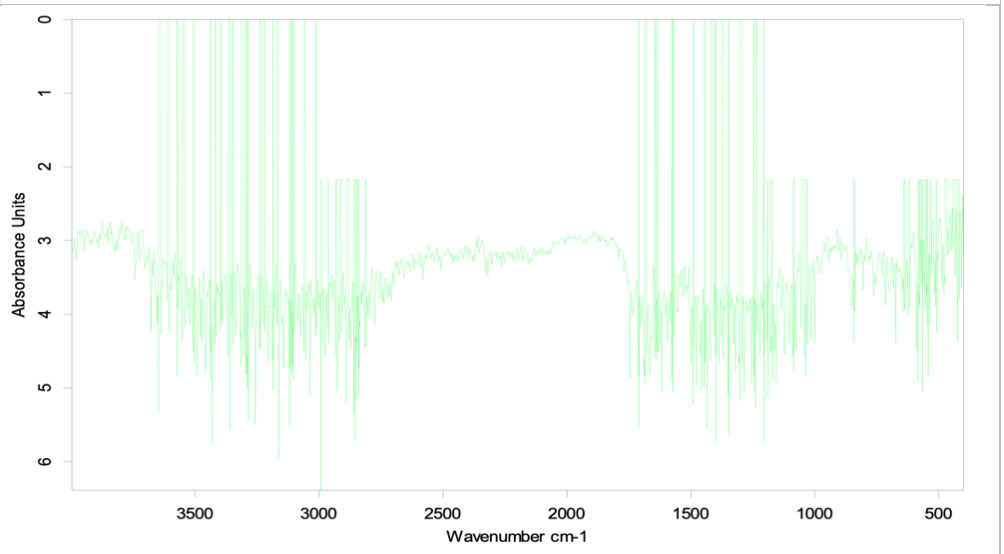
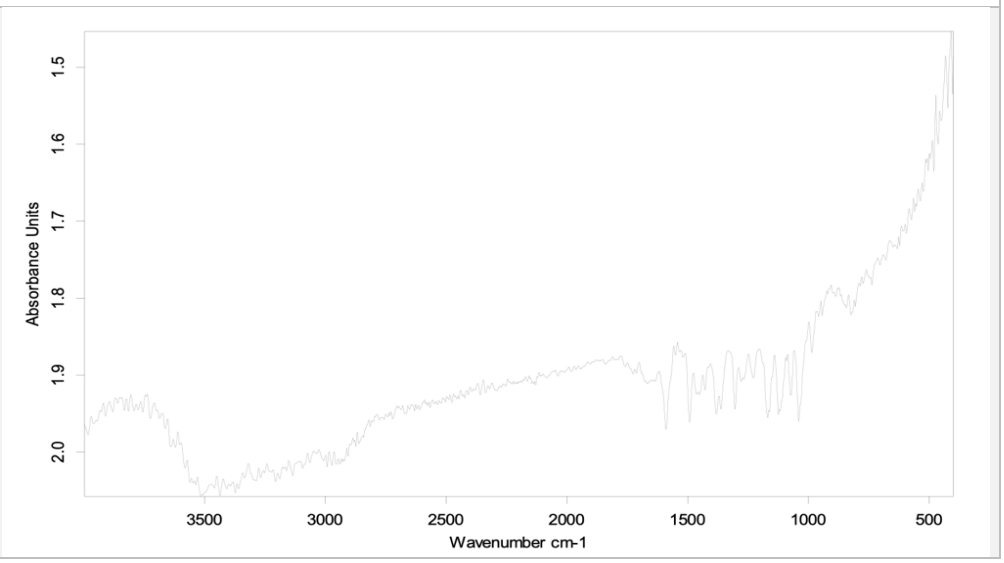
14	XRD-PVA	
15	XRD-PVP	
16	XRD-All samples	

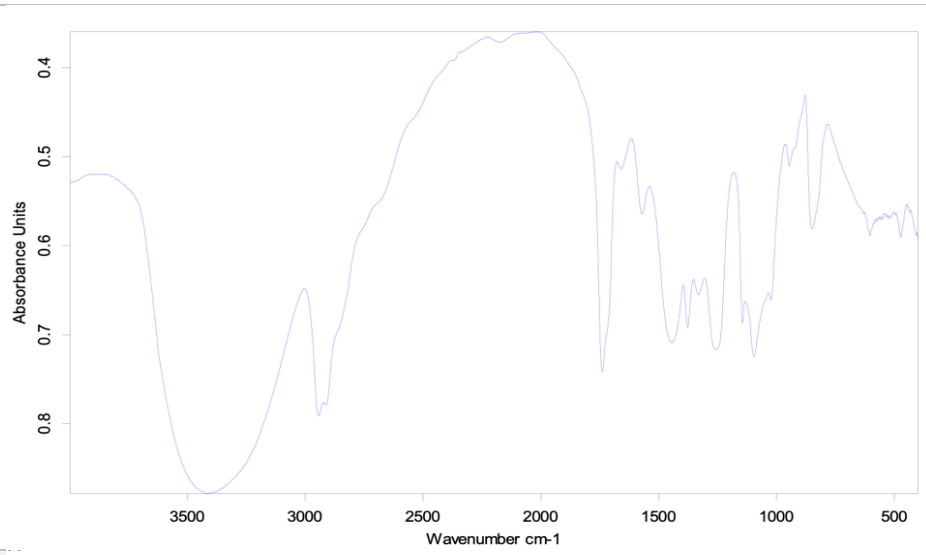
III- DSC- THERMOGRAM

17	DSC-XRD-Pantoprazole	
18	DSC-drug loaded film F8	
19	DSC-blank film F9	

20	DSC-PVA	
21	DSC-PVP	
22	DSC-All samples	

IV- FT-IR spectroscopy

23	FT-IR PANTOPRAZOLE	
24	FT-IR drug loaded film F8	
25	FT-IR blank film f9	

26	FT-IR PVA	
27	FT-IR PVP