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Formulation and in vitro Evaluation of Fast Dissolving Oral Films of Ketorolac for management of pains following dental procedures

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ABSTRACT

The purpose of this research is to determine the best model through in vitro tests. Ketorolac Tromethamine is NSAIDS drug with a duration of four to six hours (bioavailability: 90%) and Severe stomach upset. Due to these the purpose of this study is to create an oral composition of Ketorolac tromethamine that raising the duration of the drug, treatment efficiency and patient Compliance, and has the ability to overcome intestinal disorders. The ingredients of Ketorolac Tromethamine Sublingual Film include HPMC E15 and HPMC E5. These polymers are Produced using a heavy casting process. Mucoadhesion strength, swelling behavior, surface pH testing, hygroscopicity, water loss, tensile strength, texture, thickness, weight and content integrity.

Oral forms (ODFs) have become a simpler, faster and patient-friendly way to deliver Medications. The potent non-steroidal anti-inflammatory drug ketorolac has shown potential to Alleviate postoperative pain. The purpose of that study was to create and assess ketorolac ODF To improve patient compliance and reduce pain.

Rapid preparation of antibiotics was attempted in this study to increase patient compliance, Increase treatment efficiency, and reduce gastrointestinal side effects by preventing direct Contact between ketorolac tromethamine and the gastric mucosa.

In the present work the ODF is prepared using HPMC E 15 and HPMC E 5 in ratio 1:1, the API used is Ketorolac, the formulation shown excellent drug release profile and passed the evaluation parameters like folding endurance.

Keywords: *Ketorolac Tromethamine, mucoadhesive film, Mucoadhesive strength, Solvent Casting method, Swelling behavior.*

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INTRODUCTION

For many years, the way to treat severe pain, usually acute or chronic pain, has been to treat The pain with a variety of medications. [1] Oral medications are used in many ways . This Would be the best situation for patients and doctors. Targeted drug delivery system. In general, Oral medications are preferred. [2]

Ketorolac trometamol instant film has the ability to improve pain, which is why it is so Important. Oral medications generally have disadvantages such as slow onset of action, poor Absorption, and patient compliance problems. [3] The powerful nonsteroidal anti-inflammatory Drug (NSAID) ketorolac is often used to treat pain; However, these adverse effects may reduce The effectiveness of the drug. [4]

Fast-dissolving films are suitable options due to their rapid drug release, improved Bioavailability, and ease of application without the need for water. This is especially helpful for patients who have difficulty swallowing or are in post-operative care, the emergency Room, or other areas where urgent care is needed. [5]

Widely used drug delivery systems have certain advantages such as dose uniformity, self-administration, and stability. Oral thin films were first developed as a new dosage form in 1970 And released in 2004. [6]

Rapidly disintegrating orally disintegrating film produces immediate drug release in advance [7]. It is absorbed quickly orally (within 1 minute) from the formulation and enters the blood Circulation quickly. Maximum bioavailability is achieved. Ketorolac is a nonsteroidal anti-inflammatory drug. It is used to treat severe pain and is also used for pain management after Surgery. [6][7] KT has a short plasma half-life of 3 to 6 hours, so its administration frequency is High. NSAIDs, such as KT, cause stomach ulcers, bleeding, and other stomach Complications. Due to problems such as stomach ulcers and bleeding, we chose an oral Dissolving film. Avoid first-pass dialogue and reach directly. [8]

It started to circulate in the blood. The film is used to treat allergies, hypertension, angina, Epilepsy, severe pain, and other conditions. [9]It is mainly used for bedridden patients, the Elderly and children. Drugs that have first-pass metabolism and are not well tolerated in the Stomach may be candidates for low-dose, high-molecular-weight film formulations. [10]

MATERIALS AND METHODOLOGY

Solvent Casting Method

MATERIAL AND METHOD

Material Drug, polymers and other additives. [11]

Method:

There are different methods are used for the formulation of film, [12]

Solvent casting method

Hot – melt extrusion method

Semisolid casting method

Rolling method

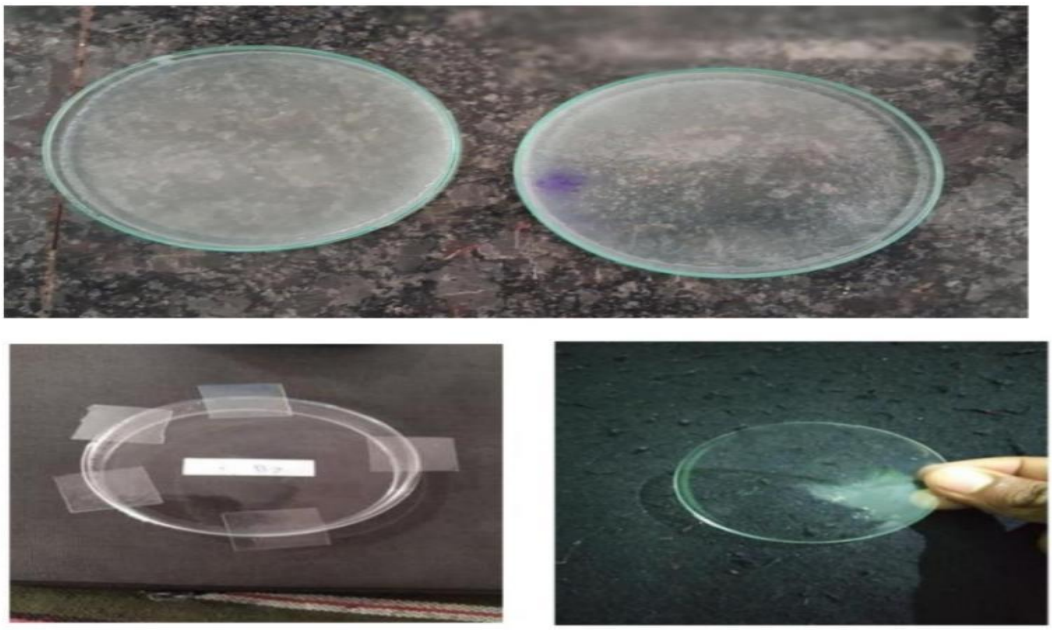


Figure No 1: Mouth Dissolving Film Images

Formulation of Film

Formulation of mouth dissolving film prepared by using solvent casting method.[13]

Initially Weight all excipient accurately, take few quantities of water to it add HPMC E15 and HPMC ES In two separate beakers. [14]

Stir both polymeric solution by using glass rod until it become clear Solution. [15]

After that mix both polymer solution and keep it 30 min for sonication. In another Beaker dissolve sodium benzoate and sodium saccharin into water, stir this until completely Solution then add this solution into above polymeric solution. [16]

Thereafter addition of PEG- 400 Dropwise into the above solvent along with tween-80.

At the finally dissolve drug into separate Beaker into the water and pour this solution into above mixture, Sonicate the solution for 30 Min for removing air bubble from mixture. [17]

Then add solution into Petri dish and kept into oven for 24 hr at 40 °C. After drying of film cut into 2*2 cm pieces. [18]

Composition of Film

Oral dissolving film preparation is made from chemicals, plasticizers, Preservatives, sweeteners, and water-soluble polymers. [19] This model uses a Different version of HPMC E15 and HPMC E5.

INGREDIENTS	**B1**	**B2**	**B3**
Drug (mg)	6.5 mg	6.5 mg	6.5 mg
HPMC E15 (mg)	3 mg	3 mg	3 mg
HPMC E5 (mg)	3 mg	3 mg	3 mg
Citric acid (mg)	3 mg	3 mg	3 mg
PEG -400 (ml)	q.s	q.s	q.s
Polysorbate- 80 (ml)	1 ml	1 ml	1 ml

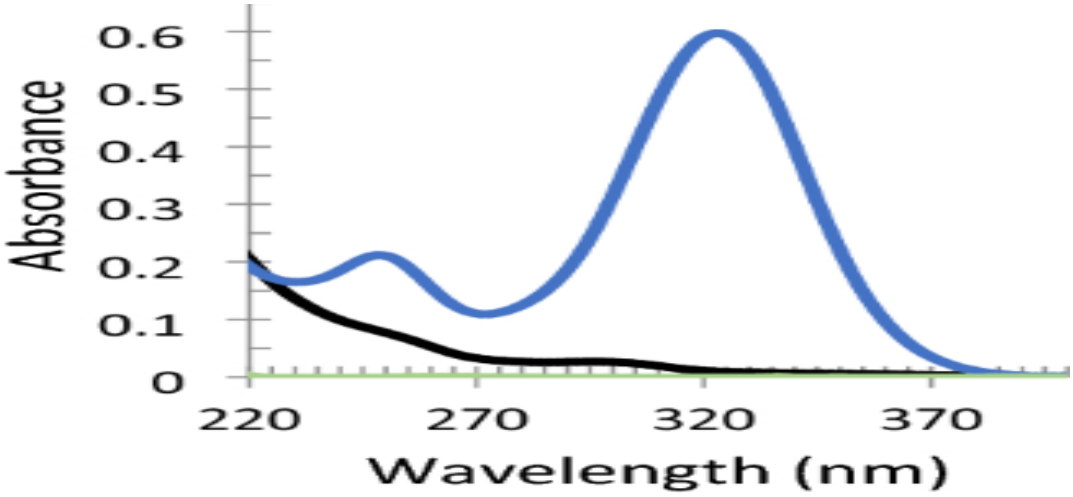
Sodium Saccharin (mg)	1 mg	1 mg	1 mg
Sodium Benzoate (mg)	q.s	q.s	q.s
Pineapple Flavour (ml)	2.5 ml	2.5 ml	2.5 ml
Water (ml)	5 ml	5 ml	5 ml

Table No. 1: Composition of Film

Reformulation Study

Reformulation testing generally aims to collect data that will help formulation Manufacturers develop stable, bioavailable formulations. [20] Interpreting FT-IR spectra To examine the interaction between the drug and polymers, FT-IR investigations Were conducted on the pure drug and polymers separately and in combination. [21]

UV Spectrophotometric Quantification of Ketorolac



Graph No.1: UV Spectrum of Ketorolac Showing Linearity at 322 nm

Procedure of UV for Ketorolac Tromethamine

Determination of KET

Calibration standards in the range of 3.0–12.0 µg/mL in water were prepared using KET working standard solution. The UV spectra of KET solutions were recorded in the range of 200–400 nm (scanning speed: fast, sampling interval: 1 nm), smoothed at dλ 1 nm and saved in the computer. The absorbance of KET was recorded at λmax 323 nm directly from zero order spectra. Plotting A323nm versus the concentration in µg/mL is used for construction of calibration curve and computation of regression equation. [22]

Scanning Eletron Microscope of Ketorolac

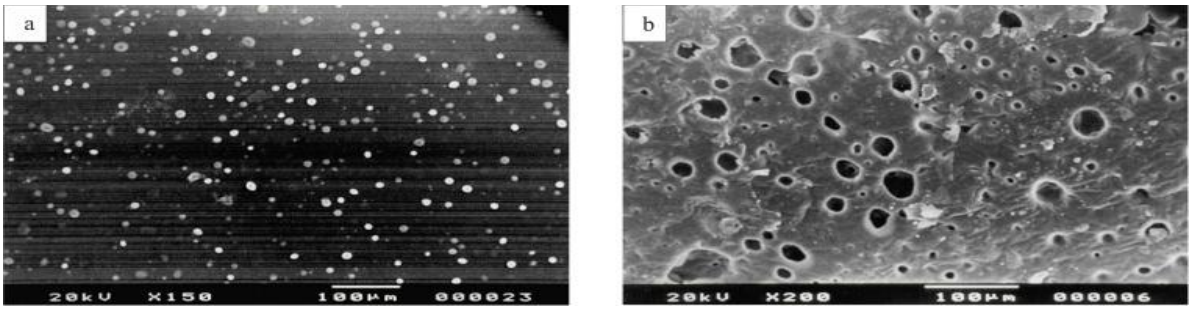


Figure No.2 : SEM of ketorolac

SEM of quantification of ketorolac

The fast-dissolving oral film of Ketorolac Tromethamine were analyzed by using a scanning elecron microscope. (JSM 6100, JEOL,Tokyo Japan).[23]

SEM was done to study of fast dissolving oral film of ketorolac before and after the release of drug from the film. 24 h of drug permeation. It shows the number of holes present in the film after the release of drug clusters. [24]

Evaluation Tests

Size shape and thickness:

Magnetic density is determined by film thickness. The thickness was measured from 5 different places and the average value was determined. [25] Use a Micrometer, screw micrometer, or vernier caliper to check the thickness of the Film.

Weight variation:

The key for ensuring the same amount of film is used per film is weight variation. Divide the negative into 2 x 2 cm squares and weigh them using a digital scale. [26] Select the average weight of three different movie segments. In addition, the film is tested by ensuring that it contains the necessary chemicals and additives.

Folding Endurance:

After the film is cut, it is folded repeatedly whether it get breaks. A film's foldability value indicates how many folds it can withstand before Breaking. The folding strength rating is generally between 100 and 150. [25][26]

Tensile strength:

Tensile strength is the highest stress applied at strip's breaking point. This formula Is used to determine tensile strength. [27]

$$\frac{\text{Load at break}}{\text{Strip break} \times \text{strip width}}$$

pH Determination

Cut the film to 2 x 2 cm and place it in Petri plate containing five ml distilled Water. After few minutes, check pH of above solution by the use of digital pH meter. [28]

Drug Content

The content of the medicine indicates the amount of the medicine is in the formula. This measurement is used to determine the amount of medicine that will pass into the milk and whether the loading is successful [29]. Usually, UV spectrophotometer is used for the Determination of content of the drug.

In vitro drug release study

That test was performed by using USP Type 2 (flap device) measures the rate of drug release Over time. [28][29] For this experiment, 900 ml of phosphate buffer 6.8 was used using a paddle Machine Remove an equal portion every minute for up to five minutes. Determine the percentage of chemical released by UV light. [30]

RESULT

Batch	Weight (mg)	Surface PH	Disintegration Time (min/sec)	Folding Endurance	Thickness (mm)	% Dg Content	% Dr At 5 min
B1	15	5.4	36	48	0.4	86.45	42
B2	18	5.4	42	55	0.4	87.69	36
B3	20	6	39	68	0.6	86.45	30

Table No. 2: Result of Parameters

Drug Uniformity

Drug uniformity was found good by using Scanning electron Microscope (SEM).
Models of SEM are JSM 6100, JEOL, Tokyo Japan.

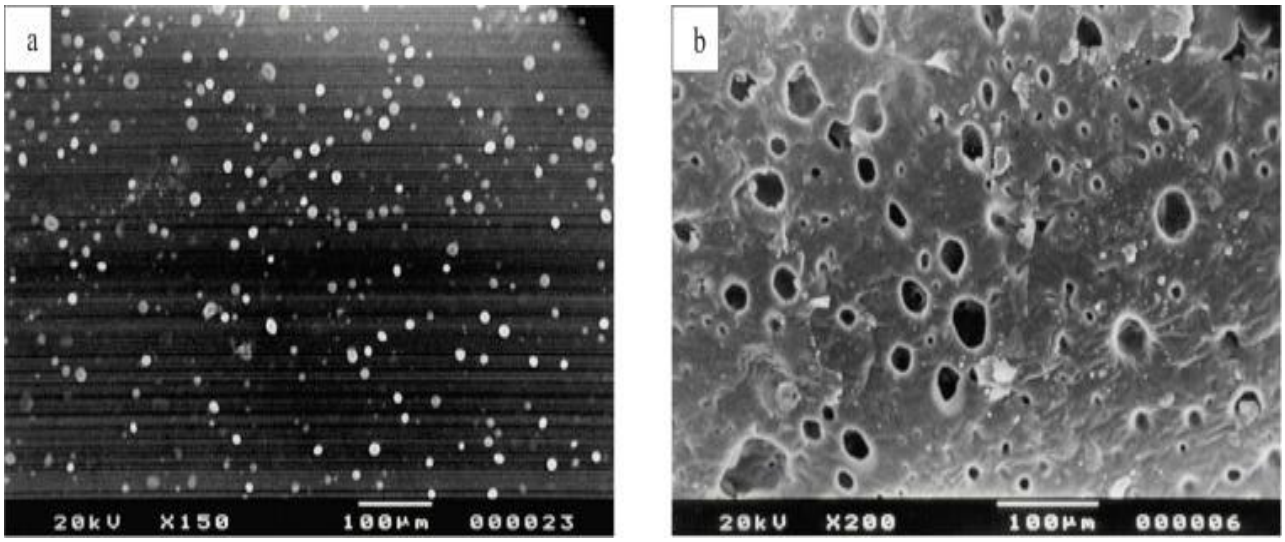


Figure No.3: SEM of ketorolac

DISCUSSION

The appearance and thickness consistency ensure that the films are well-prepared for uniform dosing. Mechanical properties like tensile strength and elongation at break are essential for the handling and usability of the films. Good flexibility and strength suggest that the films are durable and less likely to break during handling or administration.

CONCLUSION

Using HPMC E15 and E5 polymers and plasticizer polyethylene glycol 400, a readily Dissolving sublingual film containing ketorolac tromethamine was successfully prepared by the Heavy casting method. For this reason, it is thought that patients can quickly reduce stomach Pain with almost no side effects by using the sublingual preparation.

The current study concludes that: ~

Solvents can be used to produce sublingual ketorolac tromethamine films.

Polymers and plasticizers can be used to optimize the production of sublingual films to Improve physicochemical properties.

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