

## Original Research Article

# Hydroxypropyl cellulose-based orally disintegrating films of promethazine HCl for the treatment of motion sickness

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### Abstract

**Purpose:** To prepare and characterize orally disintegrating films (ODFs) of promethazine hydrochloride (HCl) for prompt treatment of motion sickness.

**Methods:** Films were prepared by solvent casting method using hydroxypropyl cellulose (HPC) as film former and glycerin as plasticizer along with a saliva stimulating and sweetening agent. Nine different film formulations were prepared and evaluated for their characteristics including thickness, disintegration time, tensile strength and drug release behavior.

**Results:** The prepared films were transparent and slightly sticky in nature with thickness that ranged from 0.22 mm to 0.29 mm and tensile strength of 0.56 N/cm<sup>2</sup> to 2.49 N/cm<sup>2</sup>. The disintegration time of film formulations ranged from 26.3 to 52.7 s and a majority of formulations released approx. 80 % of the drug within 10 min with a non-Fickian diffusion pattern.

**Conclusion:** The study concludes that the orally disintegrating films of promethazine HCl can be prepared using HPC as film former.

**Key words:** Orally disintegrating films, Promethazine, Solvent casting, Motion sickness

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## INTRODUCTION

Tablets and capsules are most preferred dosage forms for drug delivery due to their ease of administration, accurate dosage and portability [1]. However, in conditions like motion sickness the patient requires prompt treatment [2]. Orally disintegrating films (ODFs) of APIs have gained attention as an alternate dosage form in such cases [3]. ODFs are the thin oral strips consisting of polymeric base material, drug and other excipients [4]. These strips readily wet by saliva

and disintegrate within seconds when placed in the oral cavity to release the medication for absorption from buccal cavity [5].

Promethazine HCl is a selective histamine H<sub>1</sub>-receptor antagonist, an effective drug approved by FDA in 2009 for the treatment of motion sickness [6]. Although the drug is effective for the treatment of motion sickness; however, its oral bioavailability is poor as it undergoes extensive first pass effect allowing only 35 % of drug to reach the systemic circulation. As the patient

feels extremely restless and nauseous during the motion sickness therefore, an oral formulation in the form of tablet or capsule might be inconvenient. In addition, sustained release dosage forms might be helpful to maintain plasma level of drug and prevent symptoms of motion sickness during long travels. However, an appropriate drug delivery system with rapid onset of action is desired to relieve the symptoms immediately. ODFs are the possible solution as they can provide rapid onset of action due to their ability to allow direct absorption into the systemic circulation through mucosal tissues [7]. Orally disintegrating films of promethazine HCl by using HPMC (a cellulose derivative) were prepared [8] which gave a relative slow release profile due to the retardant nature of HPMC [9]. As our ultimate target is to achieve a rapid action therefore, we propose to use Hydroxypropyl cellulose (HPC), an alternate cellulose derivative that is known to produce soluble films (in the concentration range of 1-10 %) having good surface and adhesion properties [10-12]. In the present study we have prepared HPC-based films of promethazine HCl by solvent casting method (a preferred method because of its feasibility and low cost processing [9] and characterised by various techniques. The study also explored the effect of different concentrations of polymer (HPC) and plasticizer (glycerin) on the films in order to determine the optimum release kinetics of promethazine HCl.

## EXPERIMENTAL

Promethazine HCl was a generous gift from Unexo Pharmaceuticals (Pvt) Ltd, Lahore, Pakistan. HPC-SL obtained from Nippon Soda Co., Ltd. Tokyo, Japan. Glycerine from Sigma-Aldrich, citric Acid monohydrate from BDH, sodium lauryl sulfate from Duksan Pure Chemicals, Korea and Sucrose was purchased from local market.

## Preparation of films

### Screening trials

Initial screening studies were conducted to determine the minimum and maximum concentration of HPC (films forming polymer) and glycerin (plasticizer). The concentration ranges of HPC (1-10% w/v) and glycerin (10-20 % w/w) of polymer (HPC) were selected from literature.

Films were prepared by solvent casting method as adopted from [8]. Briefly, the accurate quantity of polymer was dissolved in 10 mL of distilled water (Solution A) and plasticizer was dissolved in ~3 mL of distilled water (Solution B). The solution B was slowly added into solution A while stirring and the final volume was made up to 15 mL (Solution C). The final solution C was poured into petri dishes and then dried in an oven at 60 °C for 24 h. Prepared films were peeled out, covered in aluminium foil and stored in desiccator for further testing.

### Drug loading in films

From the results of screening phase (see results), it was indicated that polymer concentration ranging from 4-6 % w/v along with plasticizer in the range of 10-20 % w/w produced films with acceptable characteristics. Therefore; nine different film formulations (F1 - F9) were prepared for drug loading using the above stated concentrations of polymer and plasticizer as described in Table 1. The dose of promethazine HCl for each 2x2 cm<sup>2</sup> film was calculated based on 25 mg adult dose in motion sickness.

In the preparation of drug loaded films; HPC was dissolved in 10 mL of distilled water with stirring and the drug is added in this polymeric solution and continuously stirred for 30 min to obtain a clear solution. Glycerin was then added in the HPC/drug solution and stirred to make clear solution.

**Table 1:** Composition of nine film formulations of promethazine HCl

Formulation Code	Promethazine HCl (mg)	HPC (% w/v)	Glycerin (% w/w) of polymer	SLS (mg)	Citric acid (mg)	Sucrose (mg)
F1	240	4	10	50	100	100
F2	240	4	15	50	100	100
F3	240	4	20	50	100	100
F4	240	5	10	50	100	100
F5	240	5	15	50	100	100
F6	240	5	20	50	100	100
F7	240	6	10	50	100	100
F8	240	6	15	50	100	100
F9	240	6	20	50	100	100

Other ingredients i.e. Citric acid (salivary stimulating agent), Sodium Lauryl sulfate (surfactant) and sucrose (sweetening agent) were dissolved in 4 mL of water to make a clear solution. Both above solution were mixed together and resulted in a milky solution that was sonicated for 5 min to remove any air bubbles. The final solution was poured in dried petri dishes of 7 cm<sup>2</sup> area and dried in an oven at 60 °C. Films were peeled from petri dishes and cut in 2 x 2 cm<sup>2</sup> strips size and kept in desiccator until further testing.

## Characterization of films

### Film thickness

Thickness is an important characteristic of orally disintegrating films as the thickness uniformity is directly related to the dose uniformity in each film [13]. The thickness of each film was measured at six different points (n = 6) using micrometer screw gauge and the mean value was reported.

### Tensile strength

Tensile strength represents the mechanical strength and elasticity of films. Tensile strength is defined as maximum load force to break orally disintegrating films. It was calculated by dividing the maximum load to the area of the film. Film of size 2 x 2 cm<sup>2</sup> was held between two clamps of Universal material testing machine (Lloyd Lf Plus series, Lloyd Instruments Ltd, Largo FL, USA) in such a way that there is 5 mm distance between the two grips. The machine was operated to find the maximum load at rupture. Six films of each formulation (n=6) were tested and tensile strength ( $\sigma$ ) was calculated as in Eq 1 [14].

$$\sigma = \frac{F}{A} \dots\dots\dots (1)$$

where 'F' is the force at which the film breaks and 'A' is the area of film.

### Disintegration time

Disintegration time of each film formulation was determined using Petri dish method [3]. A film strip of 2 x 2 cm<sup>2</sup> dimension was placed in a petri dish containing 25 mL of phosphate buffer, pH 6.8 at 37 °C and stirred. The time at which film started to disintegrate was noted. The test was repeated for three films of each formulation (n = 3) and the mean value was reported.

## In-vitro dissolution test

In-vitro dissolution test is performed using USP type II paddle apparatus (Curio, Pakistan). Simulated salivary fluid of pH 6.8 was used as dissolution medium. The volume of dissolution medium was selected depending upon the API dose to ensure sink conditions and sample was maintained at 37.0 ± 0.2 °C. This medium was then stirred at 50 rpm. An aliquot of 3 mL was withdrawn at every 2 min time interval until 10 min and the equal amount was replaced with fresh medium. All samples were diluted adequately and analyzed by using UV/Vis spectroscopy (2550 Shimadzu, Japan) at 249.2 nm and concentration was calculated using a calibration curve. All the values were recorded in triplicate (n = 3) and average values and standard deviation were reported.

For the determination of dissolution kinetics, the release data of different film formulations was subjected to various kinetic models, i.e. zero order, First order, Higuchi and Korsemeyer-Peppas using DD-solver software. The results were derived based upon highest R<sup>2</sup> value and the minimum slope value indicate that the model is best fit [15].

## FTIR spectroscopy

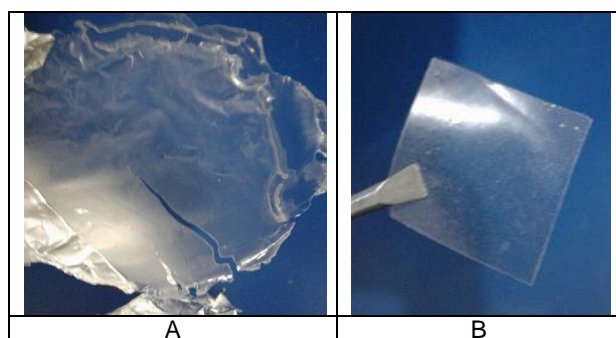
FTIR spectroscopy detects the interaction between drug and all other excipients used in formulation. IR spectra of different samples were analyzed and recorded on Attenuated Total Reflectance Infrared Spectrophotometer (Bruker, Japan). For analysis, drug and films were placed in the machine and spectra were recorded from 4000 to 400 cm<sup>-1</sup>.

## Statistical analysis

Drug release are presented as mean ± standard deviation (SD) and were analyzed by one-way ANOVA using Microsoft Excel 2017. Statistical differences were set at  $p < 0.05$ .

## RESULTS

The screening trials indicated that the films of HPC alone were not peelable from the petri dish or aluminium foil and were too brittle (Figure 1A). However, the films prepared by incorporating the plasticizer (glycerin) were transparent, flexible, slightly sticky in nature and easily peel-able (Figure 1B). These studies also showed that the 4-6 % w/v concentration of HPC is optimum for films along with 10-20 % w/w plasticizer.



**Figure 1:** A) film prepared with 5 % w/v polymer alone shows brittleness and cracks and was difficult to peel out of aluminium foil; B) Film prepared with 5 % polymer and 10 % w/w plasticizer was clear, smooth and easily peelable

### Thickness of films

The film thickness for formulations F1 to F9 ranged from 0.22 mm to 0.29 mm (Table 2). The thickness of all films lies within the acceptable limit (<0.3 mm) reported for oral films [8].

### Tensile strength

The tensile strength values of prepared film formulations ranged from 0.56 N/cm<sup>2</sup> for F3 to 2.49 N/cm<sup>2</sup> for F10 (Table 2).

### Disintegration time

The disintegration time of film formulations ranged from 26.3 sec to 52.7 sec (table 2). there is no specific range of disintegration time of odfs reported in literature. However, it can be compared with disintegration time limit of orodispersible tablets i.e. < 180 s described in European pharmacopoeia [16].

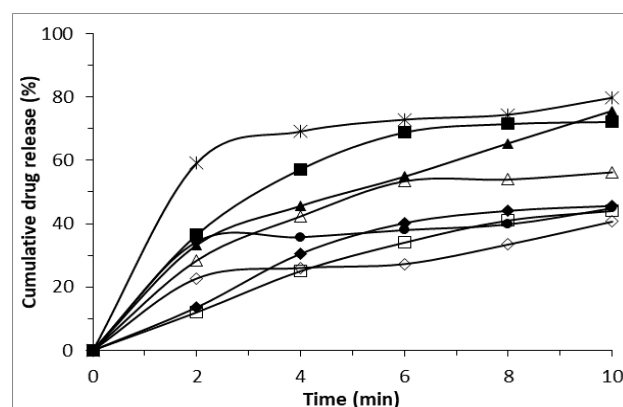
**Table 2:** Thickness, tensile strength and disintegration time of orally disintegrating films

Formulation code	Thickness (mm)	Tensile strength (N/cm <sup>2</sup> )	Disintegration time (sec)
F1	0.23±0.045	1.43±0.33	44.0±10.03
F2	0.26±0.044	1.01±0.038	46.0±2.16
F3	0.28±0.108	0.56±0.039	36.7±11.61
F4	0.25±0.034	2.08±0.15	26.3±2.49
F5	0.25±0.023	1.02±0.019	52.7±5.25
F6	0.29±0.036	0.78±0.022	28.3±1.69
F7	0.24±0.045	2.49±0.215	52.7±2.05
F8	0.28±0.056	1.52±0.413	48.0±1.63
F9	0.22±0.017	1.04±0.024	44.7±2.32

### In-vitro dissolution

The dissolution profiles (Figure 2) has shown that the drug release from film formulations containing 4 % polymer, i.e., F1- F3 was 45 to 70

% in first 4 min and 55 to 80% in 10 min. However, the formulations made with 5 and 6 % polymer (F4 - F6 and F7 - F9, respectively) have shown relatively slow release of drug (up to 45 % in 10 min). These results indicated that the polymer concentration has a direct effect on release of drug and the lower concentration of HPC along with the presence of plasticizer (10 - 20 %) in F1-F3 can provide fast release of drug for prompt treatment of motion sickness.



**Figure 2:** In-vitro release profile of film formulations; F1 (\*), F2 (•), F3 ( ), F4 (•), F5 (◇), F6 (□), F7 (Δ), F8 (○) and F9 ( ) in phosphate buffer pH 6.8

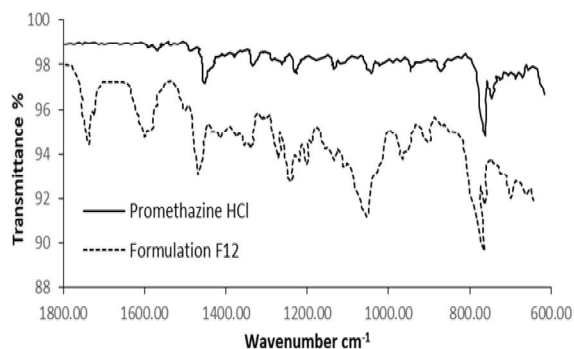
There was significant difference in drug release ( $p < 0.05$ ) from all nine formulations prepared. This indicated the significant role of polymer and plasticizer in drug release.

### FTIR spectra

FTIR Spectra of Promethazine HCl drug showed peaks at 1453.74, 1224.91, 1033.00, 756.97cm<sup>-1</sup> (Figure 3). These peaks relate to C=C, C-N, C=S and C-Cl groups in the drug, respectively. FTIR spectra of prepared film formulation showed all peaks observed in the drug spectra (Figure 3). This indicated that all the ingredients in the formulation are compatible.

### DISCUSSION

In this study, orally disintegrating films of Promethazine HCl were prepared. Thickness of prepared films was almost the same regardless of polymer concentrations i.e. 4, 5 or 6 %w/v. It may be due to the reason that the total concentration of each formulation is closely related or comparable. The small variation in thickness might be due to the uneven glass surface, variation in drying time and inherent experimental variability. The tensile strength of films was dependent upon the concentration of HPC and glycerin in the formulations. As the concentration of HPC is increased from 4 to 6 %,



**Figure 3:** FTIR spectra of promethazine HCl and a film formulation (F12) prepared by incorporating in HPC

the tensile strength increased from 1.5 to 2 times in formulations containing different percentages of plasticizer. This shows the film forming property of this polymer [17]. Furthermore, the addition of glycerin decreases the tensile strength. By each 5 % increment of plasticizer, there is 40 - 50 % reduction in the value of tensile strength of each film formulation. Decrease in tensile strength by addition of glycerin indicates its plasticizer action [18].

The disintegration time of films was not dependent on concentration of polymer, as there was hardly any change in disintegration time of films prepared with 4 or 6 % of HPC. However, the addition of plasticizer decreased the disintegration time for films of each polymer concentration. This indicated that the presence of plasticizer eased the entry of solvent in films and help in fast disintegration [19]. The films prepared with 5 % HPC concentration have shown minimum disintegration times (except F5) although the thickness and tensile strength of these films were comparable to those prepared with 4 or 6 % HPC. This indicates that the disintegration time is not merely dependent on the thickness or tensile strength of film.

From the drug release profiles of all film formulations, it was shown that the HPC based films exhibited faster release than that of HPMC based films of Promethazine HCl, i.e., 82.29 % in 10 min as compared to HPMC based promethazine HCl films [8]. This is most likely due to the fact that HPMC forms a thicker swollen gel layer than that of HPC films resulting in longer diffusion pathway for drug molecules [20]. The dissolution profile of all the formulations fitted to first order and Higuchi models with Kormeyer-Peppas release coefficient of 0.56. This indicates the concentration dependent release from the film formulation that followed

non-Fickian (anomalous) drug release ( $0.45 \leq n \leq 0.89$ ) [21].

## CONCLUSION

Orally disintegrating films of a hydrophilic film former (hydroxypropyl cellulose) in combination with plasticizer (glycerin) have been successfully formulated to deliver promethazine HCl for motion sickness. Formulation attributes such as tensile strength, disintegrations time and drug release confirms the superiority of the formulations over the conventional tablets which require water for their oral administration.

## DECLARATIONS

### Acknowledgement

Authors express their gratitude to Unexo Laboratories Pvt Ltd, Lahore, Pakistan for providing promethazine HCl as a gift.

### Conflict of interest

No conflict of interest is associated with this work.

### Authors' contribution

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Amjad Hussain has conceived and designed the study, Sadia Latif has performed the experimental work, Muhammad Sohail Arshad and Nasir Abbas helped in data analysis, Amjad Hussain wrote the manuscript, while Nadeem Irfan Bukhari and Muhammad Irfan have reviewed it. Finally, all authors read and approved the manuscript for publication.

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