FORMULATION AND EVALUATION OF CIMETIDINE FAST DISSOLVING ORAL FILM USING NOVEL POLYMERS

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Abstract : Cimetidine, a histamine H2-receptor antagonist, is widely used for the treatment of peptic ulcers and gastroesophageal reflux disease (GERD). Conventional oral dosage forms often face challenges such as delayed onset of action, poor patient compliance, and difficulty in swallowing, especially among pediatric and geriatric patients. To overcome these limitations, this study focuses on the formulation and evaluation of fast-dissolving oral film patches of cimetidine using novel film-forming polymers.The objective was to develop a patient-friendly, fast-releasing dosage form that dissolves rapidly in the oral cavity without the need for water. Novel polymers such as pullulan, hydroxypropyl methylcellulose (HPMC), and natural alternatives like pectin and sodium alginate were investigated for their film-forming ability, mechanical strength, and disintegration properties. The films were prepared using the solvent casting technique and optimized based on physicochemical parameters including thickness, folding endurance, surface pH, tensile strength, disintegration time, drug content uniformity, and in vitro drug release profile. The optimized formulation showed a disintegration time of less than 30 seconds and released more than 85% of the drug with in 5 minutes ,indicating rapid onset of action. The study concludes that oral film patches of cimetidine formulated with novel polymers offer a promising alternative to conventional oral dosage forms ,enhancing therapeutic efficacy and patient compliance

***IndexTerms*-H2 receptor anatgonist, GERD, Surface pH, Cimetidine, Oral Films,Pullulan**

INTRODUCTION

Buccal drug delivery has recently emerged as a significant route of drug administration. Different bio adhesive mucosal dosage forms have been formulated including adhesive tablets, gels, ointments, patches and increased application of polymeric films for buccal delivery, also referred to as mouth dissolving films [1]. Mouth dissolving films, a novel drug delivery system for oral delivery of the drugs, was created using the technology of the transdermal patch. The delivery system is a very thin oral strip, which is merely placed on the patients tongue or any oral mucosal tissue, immediately wet by saliva the film quickly hydrates and sticks on to the application site [2]. OTFs are generally postage stamp-sized and dissolve on a patient's tongue within few seconds for the quick release of one or more APIs [3]. Oral fast dissolving film is a novel delivery system for oral delivery of the drugs. It is based on the technology of transdermal patch [2].

A study revealed that 26% of 1576 patients had swallowing problems with tablets. Tablet size was the most frequent complaint, followed by surface shape and taste which is problematic in children and Elderly patients [4]. Thus, fast dissolving drug delivery system entered into existence in the late 1970s as a substitute for tablets, capsules and syrups in pediatric and geriatric patients who experience swallowing difficulty with conventional oral solid dosage forms [4].

Advantages of Oral films:

Absorption: Two peak plasma concentrations are often observed after oral administration of cimetidine, likely as a result of discontinuous absorption in the gastrointestinal tract [5]. In healthy patients, the absolute bioavailability of cimetidine is approximately 60%; however, the bioavailability can be as high as 70% in patients with peptic ulcer disease. Overall, rates of bioavailability are much more variable in patients with peptic ulcer disease [6].

Present Research

Cimetidine is a H_2 receptor antagonist used as an anti-ulcerative agent [7]. The present investigation highlights the development and evaluation of novel muco-adhesive films of Cimetidine [8]. Cimetidine oral thin films have shown a good in-vitro to in-vivo drug release correlation, improve duration of action and have produced an immediate release drug-delivery system. There is good potential for delivery through the mucosal membrane in the oral mucosal cavity [9]. Cimetidine is widely prescribed for gastric ulcers and duodenal ulcers [7].

The present study aims to design and develop oral fast dissolving films (OFDFs) of cimetidine using two hydrophilic polymers, starch and sodium alginate. The primary objective is to formulate a patient-friendly dosage form capable of rapid disintegration and drug release in the oral cavity. Such a system is intended to reduce the limitations associated with conventional oral tablets, particularly swallowing difficulties and delayed onset of action [7,8]. Additionally, the buccal/oral mucosal route offers the potential advantage of partially avoiding hepatic first-pass metabolism, thereby improving bioavailability and enabling dose minimization [9].

Cimetidine, a histamine H_2-receptor antagonist widely used in the management of gastric acid-related disorders, exhibits variable oral bioavailability following conventional administration. Literature reports indicate that specific plasma concentrations of cimetidine are associated with approximately 50% inhibition of pentagastrin-stimulated gastric acid secretion, suggesting that rapid attainment of such levels is critical for therapeutic effectiveness [10]. Therefore, developing a fast dissolving wafer/film formulation

may facilitate quicker drug availability, potentially achieving effective plasma concentrations within approximately 0.5 hours post-dose.

Furthermore, the study seeks to compare the in-vitro drug release profile of the optimized OFDF formulation with that of a marketed cimetidine tablet to evaluate performance differences [11]. An additional objective is to enhance patient compliance, particularly among pediatric, geriatric, and dysphagic patients who experience difficulty or reluctance in swallowing conventional tablets and capsules.

Cimetidine is a histamine H_2-receptor antagonist widely used in the management of peptic ulcer disease and other gastric acid–related disorders. It acts by competitively inhibiting histamine at H_2 receptors of the gastric parietal cells, thereby reducing gastric acid secretion.

OBJECTIVES:

To design oral fast dissolving films of Cimetidine by using two hydrophilic polymers that is Starch and sodium alginate.

To avoid the first pass effect, and to improve bio-availability, minimize the dose.

The plasma concentration of Cimetidine associated with 50% inhibition of penta gastric stimulated gastric acid secretion on an average within 0.5 hrs post dose for the wafer. To compare the release profiles of optimized formulation with the marketed tablet.

To improve patient compliance for patients who dislike or have difficulty of taking tablets and capsule.

In this portion, the main problem, selected in the study should be discussed with the relevant earlier literature and the proposed method or solution. Proper references should be used in support to the content.

MATERIALS AND METHODS:

List of Materials Used:

S.no	Category	Materials	Manufacturer	Percentage of Ingredient
1	Active Pharmaceutical Ingredient	Cimetidine	Molychem	1-25%
2	Polymer	Sodium alginate	Molychem	40-60%
3	Sweetner	Mannitol	Oxford lab fine chem LLP	0-2%
4	Plasticizer	Propylene glycol	Oxford lab fine chem LLP	0-20%
5	Solvent	Water	Oxford lab fine chem LLP	0-2%
6	Surfectant	Tween 80	Oxford lab fine chem LLP	

DRUG PROFILE

Cimetidine Synonyms: Tagamet

Brand names: Cimwell 200, Tagamet, Equate, Cimlex Tagmate HB, Acitak, C met, Tagsec, Cimetiget, Bisotidine, Tymidin, Ulciban.

Chemical formula: C10H16N6S

Molecular Struture:

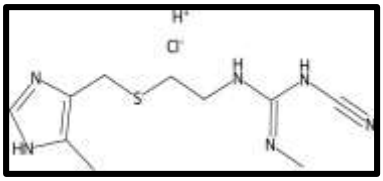
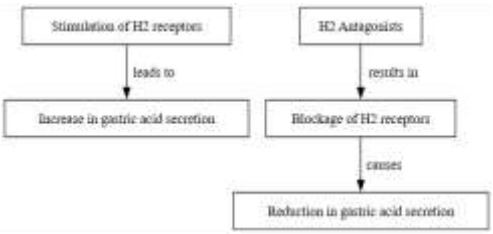


Fig: 1- Molecular structure of Cimetidine

MECHANISM OF ACTION:



Cimetidine binds to an H2-receptor located on the basolateral membrane of the gastric parietal cell, blocking histamine effects. This competitive inhibition results in reduced gastric acid secretion and a reduction in gastric volume and acidity.

PHARMACOKINETICS OF CIMETIDINE

Absorption:

Two peak plasma concentrations are often observed after oral administration of cimetidine, which is believed to result from discontinuous absorption occurring along different regions of the gastrointestinal tract. In healthy individuals, the absolute bioavailability of cimetidine is approximately 60%; however, in patients with peptic ulcer disease, the bioavailability may increase to around 70%. Additionally, the bioavailability tends to be more variable in patients suffering from peptic ulcer disease due to alterations in gastric physiology and absorption patterns [12,13].

Distribution:

Cimetidine is widely distributed throughout body tissues and is capable of entering red blood cells, indicating extensive systemic distribution. The reported volume of distribution is approximately 1 L/kg, which reflects significant penetration beyond the vascular compartment [13].

Metabolism:

Cimetidine undergoes minimal hepatic metabolism, with only about 15% of the administered dose metabolized in the liver. This limited metabolism contributes to the relatively high proportion of unchanged drug eliminated from the body [13,14].

Excretion:

The drug is eliminated primarily through the renal route. Approximately 70% of the administered dose is excreted unchanged in urine, while about 10% is eliminated through fecal excretion. Because renal excretion is the main elimination pathway, dose adjustment may be necessary in patients with impaired kidney function to prevent drug accumulation [13,14].

Physicochemical properties

Cimetidine has a molecular weight of 252.34 g/mol and a log P value of 0.4, indicating moderate hydrophilicity . The drug is slightly soluble in water (approximately 0.5 g/100 mL at 20 °C) and is soluble in ethanol. It exhibits a melting point in the range of 139–144 °C [15,16].

Pharmacological classification

Cimetidine is categorized as:

- Anti-ulcer agent
- Gastrointestinal agent
- Histamine antagonist
- H_2-receptor antagonist
- Neurotransmitter modulator

Toxicity and safety profile

Overdose with cimetidine is considered rare. In cases of toxicity, clinical management prioritizes maintenance of airway and cardiovascular stability. Gastrointestinal decontamination methods may include gastric lavage and administration of activated charcoal to reduce drug absorption.

Acute toxicity is generally low; doses up to 20 g have been reported to produce only transient symptoms such as confusion, dizziness, and agitation. Documented overdose symptoms include:

- Central nervous system effects (confusion, hallucinations)
- Tachycardia
- Vomiting
- Rarely, coma

Chronic toxicity

Long-term administration has been associated with:

- Gynecomastia
- Galactorrhea (due to anti-androgenic effects)
- Hepatotoxicity (rare but clinically relevant)

Special populations

Elderly patients and individuals with renal or hepatic impairment are more susceptible to:

- CNS adverse effects
- Drug accumulation
- Enhanced toxicity risk

Dose adjustment is therefore recommended in these populations [16,17].

Following oral administration, cimetidine exhibits a characteristic pharmacokinetic behaviour. Two peak plasma concentrations are often observed, which is believed to result from discontinuous absorption along the gastrointestinal tract. In healthy individuals, the absolute bioavailability of cimetidine is approximately 60%, whereas values as high as 70% have been reported in patients with peptic ulcer disease. Additionally, bioavailability tends to be more variable in ulcer patients, possibly due to altered gastric physiology and motility [15,16].

Cimetidine is widely distributed throughout the body and has been reported to enter red blood cells, indicating extensive tissue distribution. The volume of distribution (Vd) is approximately 1 L/kg, suggesting significant extravascular penetration.

Metabolism of cimetidine is relatively limited. The drug undergoes minimal hepatic metabolism, with only about 15% metabolized in the liver. The majority of the administered dose is eliminated unchanged, with approximately 70% excreted in urine and around 10% lost via faeces.

Excretion of cimetidine occurs primarily through the renal route, predominantly as unchanged drug. This highlights the importance of dose adjustment in patients with renal impairment to avoid drug accumulation and toxicity.

ADVERSE EFFECTS OF CIMETIDINE

Cimetidine is generally well tolerated; however, several side effects have been documented.

Common adverse effects include:

- Headache
- Diarrhea
- Dizziness
- Drowsiness
- Breast enlargement (gynecomastia)

Serious adverse effects (less frequent) may include:

- Confusion
- Excitement
- Depression
- Nervousness
- Hallucinations (visual or auditory disturbances)

These CNS-related effects are more likely to occur in elderly patients and those with renal or hepatic dysfunction [16,17].

EXCIPIENT PROFILE: Sodium Alginate

Applications:

Sodium alginate is widely used in several industries, including food and pharmaceutical applications. In the food industry, it functions as a thickening agent, gelling agent, emulsifier, and stabilizer. It is commonly incorporated into products such as ice cream, yogurt, processed meat products, sauces, and beverages to improve texture and stability. In the pharmaceutical industry, sodium alginate is extensively used as an excipient in drug formulations, particularly in controlled-release systems, mucoadhesive preparations, and oral film formulations [18,19].

Description:

Sodium alginate is considered a safe, biocompatible, and non-toxic polymer with wide pharmaceutical applicability. It is water soluble and forms a viscous colloidal solution upon hydration. The viscosity and gel strength of sodium alginate solutions can be adjusted depending on polymer concentration and cross-linking conditions. Due to its stability, ease of handling, and long shelf life, sodium alginate is widely used in pharmaceutical processing and formulation development [19,20].

Non-proprietary names

- BP: Sodium Alginate
- JP: Sodium Alginate
- USP: Sodium Alginate

Synonyms

Sodium alginate is also known as:

- Alginic acid monosodium salt
- Brown algae extract
- E401

Functional category

Sodium alginate is widely used in pharmaceutical formulations as a:

- Film-forming agent
- Coating agent
- Stabilizing agent
- Suspending agent
- Tablet binder
- Viscosity-increasing agent [21,22]

Solubility:

Sodium alginate is freely soluble in water, producing a viscous solution suitable for film formation and gel-based drug delivery systems [19].

Excipient Profile: Polyethylene Glycol (PEG)

Non-Proprietary Names

- BP: Macrogols
- JP: Macrogol 400, Macrogol 1500, Macrogol 4000, Macrogol 6000, Macrogol 20000
- PhEur: Macrogola
- USP–NF: Polyethylene Glycol

Synonyms

Polyethylene glycol is also known as:

- Carbowax
- Carbowax Sentry
- Lipoxol
- Lutrol E
- PEG
- Pluriol E
- Polyoxyethylene glycol

Chemical nature

α-Hydro-ω-hydroxypoly (oxy-1,2-ethanediyl)

Molecular weight
Typically ranges from 380–420 for PEG 400 grades.
Description
Polyethylene glycol (PEG) is described in the USP–NF as an addition polymer of ethylene oxide and water. PEG exists in different grades depending on molecular weight. Lower molecular weight grades such as PEG 200–600 are liquids, whereas higher molecular weight grades such as PEG 1000 and above are solids at room temperature. Liquid PEGs appear as clear, colourless to slightly yellow viscous liquids with a faint characteristic odor and a slightly bitter taste.
Solubility
All grades of polyethylene glycol are freely soluble in water and are miscible with other polyethylene glycols in all proportions. Liquid polyethylene glycols are also soluble in acetone, alcohols, benzene, glycerin, and glycols, which makes them useful as solvents and plasticizers in pharmaceutical formulations
PROPYLENE GLYCOL (Non-proprietary Names:)
- BP: Propylene Glycol
- JP: Propylene Glycol
- PhEur: Propylenglycolum
- USP: Propylene Glycol

Synonyms
Propylene glycol is also known as:
- 1,2-Dihydroxypropane
- 1,2-Propanediol
- E1520
- 2-Hydroxypropanol
- Methylethylene glycol
- Methyl glycol

Chemical name: 1,2-Propanediol
Empirical formula: $C_3H_8O_2$
Molecular weight: 76.09 g/mol
Functional category
Propylene glycol is widely used in pharmaceutical formulations as:
- Solvent
- Co-solvent
- Plasticizer
- Humectant
- Stabilizer
- Antimicrobial preservative

Description
Propylene glycol is a clear, colourless, viscous, and practically odourless liquid with a sweet, slightly acrid taste resembling glycerin. It exhibits good chemical stability and compatibility with a wide range of active pharmaceutical ingredients (APIs).
Solubility
Propylene glycol is:
- Miscible with water, acetone, chloroform, ethanol (95%), and glycerin
- Soluble in ether (1 in 6 parts)
- Immiscible with light mineral oils and fixed oils
- Capable of dissolving certain essential oils

Applications
Propylene glycol is widely used as a solvent, extractant, and preservative in various parenteral and non-parenteral pharmaceutical formulations. It is considered a more effective general solvent than glycerin and is capable of dissolving a wide range of pharmaceutical compounds including corticosteroids, phenols, sulfonamides, barbiturates, most alkaloids, and several local anesthetics. Due to its excellent solvent properties and compatibility with many active pharmaceutical ingredients, propylene glycol is frequently used in oral, topical, and injectable dosage forms.
In addition to pharmaceutical applications, propylene glycol is also used in the cosmetic and food industries. It serves as a carrier for emulsifiers and flavoring agents, and is often preferred over ethanol because of its low volatility, which helps maintain a more uniform and stable flavor distribution in formulations [23,24].
Propylene glycol is extensively employed as a solvent, co-solvent, extractant, humectant, and plasticizer in both parenteral and non-parenteral dosage forms. It dissolves a broad spectrum of compounds, including:
- Corticosteroids
- Phenols
- Sulfonamides
- Barbiturates
- Alkaloids
- Local anesthetics

In oral thin films and fast dissolving films, propylene glycol functions primarily as a plasticizer, improving:
- Film flexibility
- Mechanical strength
- Folding endurance

- Prevention of brittleness

Additionally, due to its low volatility, it is preferred over ethanol as a vehicle for flavours in pharmaceutical and cosmetic formulations.

Equipment Used in the Study

S. No.	Equipment
1	Digital weighing balance
2	Vacuum oven
3	Micropipettes
4	Dissolution apparatus
5	pH meter
6	Sonicator
7	Glassware
8	Digital screw gauge
9	UV–Visible spectrophotometer
10	Differential Scanning Calorimeter (DSC)

Formulation Method

To formulate cimetidine oral fast dissolving films (OFDFs), the solvent casting method was employed.

Solvent Casting Method

In this method, the required quantity of water-soluble polymers was dispersed in purified water under continuous stirring at approximately 1000 rpm. Mild heating was applied where necessary to ensure complete polymer hydration and dissolution. The remaining excipients, including plasticizer, surfactant, sweetening agent, colour, and flavour, were dissolved separately.

Both solutions were then combined and stirred at 1000 rpm to obtain a homogeneous mixture. The active pharmaceutical ingredient (API), cimetidine, previously dissolved in a suitable solvent, was incorporated into the polymeric solution. The resulting solution was subjected to vacuum deaeration to remove entrapped air bubbles.

The final bubble-free solution was cast onto a suitable flat surface (casting plate/petri dish) and dried under controlled conditions. After drying, the films were carefully peeled and cut into uniformly sized strips.

General Formulation Composition

The oral fast dissolving film was formulated using the following components:

S. No.	Ingredient	Function	Percentage (%)
1	Cimetidine	Active Pharmaceutical Ingredient (API)	30%
2	Sodium Alginate	Film-forming polymer	44–55%
3	Tween 80	Surfactant / wetting agent	5–15%
4	Mannitol	Sweetening agent / saliva stimulant	4–6%
5	Propylene Glycol	Plasticizer	20%
6	Purified Water	Solvent	q.s. (100 mL)

Evaluation of Oral Fast Dissolving Films

The prepared OFDFs were evaluated using various quality control and in-vitro characterization tests:

- Film thickness
- Weight variation
- Drug content / Assay
- Mechanical properties
- Tensile strength
- Percentage elongation
- Folding endurance
- Physical appearance
- Surface texture
- In-vitro disintegration time
- In-vitro dissolution study

In-Vitro Dissolution Study Conditions

Apparatus: Franz diffusion cell

Dissolution medium: Phosphate buffer (pH 7.4), 900 mL

Agitation speed: 200–400 rpm

Temperature: 37 ± 0.5 °C

Sample volume withdrawn: 5 mL

Sampling intervals: 2, 4, 6, 8, 10, 12, 14, 16 minutes

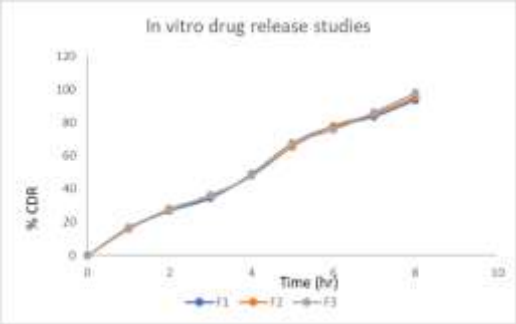
The withdrawn samples were analyzed using a UV–Visible spectrophotometer at the predetermined λmax of cimetidine.

In-Vitro Drug Release Studies

The in-vitro drug release profiles of cimetidine oral fast dissolving film formulations (F1, F2, and F3) were evaluated over a period of 8 hours.

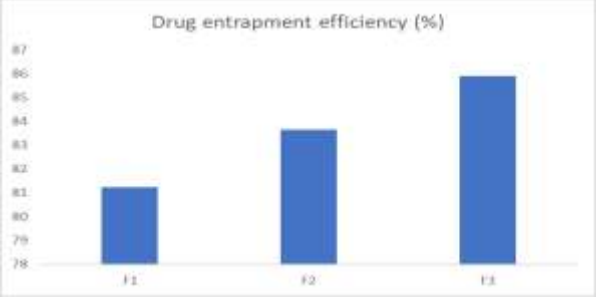
Time (hr)	F1 (%)	F2 (%)	F3 (%)
0	0	0	0
1	16.39	15.98	16.93
2	26.89	28.16	27.48
3	34.65	35.82	36.59
4	48.93	47.93	48.10
5	67.58	69.67	67.80
6	77.55	78.10	77.81
7	83.69	85.16	86.39
8	93.67	96.53	97.85

Standard graph of invitro drug release studies :



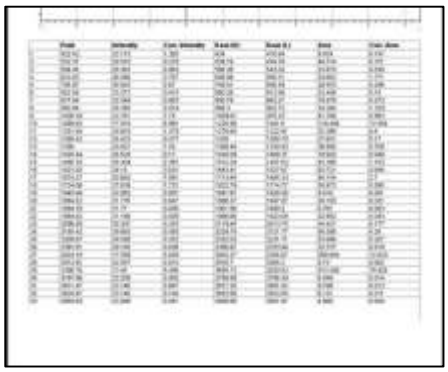
Drug entrapment efficiency:

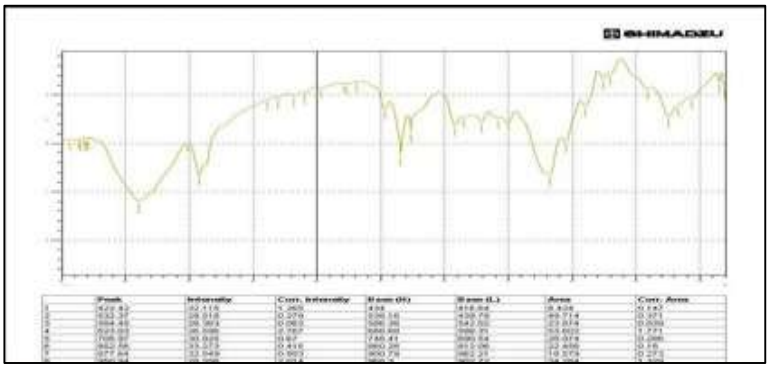
Formulation code	Drug entrapment Efficiency (%)
F1	81.25
F2	83.64
F3	85.89

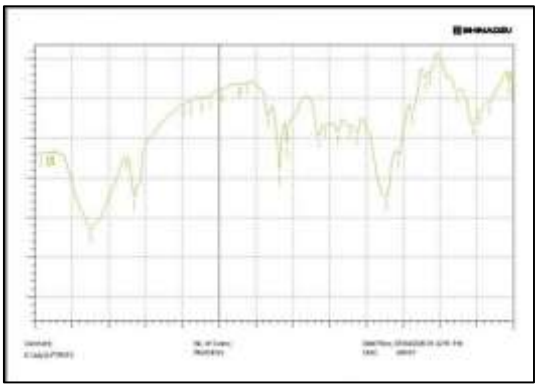


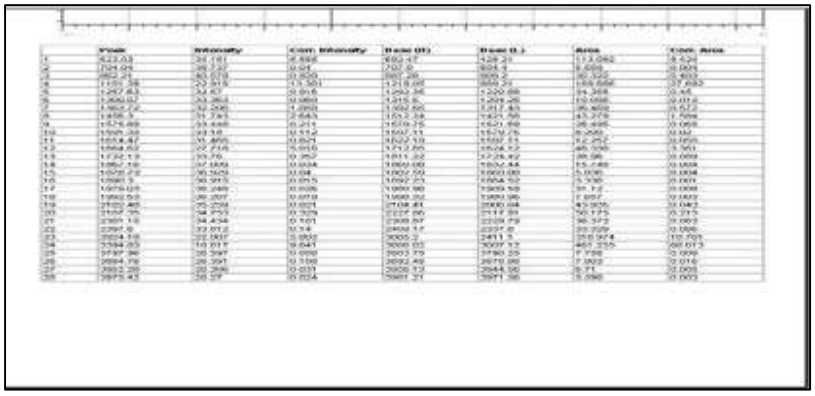
Results

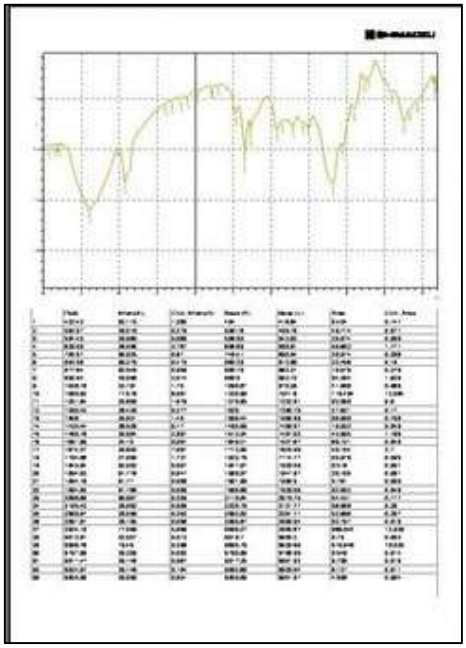
Standard graph of cimetidine in 0.1N Hcl

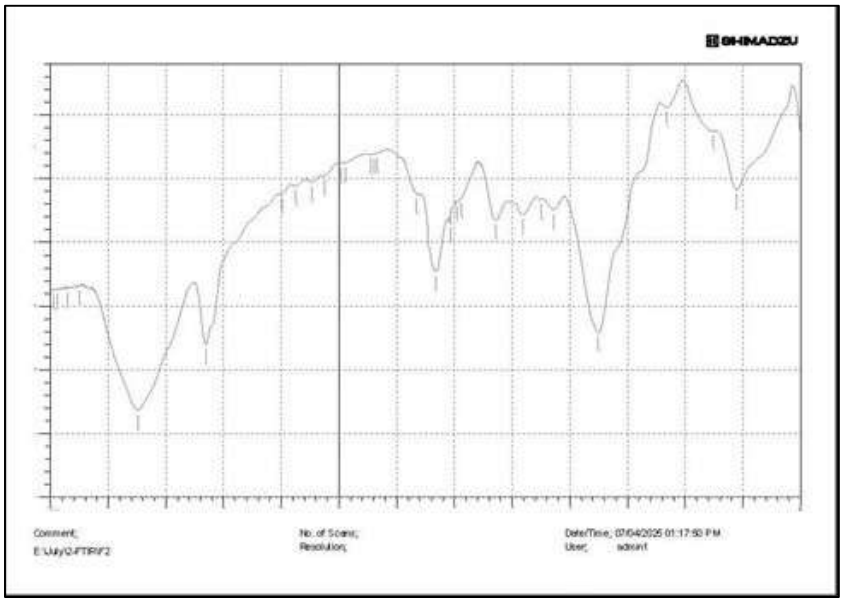


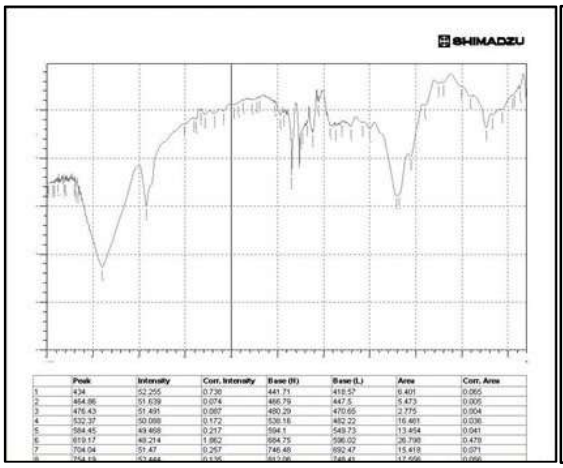


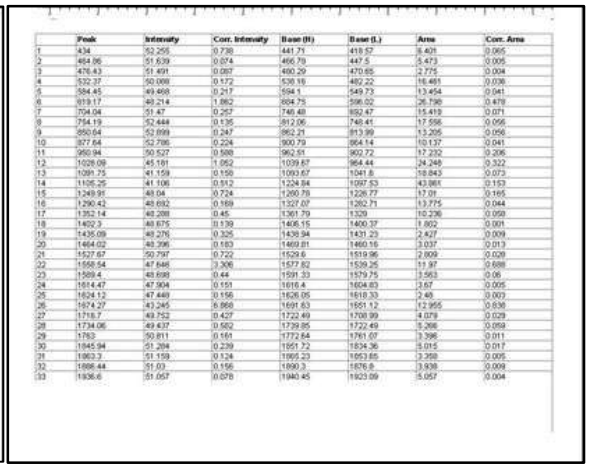


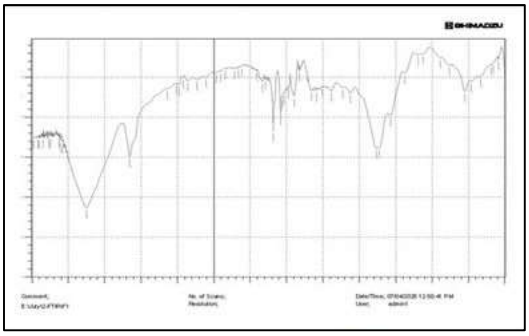












Conclusion:
Last but not least, rapid dissolving oral films of cimetidine through sodium alginate were obtained which are employed as antacid, which are rapidly soluble and exhibits better action.

The films that were prepared with the sodium alginate as a polymer and propylene glycol as a plasticizer had exhibited improved results by way of mechanical strength, drug release, disintegration time and stability.

Thus, cimetidine can be the given in the form fast dissolving film which will be the promising. New drug form for pediatrics, geriatrics and even general population by ensuring quicker release and higher compliance. To study the drug- excipients compatibility studies and for improving stability of various formulations..

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