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Research article

Formulation and evaluation of fast dissolving oral film of promethazine hydrochloride using different surfactant

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Abstract

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or chewing. This facilitates the rapid absorption in the oral cavity and reduces first-pass effects. The aim of this study is to formulate and evaluate the Fast dissolving Oral film of Promethazine hydrochloride as a strong antihistamine which are used to reduce nausea, motion sickness and improved bioavailability of drugs as compared to conventional solid oral dosage forms. The films were prepared Hydroxy propylmethyl cellulose E15 as a film base synthetic polymer and PEG400 (Poly Ethylene Glycol 400) as a plasticizer by solvent casting method. SLS (Sodium Lauryl Sulfate) and MCC (Micro Crystalline Cellulose) used as a surfactant in different concentration. Sucrose used as a sweetening agent and strawberry as a flavoring agent. Films were found to be satisfactory when evaluated for thickness, weight uniformity, in-vitro drug release, folding endurance, drug content and disintegration time. The surface pH of all the films was found to be neutral or minor change. Films in vitro drug release studies also done by using USP dissolution apparatus. The in vitro drug release in optimized formulation F2 was found to be 14.36% in 2 min. The optimized formulation F2 also showed satisfactory pH, drug content (97.41±0.54%), effective in vitro drug release (96.03±0.68% in 16 min), disintegration time of 09 seconds and satisfactory stability. The Promethazine hydrochloride fast dissolving oral film was formulated. The given film disintegrates within nine seconds which release drug rapidly and gives action.

Key words: Antihistamine drug, Promethazine hydrochloride, Fast Dissolving Oral Film, HPMC, PEG400, SLS, MCC, Solvent casting method.

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1. Introduction

Fast-dissolving drug delivery is rapidly gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within a minute, without needing water or chewing. An important benefit is the accurate dosing as compared to liquid dosage forms, mostly used with pediatric patients or in case of dysphasia. Many pediatric and geriatric patients who having difficulty in

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swallowing are unwilling to take solid preparations as a result of concern of choking. The fast dissolving drug delivery system consists of a very thin strip that is just placed on the patient's tongue or any oral mucosal tissue, instantly wet by secretion the film rapidly hydrates and adheres onto the location. It then quickly disintegrates and dissolves to release the drug for oromucosal and intragastric absorption.

Oral dissolving films can be administered without water, anywhere, any time. Fast dissolving film has Minimum disintegration time and faster dissolution rate giving quick onset of action. Also Fast dissolving film prepared using different sweeteners and flavors, which improves patient compliance [2, 3, 7, 18].

The development of fast dissolving oral films containing Promethazine hydrochloride offers an alternative to conventional tablets, syrups and injections for the treatment of emetics.

Pharmacology of Promethazine Hydrochloride

Promethazine, a phenothiazine derivative, is a long acting antihistamine with mild atropine-like anticholinergic effects and some antiserotonin effects, and because of its marked effect on the central nervous system (CNS), it acts as an antiemetic, hypnotic, tranquilizer, and a potentiator of anaesthetics, hypnotics, sedatives and analgesics [1, 19, 20, 21].

Pharmacokinetics of Promethazine Hydrochloride

Promethazine is well absorbed after oral administration. Peak plasma concentrations are reached 2 to 3 hours after administration by this route, although there is low systemic bioavailability after oral administration, due to high first-pass metabolism in the liver. Promethazine crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is highly bound to plasma proteins (76-93%). Promethazine undergoes extensive metabolism, predominantly to promethazine sulfoxide, and also to N-desmethyl promethazine. It is excreted slowly via the urine and bile, mainly as metabolites. Elimination half-lives of 5 to 14 hours have been reported. The antihistamine action has been reported to be between 4 and 12 hours [1,21].

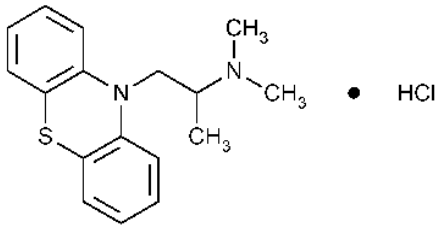
In the view of above fact, in the present investigation an attempt was made to develop mouth dissolving film of Promethazine hydrochloride using suitable polymer like Hydroxypropyl methyl cellulose (HPMC E15), Sucrose as sweetening agent, citric acid as saliva stimulating agent, Strawberry as flavoring agent, Titanium dioxide as colouring agent, Polyethylene glycol as plasticizer, Sodium lauryl sulfate and microcrystalline cellulose as surfactant.

Drug Profile[1,20,21]

Promethazine hydrochloride (H1antihistaminics) (Antiemetic Drug).

IUPAC Name: N, N-dimethyl-1-phenothiazin-10-ylpropan-2-amine.

Chemical structure:



Chemical formula:	**$C_{17}H_{20}N_2S{\cdot}HCl$**
Molecular weight:	**320.88**

Appearance:	**crystals White to faint yellow crystalline powder**
Adour:	**odorless**

2. Materials and Methods

Promethazine Hydrochloride was obtained as gift sample from Syncom Healthcare Limited Indore, Madhya Pradesh. HPMC E15, PEG400, sucrose, citric acid, Titanium dioxide, strawberry and sodium lauryl sulfate, microcrystalline cellulose used were of analytical grade.

Preparation of Fast Dissolving Oral Films: [5, 8, 13, 14]

The fast dissolving oral film of promethazine hydrochloride were prepared by the solvent casting technique using HPMC E-15 as a film forming polymer and PEG as a plasticizer. SLS and MCC were used as a surfactant. Citric acid as saliva stimulating agent. Sucrose as a sweetening agent and strawberry as a flavoring agent. The formulations were prepared as per table no. 1. The hydrophilic polymers namely hydroxy propyl Methyl cellulose (HPMC) and Polyethylene glycol (PEG) were accurately weighed and dissolved in 10ml hot distilled water and was stirred for 2 hours. In second solution Drug (dissolves in ethanol and chloroform 1:1 mixture) and other ingredients Titanium dioxide, SLS / MCC (according to formulation) mixed. Sucrose and citric acid was dissolving in 10ml distilled water constant stirring with a magnetic stirrer. The third solution was prepared by blending second solution in first solution. Add strawberry flavor in third solution and kept for 2 hours to remove air bubble and the resultant homogeneous solution was poured into a petri dish. Then the films were dried in an oven at 50^0C for 24 h. The dried films were wrapped in a butter paper and cut into 3x2 cm^2 area, covered with an aluminum foil and kept in a desiccators. Selected films were subjected to different evaluation parameters.

Table 1. Formulation of Fast Dissolving Films of Promethazine hydrochloride

Ingredients (w/w)	Formulation 0	Formulation 1	Formulation 2	Formulation 3	Formulation 4
PMZ. HCl (mg)	250	250	250	250	250
HPMC E15(mg)	400	400	400	400	400
Poly Ethylene Glycol 400 (mg)	120	120	120	120	120
SLS (mg)	-	15	20	-	-
MCC (mg)	-	-	-	15	20
Citric acid anhydrous (mg)	40	40	40	40	40
Sucrose (mg)	120	120	120	120	120
Titanium Dioxide (mg)	5	5	5	5	5
Strawberry (ml)	10	10	10	10	10
Distilled Water (ml)	qs	qs	qs	qs	qs

Formulation of Promethazine Hydrochloride Oral Film:

Evaluation of Fast Dissolving Oral Films: [9, 14, 15, 16]

Transparency:

Transparency was evaluated by visual appearance of oral film and categorized in various levels such as best, good, medium, bad for transparency.

Film Weight variation:

For evaluation of film weight three films of each formulation were taken and weighed individually. The average weight were calculated and reported**.**

Thickness:

For evaluation of film thickness three films of each formulation were taken and the film thickness was measured using micrometer screw gauge at three different places and the mean thickness of films were calculated and reported.

Tensile strength:

For evaluation of film Tensile strength (TS) of each formulation were taken and calculate tensile strength with the help of formula:

$$\text{Tensile strength} = \frac{\text{load at failure} \times 100}{\text{Film Thickness} \times \text{Film Width}}$$

Folding Endurance:

Folding endurance is measured by manual repeated folding of film at same place till it broke. The number of time the film is folded without breaking is known as the folding endurance value. A strip of 3 × 2cm diameter (an area of 6 cm^2) was subjected to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed, and the average values were calculated and reported**.**

Surface pH:

Surface pH of the films was determined in order to investigate the possible side effects due to change in pH in vivo, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film was placed in a Petri dish and moistened with 0.5 ml of distilled water and kept for 1 h. pH was noted with the electrode of the pH meter. The average of three determinations for each formulation was done.

Surface texture:

Surface texture was evaluated by visual appearance of oral film and categorized in smooth to rough surface indicates by mathematical + sign.

Moisture absorption:

The film sample is weighed and placed on a pre weighed stainless steel wire mesh. The wire mesh is then submerged in a petridish containing 20 ml distilled water. Increase in weight of the film is determined at regular time intervals (10 min) until a constant weight is obtained the hydration ratio of the film is calculated and average moisture absorption is calculated and reported.

$$\textbf{Hydration ratio} = Wt\text{-}W0 \times 100 / W0$$

Where Wt = weight of film at time t and
W0 = weight of film at zero time.

Moisture loss:

The percent moisture loss was determined by placing prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. Average percent moisture loss was calculated.

$$\textbf{Moisture loss} = W0/W0\text{-}Wt \times 100$$

Where W0= initial weight Wt = final weight

Drug content:
A specified area of strip (3cm×2cm) was dissolved in 100 ml water in volumetric flask and shaken continuously for 10 min. Filter the solution by 0.45µm membrane filter paper. After filtration, 1ml of solution was withdrawn from the solution and diluted up to10ml with water. The absorbance of the solution was measured at 248nm and concentration was calculated and determined the drug content.

In vitro drug release test:[16]
Dissolution profile of promethazine hydrochloride was carried out in a beaker containing 30 ml of the simulated salivary fluid pH 6.8 as a dissolution medium, maintained at 37±0.20°C. The medium was stirred at 100 rpm with magnetic stirrer. Aliquots of the medium were withdrawn at regular interval of 2 min and the same amount was replaced with fresh medium. Samples were analyzed for cumulative percentage drug release by Shimadzu UV- visible spectrophotometry at 248nm. Three trials were carried out for all the samples and average was taken.

In vitro release of drug from all formulations was determined using USP apparatus type II (Paddle method). The following conditions were followed to study the in-vitro dissolution study of promethazine hydrochloride mouth dissolving film -

1. Dissolution apparatus: USP Type II (Paddle method)
2. Volume of dissolution medium: 900 ml
3. Temperature: 37±0.20^{0}C
4. Dissolution medium: simulated salivary fluid (pH6.8)
5. Sampling interval: 2 min
6. Quantity of sample withdrawn: 10ml

3. Results and Discussion

FT –IR Compatibility Study

The compatibility of drug in the formulation was confirmed by IR spectra of pure drug and formulations were determined using Shimadzu FTIR-8400S Spectrophotometer by NaCl Disc method.

1) The FT-IR spectrum of pure drug of Promethazine hydrochloride shows the peaks according to chemical groups.

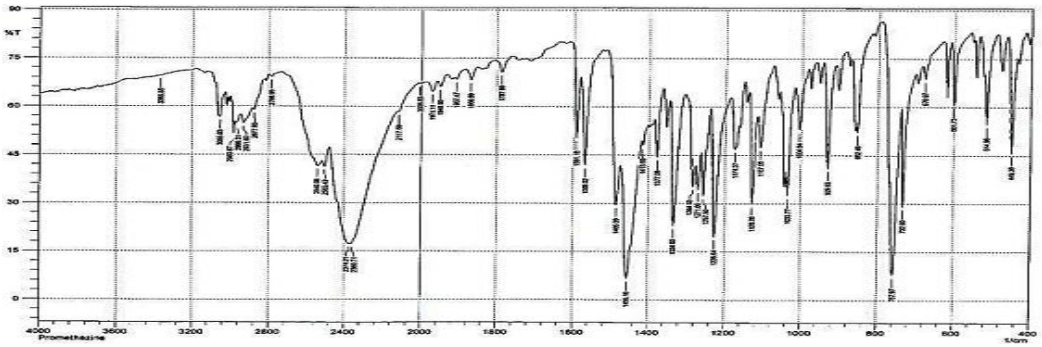


Figure 1: FTIR spectrum of pure Promethazine Hydrochloride

Table 2. FTIR Spectra Peaks of Pure Promethazine Hydrochloride

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
N-H	3390	3300-3500
C-H	2890	2800-3100
C-N	1166	1020-1250
C=C	1476	1560-1710
C=S	1135	1000-1200

2) The FT-IR spectrum of Promethazine hydrochloride with polymer HPMC E15 and SLS show the peaks according to Chemical groups.

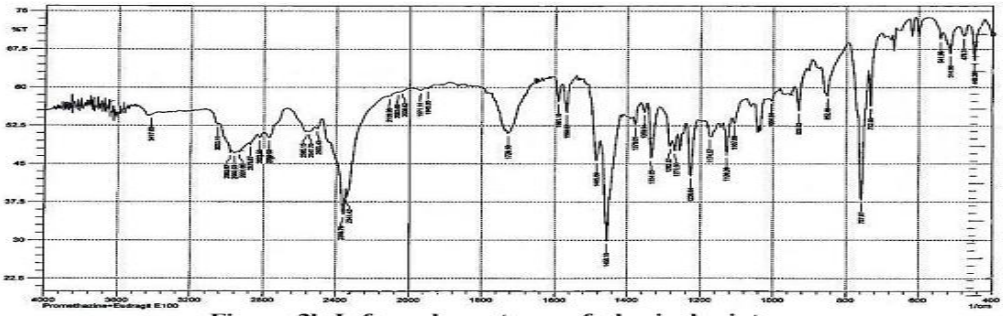


Figure 2: Infra red spectra of Promethazine Hydrochloride drug with HPMC E15 and SLS

Table 3. FTIR Spectra Peaks of Drug+ HPMC15 + SLS

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
C=O	1795	1600-1900
N-H	3384	3300-3500
C-O	1123	900-1300
C-H	1445	1300-1500
C=S	1121	1000-1200
C-C	1678	1400-1900

The combination of Drug, Polymer and surfactant were showed significant changes in the peak. So FT-IR spectroscopic studies indicate that drug is compatible with polymer and surfactant.

Table 4. Evaluation Parameters of Formulation

Formulation	Transparency	Weight variation (mg)	Film Thickness (mm)±SD	Tensile strength (kg/mm^2)	Folding endurance	Surface pH
F0	Good	20.15±0.24	0.150±0.022	7.48±0.88	184±2.54	6.72±0.01
F1	Best	21.30±0.36	0.160±0.029	8.93±0.96	164±3.15	6.59±0.05
F2	Best	22.11±0.11	0.169±0.025	10.90±0.10	154±3.91	6.82±0.02
F3	Best	22.21±0.20	0.177±0.019	10.51±0.11	169±1.42	6.81±0.07
F4	Good	24.56±0.09	0.191±0.020	11.15±0.64	172±2.12	6.97±0.05

Table 5. Evaluation Parameters of Formulation

Formulation	Surface texture	% moisture absorption	%moisture loss	%drug content	In vitro disintegration time (s)
F 0	++ -	2.4±0.54	2.10±0.89	90.44±0.01	21.3±1.25
F 1	+++	3.9±0.47	2.97±0.33	95.95±0.08	12.5±1.14
F 2	+++	3.7±0.99	2.99±0.12	97.41±0.54	09.9±1.04
F3	+++	4.2±0.19	3.16±0.74	97.01±0.51	17.4±1.33
F4	+++	4.7±0.77	3.93±0.14	96.15±0.78	14.7±1.02

(+) Indicates Smooth Surface, (-) Indicate Rough Surface.

Table 6. Drug Release Profile of Formulation

Time (in min)	Cumulative % Drug Release of Formulation				
	F 0	**F1**	**F2**	**F3**	**F4**
0	0	0	0	0	0
2	4.36±1.02	7.24±0.87	14.36±0.23	9.62±0.98	11.44±0.66
4	9.92±0.99	14.32±o.76	29.82±0.45	20.40±0.75	25.39±0.92
6	20.91±0.56	27.42±0.89	41.09±0.88	32.99±0.24	37.00±0.58
8	28.48±0.94	39.38±1.08	54.99±0.34	41.62±0.78	50.63±0.67
10	36.39±0.78	52.33±1.25	69.83±0.45	57.72±0.31	62.30±0.39
12	45.92±0.59	68.64±0.98	83.22±0.36	74.02±1.34	75.04±0.88
14	59.12±1.45	76.68±1.76	91.90±0.78	85.97±0.76	87.02±0.81
16	69.98±0.99	84.33±1.02	96.03±0.68	90.48±0.19	92.45±0.97

Each value is the mean ± SD, n = 3 determinations

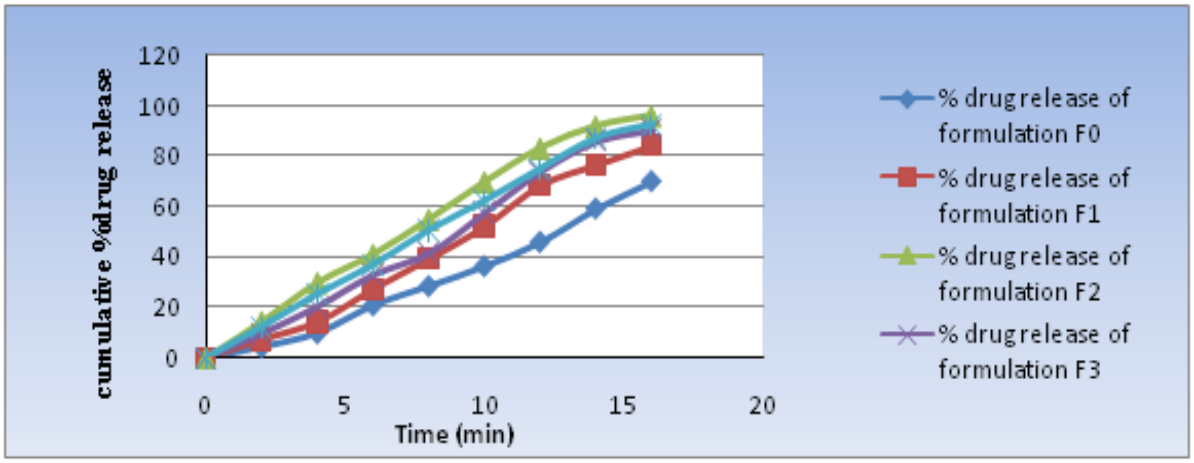


Figure 3. Dissolution Profile of Formulation F0-F4

Stability studies of optimized formulation

The optimized F2 formulation was selected for stability studies on the basis of high % drug release, results of in vitro disintegration time and results of folding endurance. From these results it was concluded that, formulations F2 is stable and retained their original properties with minor differences. The in vitro release profile of F2 formulation at 40°C/75% RH conditions after 60 days was 94.68 ± 0.45 in 16min which indicated that there is no or minor alteration of original properties after storage.

Mechanical properties of formulation F2 after stability studies:

Table 7. Stability studies of optimized formulation F2 of mechanical properties

Parameters	Initial	After 7days	After 30 days	After 60 days
Surface pH	6.82±0.02	6.82±0.04	6.89±0.05	6.7±0.08
Tensile strength (kg/mm^2)	10.90±0.10	10.90±0.03	10.65±0.08	10.00±0.02
Folding endurance	154±3.91	154±3.87	155±2.56	157±1.12
Drug content (%)	97.41±0.54	97.41±0.22	97.01±0.39	96.65±0.88
Disintegration time (sec)	09.9±1.04	09.9±2.22	10.1±1.39	11.4±1.01

Drug release profile of formulation F2 after stability studies:

Table 8. Cumulative % Drug Release of optimized Formulation

Time (min)	% CDR before stability study	% CDR after 7 days stability study	% CDR after 30 days stability study	% CDR after 60 days stability study
0	0	0	0	0
2	14.36±0.23	14.31±0.19	14.11±1.09	13.84±0.96
4	29.82±0.45	29.81±0.76	28.03±0.67	27.65±0.56
6	41.09±0.88	41.00±0.56	40.89±0.98	40.01±0.29
8	54.99±0.34	54.96±0.67	54.02±1.03	53.10±0.98
10	69.83±0.45	69.79±0.21	68.00±0.49	67.09±1.36
12	83.22±0.36	83.19±0.45	82.98±0.88	81.05±1.24
14	91.90±0.78	91.85±0.47	90.94±1.42	89.90±0.76
16	96.03±0.68	96.00±0.89	95.34±0.99	94.68±0.45

Summary

Main purpose of this study was effect of surfactant on the mouth dissolving film and which quantity of surfactant was used for this film.

In the present study, fast dissolving oral thin films of Promethazine hydrochloride were prepared successfully by using film forming polymer hydroxy propyl methyl cellulose E 15(HPMC) were prepared by solvent casting method. Promethazine hydrochloride fast dissolving films were designed to improved patient compliance and better bioavailability.

All the prepared film was good, almost transparent with better flexibility. Total five formulations were prepared. Hydroxy propyl methyl cellulose E15 only was used as film former in formulation F0, and in this formulation no surfactant were used,

whereas Polyethylene glycol 400(plasticizer) was used in constant ratio in formulation F0-F4. Sodium lauryl sulfate (surfactant) was used in different ratio in the formulation F1-F2, And Microcrystlline cellulose (surfactant) was used in different ratio in the formulation F3-F4. And the other ingredients were used in same ratio in all formulation.

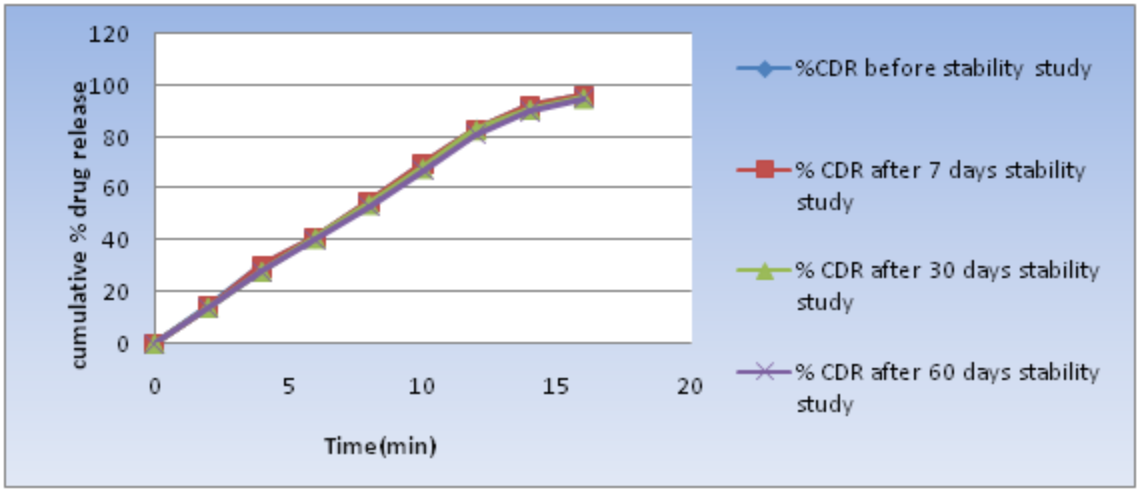


Figure 4. Dissolution Profile of Optimized Formulation

The films were evaluated for various properties including: Transparency, Weight variation, Film Thickness, Tensile strength, Folding endurance, Surface pH, Surface texture, %Moisture absorption, % Moisture loss, %Drug content, In vitro disintegration time and In vitro drug release time.

The appearance of the film formulations F0 to F4 of visualize. The visual inspection of formulation F0 was good transparency and lightly smooth surface, F1, F2, F3 were best transparency and very smooth surface, and F4 was good transparency and very smooth surface.

The optimized formulation was selected for stability studies on the basis of in-vitro disintegration time and results of folding endurance. The folding endurance of the all the batches were F0 (184±2.54), F1 (164±3.15), F2(154±3.91), F3(169±1.42), F4(172±2.12). The disintegration times of the films were evaluated using simulated salivary fluid (pH6.8), and disintegration time of all batches were F0 (21.3±1.25), F1(12.5±1.14), F2(09.9±1.04) , F3(17.4±1.33),F4(14.7±1.02).

Conclusion

The present study demonstrated that SLS and MCC Surfactant can be used for the preparation of Promethazine Hydrochloride fast dissolving film.

The most important advantage of the fast dissolving films is that it contains a lower drug dose, adequate for therapeutic effect. Moreover, this film is very contented because it is non-irritant and self administration is possible.

This study shows that it is possible to formulation of different surfactant with different concentration were used in Promethazine Hydrochloride drug fast dissolving film formulation. The intention of obtaining better therapeutic efficiency

with increasing bioavailability and improving patient compliance.

Fast dissolving Films were found to be satisfactory when evaluated for thickness, weight uniformity, in-vitro drug release, folding endurance, drug content and disintegration time. The surface pH of all the films was found to be neutral.

It was observed that from the result, F2 formulation was optimized formulation and its average weight was 22.11±0.11 .F2 formulation having Promethazine Hydrochloride25.90% (5.55mg), HPMC E15 41.45% (8.89mg), Propylene Glycol 400 12.43% (2.67mg), SLS 2.07% (0.44mg), Citric acid anhydrous 4.14% (0.89mg), Sucrose 12.43% (2.67mg), Titanium Dioxide 0.51%(0.11mg), strawberry 1.03%(0.22mg) and distilled water quantity sufficient.

The in vitro drug release in optimized formulation F2 was found to be 69.83±0.45 % in 10 min and disintegrates within 09 second which release drug rapidly and gives action fast, where as other batches shown late drug releases. Thus the Present study's aim was fulfilled with Increases dissolution rate helps to giving a quick onset of action.

Stability studies of F2 formulation indicated that there is no significant change in drug content, mechanical properties and in vitro dissolution time. A Sweetening agent Sucrose and Flavoring agent strawberry improves Patient compliance and better mouth feeling. Fast dissolving film can be a potential novel drug dosage form. So, Fast dissolving films have several advantages over the conventional dosage forms, hence they are of great importance for pediatric, geriatric and also for general population.

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