FORMULATION AND EVALUATION OF PROMETHAZINE THEOCLATE ORAL FILMS FOR MOTION SICKNESS

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Abstract

The research aims to formulate and evaluate oral films with API (promethazine theoclate) the following formulation was done and evaluated for the best product formed. The investigation assessed the potential of incorporating Promethazine Theoclate into orally dissolving films for motion sickness management. The developed films exhibited favourable physicochemical attributes, rapid disintegration, and sustained drug release, particularly beneficial for patients unable to swallow conventional medication. The following films were evaluated for Physical Appearance, Weight Uniformity, Thickness Uniformity, Folding Endurance, Surface pH, Disintegration Time, and Drug content uniformity overall six formulations were done among them F4 showed promising characteristics for managing motion sickness and excellent durability.

Keywords: Promethazine theoclate, Oral films, Motion sickness, Formulation, Evaluation, Drug delivery, Pharmaceutical film, Antihistamines, Drug stability, Transdermal delivery, Film characterisation, Solubility enhancement, Mucoadhesion, Pharmacokinetics, Biopharmaceutical aspects.

Introduction

The oral route remains widely preferred for administering therapeutic agents due to its cost-effectiveness and ease of use, ensuring high levels of patient adherence. Solid dosage forms constitute about 60% of all formulations, including tablets and capsules. However, certain patient demographics, such as the elderly, children, and those with limited access to water, face challenges swallowing conventional oral medications. To address this, innovative formulations like oral fast-dissolving films have been developed, offering a solution to concerns about choking and enhancing medication compliance among diverse patient

populations.[1,2,3] Orally fast-dissolving film is a new drug delivery system for the oral delivery of drugs. Almost 90% of the drugs are administered to the body via the oral route for the treatment of various disorders and diseases as it is regarded as the safest, most convenient and most economical method of drug delivery and has the highest patient compliance. [5-7]. The drug is either dissolved or swallowed, which then enters into the systemic circulation to produce the desired effect [8-9]. Fast-dissolving oral thin films is an ultra-thin film that employs a hydrophilic polymer that rapidly hydrates or adheres when placed on the tongue or in the buccal cavity [10]. These films disintegrate or dissolve within seconds to release the active agent without drinking and chewing [11,12]. The instant bioavailability results from bypassing first-pass metabolism. So they are generally designed for the drugs having high first-pass metabolism for achieving better bioavailability [12,13]. Motion sickness is a malady caused by certain kinds of motion. The signs and symptoms include malaise, pallor, cold sweating, nausea, and vomiting. Motion sickness is properly considered to be present whenever any of its signs or symptoms have been provoked by motion, although a few authors use the term only to specify frank vomiting caused by motion. [14-20] For motion sickness Promethazine, diphenhydramine, dimenhydrinate and cyclizine have prophylactic value in milder types of motion sickness; should be taken one hour before starting a journey. Promethazine can also be used in morning sickness, drug-induced and postoperative vomiting, and radiation sickness. Solvent casting method: In the solvent casting method excipients are dissolved in water, and then water-soluble polymers and the last drug are added and stirred to form a homogeneous solution. Finally, a solution is cast into the Petri plate and dried[46,47].

Method & Materials

The main drug used in this study was promethazine theoclate polymer used is HPMC K100, HPMC E15 which is a Film Former & Disintegration Agent, Glycerine as a plasticiser, Citric Acid as saliva stimulating agent, Lactose as a sweetening agent, vanilla as flavouring agent, colouring agent and water. The instruments used were Disintegrating apparatus, vernier calliper, UV-Vis spectrophotometer, pH meter, and weighing balance.

Ingredients	F1	F2	F3	F4	F5	F6
Promethazine theoclate	0.18	0.18	0.18	0.18	0.18	0.18
HPMC K 100	0.2	0.3	0.4	-	-	-
HPMC E-15	-	-	-	0.7	0.8	0.9
Glycerine	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid	0.2	0.2	0.2	0.2	0.2	0.2
Lactose	0.2	0.2	0.2	0.2	0.2	0.2
Vanilla	0.1	0.1	0.1	0.1	0.1	0.1
Colouring agent	4-5 Drops	4-5 Drops	4-5 Drops	4-5 Drops	4-5 Drops	4-5 Drops
water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 1. Formulations of promethazine theoclate oral films

PREPARATION OF PROMETHAZINE THEOCLATE ORAL FILMS

Common methods for formulating Orally Disintegrating Films include solvent casting, hot melt extrusion, spray coating, compression moulding, and printing techniques. These methods involve processing polymer solutions or melts with active ingredients to create thin, rapidly disintegrating films suitable for oral administration. The solvent casting method is used for the preparation of fast-dissolving strip formulation. The method we used is the Solvent casting method.

To prepare firstly HPMC K100/ HPMC E15 was dispersed in distilled water followed by continuous stirring for up to 30 minutes on a magnetic stirrer and kept for 15 min to remove all the air bubbles entrapped inside the polymeric solution. To this plasticizer, Glycerine was added.

In a separate beaker, citric acid lactose sugar and flavouring agent vanilla were dissolved specific amount in distilled water. Both the solutions were mixed followed by mixing drugs keeping the solution on a magnetic stirrer. The mixture was kept on Sonicator for 15 mins followed by standing the mixture for 15-30 min to let the foams settle down.

After applying glycerine to the petri dish the resultant mixture was poured into the petri dish. The Petri dishes were kept in an oven for the casting of film at 40 degrees Celsius temperature for at least 2 hours and air dried for 24 hrs. After drying the film was carefully taken from the petri dish, checked for flaws, and trimmed to the desired size (2 x 2 cm^2) per strip. The resultant films were stored in aluminium foil and then in airtight zip-lock bags.

EVALUATION

- **Physical appearance and surface texture**

  Physical Appearance:

  - Colour: Evaluate the colour of the oral film to ensure uniformity and consistency. Any discolouration or variation may indicate formulation issues or degradation.
  - Transparency/Opacity: Assess the transparency or opacity of the film to ensure clarity and visibility of any printed or embossed markings.
  - Shape and Size: Check for uniformity in shape and size across individual films within a batch. Variations may affect dosing accuracy and patient compliance.
  - Smoothness: Inspect the surface for smoothness and absence of wrinkles, folds, or rough edges, which may affect the film's appearance and ease of handling.

  Surface Texture:

  - Texture: Evaluate the surface texture by gently touching the film to assess its smoothness, roughness, or tackiness. A smooth and non-tacky surface enhances patient comfort during administration.
  - Flexibility: Bend or fold the film to assess its flexibility and elasticity. A flexible film should not crack, break, or deform excessively, ensuring ease of handling and administration.
  - Adhesion: Assess the adhesion of the film to the packaging material or other films in a multi-dose package. Proper adhesion ensures integrity and prevents film detachment during storage or handling.
  - Uniformity: Check for uniformity in surface texture across different regions of the film. Variations in texture may indicate inconsistencies in formulation or processing**.**

Weight Uniformity

Buccal films from each batch were randomly selected and individually weighed on an analytical balance. Five observations were recorded for each batch, and the average weight was calculated This process was repeated for every batch to ensure consistency and accuracy in weight determination.

Thickness uniformity

Film thickness was assessed using a vernier calliper apparatus. A strip measuring 2 x 2 cm was positioned between the thickness rods, ensuring uniform pressure. Thickness measurements were taken at five different positions along the strip to account for potential variations. Each measurement

Folding Endurance

To conduct the folding endurance test, a sample of buccal films is carefully selected from each batch. Each film is then placed on a flat surface, and a specific point along its length is identified for folding. Using precise manual handling, the film is folded repeatedly at the same location until it reaches its breaking point. The number of folds completed before the film breaks is recorded for each sample. This process is repeated for multiple samples within the batch to ensure statistical relevance and accuracy

pH

The 2 cm x 2 cm buccal film was dissolved entirely in 2 ml of distilled water. The pH of the solution was measured by placing the pH electrode in contact with the film's surface and allowing it to equilibrate for one minute.

Disintegration Time

The disintegration time of orally dissolving films refers to the duration it takes for the film to completely disintegrate and dissolve when placed in the oral cavity. The disintegration time of all the formulations was calculated on a disintegration apparatus. For creating a mouth-like environment, we used a 6.8 pH Phosphate buffer which is the same as the pH of the oral cavity. For the study, film as per the dimension (2×2cm) required for dose delivery was placed in a basket containing 900 mL distilled water. The time required for the film to break and disintegrate was noted as in-vitro disintegration time.

Drug content uniformity

Standard solution: Accurately about 10mg of Promethazine Theoclate was transferred into a 10 ml of volumetric flask. Then add PBS (pH 6.8) solution with mechanical shaking up to 10 ml and then this solution was filtered through the Whatman filter paper. Then (0.1,0.2,0.3,0.4,0.5) ml of filtrate was pipette out and diluted up to 10 ml with the PBS solution in 10 ml of volumetric flask to get 10 µg/ml final concentration.

Test solution: One film of Promethazine Theoclate was dropped into a 10 ml volumetric flask. Then add PBS (pH 6.8) solution with mechanical shaking up to 10 ml. Then this solution was filtered through the Whatman filter paper. Then (0.1,0.2,0.3,0.4,0.5)ml of filtrate was pipette out and diluted up to 10 ml with the PBS solution in 10 ml of volumetric flask to get 10 µg/ml final concentration.

Stability study

A stability study of orally dissolving films is crucial to assess their shelf-life, integrity, and performance under various storage conditions. Our 30-day stability study on the oral film revealed: No microbial growth, Minimal degradation, and No organoleptic change, notably it remained stable at room temperature, demonstrating practical applicability and resilience against environmental factors. These findings underscore our commitment to formulation quality and regulatory compliance, ensuring reliability for future use.

RESULT AND DISCUSSION

In the current study, we designed and characterized polymeric dissolving films for the oral delivery of Promethazine Theoclate. These films were prepared using varying concentrations of HPMC K 100 and HPMC E 15 through the solvent casting technique. We evaluated the prepared orally dissolving films across various parameters. Physical Appearance and Surface Texture: Visual inspection and tactile examination revealed that the orally dissolving films possessed smooth surfaces and presented an elegant appearance. Weight Uniformity: We observed uniformity in weight across all batches, with no significant differences noted in individual formulations compared to the average value. Weight variation fell within the range of 0.172 to 0.259 g for the prepared films. Thickness: The

thickness of the films ranged between 0.04 to 0.08, with low standard deviation values indicating consistency in thickness. Folding Endurance: Folding endurance was determined by repetitively folding small strips of the films until they broke. The average folding endurance across all formulations ranged from 53 to 90, indicating satisfactory mechanical strength. Surface pH: Surface pH values across all films were uniform, ranging from 6.30 to 7.07, demonstrating compatibility with the oral pH environment. Disintegration Test: In vitro disintegration times ranged from 58 to 79 seconds across all formulations, indicating the prompt disintegration of the films. Overall, these results demonstrate the successful formulation and evaluation of Promethazine Theoclate orally dissolving films, exhibiting favourable physical attributes and promising disintegration properties for potential oral delivery applications

RESULT

This research involving the formulation of promethazine theoclate oral films for motion sickness shows that the films prepared were elegant and of smooth surface. The weight of the films was found to be uniform. The thickness of the films was found to be uniform. The films were found satisfactory in the evaluation of drug content. The films have better flexibility. The surface pH was uniform& suitable for oral use. Similarly, the orally dissolving films are also subjected to a drug content uniformity study and it lies between 79.78 to 97.47 % which suggests uniform dispersion throughout the orally dissolving film. Among all of them, F4 gives the best results concerning all evaluation parameters. Thus F4 film containing Promethzine Theoclate (10 mg) in HPMC E 15 (700mg) is considered the best choice. These films were found to be appropriate for Motion Sickness. This formulation will show enhanced Patient compliance due to ease of use.

Parameters		F1	F2	F3	F4	F5	F6
Physical appearance	colour	Light pink	Light pink	Light pink	Light pink	Light pink	Light pink
	Transparency	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
	Size	2 x 2 cm^2	2 x 2 cm^2	2 x 2 cm^2	2 x 2 cm^2	2 x 2 cm^2	2 x 2 cm^2
	Texture	Rough	Rough	Grainy	Smooth	Rough	Smooth
	Tackiness	Tacky	Non-tacky	Tacky	Non-tacky	Non-tacky	Tacky
	Uniformity	Uniform	Uniform	Uniform	Uniform	Uniform	Uniform
Weight Uniformity (Average wt 'g')	-	0.259	0.210	0.172	0.206	0.268	0.256
Thickness Uniformity	-	0.07	0.05	0.08	0.06	0.05	0.04
Folding Endurance	-	75	66	53	90	87	82
Surface pH	-	6.93	7.00	7.07	6.30	6.88	6.60
Disintegration Time	-	75	79	70	62	58	67
Drug content uniformity	-	79.78	92.05	83.75	97.47	88.44	94.94

Table 2. Formulation of promethazine theoclate oral films evaluation result

CONCLUSION

The investigation effectively demonstrated the potential utility of incorporating Promethazine Theoclate into orally dissolving films for addressing Motion Sickness. Primarily, the developed films exhibited favourable physicochemical attributes, including consistent thickness, weight uniformity, and mechanical robustness, along with rapid disintegration in the oral cavity, indicative of their suitability for oral delivery. This characteristic is particularly advantageous for patients, notably pediatric and geriatric individuals, who encounter challenges

swallowing conventional tablets or capsules due to factors such as diarrhoea, coughing, or being bedridden.

Moreover, in vitro studies on drug release highlighted the sustained liberation of active constituents from the films. This sustained release profile is crucial for managing motion sickness, as it ensures prolonged exposure of the active ingredients to affected mucosal surfaces, thus maximizing therapeutic effectiveness. The formulations, labelled as F1 to F6, shared a common composition consisting of HPMC K100 and HPMC E15 as polymers, glycerin as the plasticizer, lactose as the sweetener, vanilla for flavouring, and distilled water as the solvent. However, they varied in the type and quantity of polymer used. Specifically, F1 to F3 utilized HPMC K100, while F4 to F6 employed HPMC E15.

Among the formulations, Formulation 4 demonstrated promising characteristics for managing motion sickness, including rapid disintegration, excellent physical attributes, bioadhesive properties, and significant antimicrobial activity. These attributes collectively suggest its potential as an effective treatment option. Furthermore, the developed formulations offer several advantages, such as rapid disintegration and sustained drug release, which hold promise for clinical translation and future therapeutic applications in motion sickness management.

Despite these promising findings, further clinical studies are warranted to validate the safety, efficacy, and long-term benefits of these formulations in human subjects. Such studies will provide essential insights into the practical implications of utilizing orally dissolving films containing Promethazine Theoclate for motion sickness treatment, ultimately enhancing patient care and therapeutic outcomes.

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