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DEVELOPMENT AND CHARACTERIZATION OF TASTE MASKED ORODISPERSIBLE FILM OF CHLORPROMAZINE HYDROCHLORIDE

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Abstract: Thin-film drug delivery, also referred to as orodispersible film has emerged as an advanced alternative to the traditional tablets, capsules, and liquids. The present work investigates the improvement in solubility to have a rapid onset of action, and palatability of chlorpromazine hydrochloride (CPZ) by developing an orodispersible film (ODF) using the solvent casting method. CPZ indicated for the control of nausea and vomiting, and in the treatment of schizophrenia in adults and children, has low bioavailability (30-50%) when taken orally as a tablet due to extensive first-pass metabolism. Moreover, it is very bitter and has an unpleasant after-taste. In this study, seven placebo formulations were prepared containing different concentrations of film-forming polymers (hydroxypropyl methylcellulose E5 and polyvinyl pyrrolidone K30) and plasticizers (propylene glycol and glycerin), and the most suitable polymer-plasticizer combination was screened to obtain required physical properties. CPZ loaded film was made using an optimized polymer-plasticizer combination employing sucralose and menthol as taste-masking agents. Drug-loaded films were transparent, smooth, and disintegrated in 14.67 ± 1.53 sec. Films showed a folding endurance of >400 , tensile strength of 1.54 ± 0.11 N/mm² and percentage elongation of $18.7\% \pm 0.50$ suggesting good mechanical strength. More than 90% drug release was obtained within 3 min in dissolution media. FTIR analysis displayed no significant interactions between drug and polymer. The film was also found palatable with a sweet taste by human volunteers. Hence the taste-masked films of CPZ can be a potential alternative to conventional oral dosage forms and may also enhance patient compliance.

Keywords: Chlorpromazine HCl, orodispersible film, solvent casting, HPMC E5, sucralose, taste masking, *in vivo* taste evaluation, patient compliance

The oral route of drug administration is among the most preferred routes due to its convenience, cost-effectiveness, acceptability, and a high degree of patient compliance. However, conventional oral solid dosage forms have some problems associated with them like the first-pass effect, difficulty in swallowing, and fear of choking especially in pediatric and geriatric patients. Bedridden, nauseous, unconscious, and non-compliant patients also have limitations for the usage of the traditional oral solid dosage forms (1).

Another detrimental reason for nonadherence to medication therapy is the bitter taste of drugs and unpleasant after taste which may result in failure to achieve desired outcomes in concerned patients. Although many solid oral dosage forms (e.g., tablets

and capsules) have the advantage of masking or encapsulating bitter taste, such means have been proved futile for many children because they often cannot or will not swallow tablets or capsules. Liquid formulations typically are used between 6 and 8 years of age but there is great variation in the ability of older children (also teenagers and adults) to swallow tablets and capsules (2).

Recently, fast-dissolving drug delivery systems gained the interest of pharmaceutical technologists as an alternate approach to conventional oral solid dosage forms. The development of Oral Strip Technology has attracted much attention amongst the fast drug releasing systems. A film that rapidly disintegrates in the oral cavity is generally called an orodispersible film (ODF) as termed by European

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Medicines Agency (EMA) or simply as oral soluble film according to US FDA (3, 4). This newer drug delivery system consists of a very thin film or strip usually of the size of a postage stamp and when placed on the tongue or any oral mucosal tissue, gets hydrated on coming in contact with saliva, adheres to the site of application, and rapidly disintegrates and dissolves to release the drug for oromucosal or/ and intragastric absorption. ODFs also address swallowing issues encountered with pediatric and geriatric patients and can be effectively used in various medical conditions like motion sickness, allergic attack, acute pain, and acute coughing where a rapid onset of action is desired. The oral and sublingual drug delivery via ODF also has the potential to lower the dosing and improve the onset of action. ODFs increase patient compliance as they are easy to carry, can even be taken in conditions when there is no access to water and may enhance patient acceptability by virtue of improvement in the taste of bitter drugs (5, 6).

Chlorpromazine hydrochloride (CPZ) being one of the antipsychotic drugs included in the World Health Organization's List of Essential Medicines (2019) was selected as a model drug (7). Other than its antipsychotic uses, CPZ is indicated for the control of nausea and vomiting, is recommended in intractable hiccups, and for relief of restlessness before surgery. It is now mainly used in the treatment of schizophrenia in adults and children. Marketed preparations of CPZ include tablets (10, 25, 50, and 100 mg) and IV/IM injection (25 mg/mL) (8, 9). CPZ has low oral bioavailability (30-50%) due to extensive first-pass metabolism. Moreover, it is very bitter and has an after taste (10-12). Figure 1 represents the chemical structure of CPZ.

Figure 1. Chemical structure of Chlorpromazine HCl

The proposed study was aimed to develop ODF of CPZ by solvent casting method to enhance its clinical outcomes and improve palatability, especially in pediatric and elderly patients. Firstly, placebo films were prepared using different concentrations of film-forming polymers (hydroxypropyl methylcellulose E5 and polyvinyl pyrrolidone K30) and plasticizers (propylene glycol and glycerin), and later the most suitable polymer-plasticizer

combination, imparting film the required physical properties, was screened. Then CPZ loaded ODFs were made using an optimized polymer-plasticizer combination employing sucralose and menthol as taste-masking agents. Prepared ODFs were delineated for physicochemical and mechanical properties. Taste concealing was determined by *in vivo* taste evaluation using human volunteers. Based on a five-point scale for taste evaluation, the developed ODF was found to be palatable and acceptable by the human volunteers.

EXPERIMENTAL

Materials

Chlorpromazine HCl was purchased from XABC Biotech Co., Ltd., China. All other chemicals were obtained from different sources; Hydroxypropyl methylcellulose E5 (HPMC E5), polyvinyl pyrrolidone (PVP K-30), propylene glycol (PG) and glycerin (Hangzhou Zhongbao Import and Export Corporation, China), sucralose (Techno (Fujian) Food Ingredients Co, China), menthol (Shanghai Polar Bear Pharmaceutical Co., China), and citric acid, ethanol, hydrochloric acid (HCl), sodium hydroxide (NaOH) and sodium chloride (NaCl), potassium dihydrogen phosphate, disodium hydrogen phosphate (Merck Darmstadt Germany). All chemicals and solvents used were of analytical grade.

Preparation of placebo film

The solvent casting method was employed for the casting of ODF formulations (F1-F7) without the drug (13). Placebo films were formulated using polymers HPMC E5 and PVP K30 and the plasticizers PG and glycerin alone and in combination (Table 1). In this context, the polymer was dissolved in the solvent (with continuous stirring for one hr) followed by the addition of a plasticizer. The final volume was made up to 50 mL with the solvent (Table 1) and the film solution was sufficiently de-aerated to remove all the entrapped air bubbles. Suitable volume (10 mL) was cast onto glass Petri plates of uniform sizes and dried in the oven at 45°C for four hr or till a dry film was formed.

The most suitable placebo formulation was selected based on the transparency, smoothness, and peelability (14). Different volumes (7, 8, 9, 10 mL) of the selected placebo formulation were then cast onto the Petri plates. Films were investigated for appearance, peelability, smoothness, handling, and disintegration time (Table 2) to identify the most appropriate volume for drug loading.

Table 1. Composition and physical properties of placebo film formulations.

Formulations							
Ingredients	F1	F2	F3	F4	F5	F6	F7
HPMC E5 (g)	2.2	2.2	1.1	2.2	1	1	1
PVP K30 (g)					0.5	0.5	0.5
PG (g)	0.4		0.7	1.4		0.5	0.5
Glycerin (g)		0.4	0.8	1.5	0.5		0.5
Ethanol (mL)				10	20	50	
Water (mL)	50	50	50	50	50		50
Physical properties of films	Transparent, smooth, not peelable	Transparent, smooth, not peelable	Transparent, smooth, not peelable	Transparent, Smooth, peelable	Semi-transparent, rough, difficult to peel	Opaque, rough, not peelable	Opaque, rough, not peelable

Table 2. Evaluation of the physical properties and disintegration time of films obtained after casting different volumes of the selected placebo formulation.

Parameters	Volume casted into Petri plate (mL)			
	7	8	9	10
Physical properties	Transparent, smooth, difficult to peel	Transparent, smooth, peelable	Transparent, smooth, peelable	Transparent, smooth, peelable
Handling	Poor	Satisfactory	Satisfactory	Satisfactory
Disintegration time (sec)	13	24	42	55

Preparation of drug-loaded films

To prepare drug-loaded films, the selected polymer in varying concentrations as shown in Table 3 was dissolved in 30 mL of distilled water with continuous stirring for one hr (Solution 1). CPZ was added to this solution and mixed till completely dissolved. Sucralose and citric acid were added to this solution and mixed well. Accurately weighed quantities of PG and glycerin were dissolved separately in 10 mL of ethanol and 1 mL of menthol (1% ethanolic solution) was added to it (Solution 2). Solution 2 was added to Solution 1 and volume was made up to 50 mL with distilled water. The pH of the final solution was adjusted to 6.2 by adding few drops of 0.1 M NaOH (15) followed by sonication for one hr to remove all entrapped air bubbles.

The selected volume of the film solutions was cast onto glass Petri plates of area 59.42 cm² (the quantity of the drug was calculated accordingly to have 25 mg of CPZ/film/4 cm²) and allowed to dry in the oven at 40°C for 5 hr. The films were carefully removed from the Petri plate and checked for any imperfections. Films were cut according to the size required (square film: 2 cm length, 2 cm width). The best formulation was chosen based on the physical appearance, peelability, folding endurance, and disintegration time (Table 3). This final film was investigated for various physical and mechanical tests, *in vitro* dissolution, and taste masking (16).

Characterization of ODFs of CPZ

Physical appearance

The appearance of the ODFs (n = 10) was evaluated by visual observation. Films were measured regarding thickness at five points (four corners and center) using a micrometer screw gauge. Films with nicks or bubbles or those with a mean thickness variation of greater than 5% were excluded from the analysis (4, 5).

Weight variation and surface pH

The uniformity of weight of ODFs (n = 20) was checked by weighing each ODF. Surface pH measurement was performed at room temperature by adding 4 mL distilled water on the top of the film (2 × 2 cm²) contained in a petri dish. After the film was completely disintegrated, the pH of the solution was determined by pH meter (14) and the average of three determinations was calculated.

Disintegration test

A disintegration test was performed by placing the ODF in a Petri dish containing 10 mL of distilled water. The Petri dish was swirled clockwise manually after every 10 sec. The time taken by the ODF to disintegrate was noted and a mean of three determinations was taken (14).

Folding endurance test

The folding endurance test is an indication of the brittleness of the film. The folding endurance was

Table 3. Composition and physical evaluation of ODFs of CPZ.

Formulation				
Ingredients	FA	FB	FC	FD
CPZ (g)	2.321	2.321	2.321	2.321
HPMC E5 (g)	1	1.5	2.0	2.5
PG (g)	1.4	1.4	1.4	1.4
Glycerin (g)	1.5	1.5	1.5	1.5
Sucralose (g)	0.25	0.25	0.25	0.25
Citric acid (g)	0.20	0.20	0.20	0.20
1% Ethanolic solution of menthol (mL)	1	1	1	1
Ethanol (mL)	10	10	10	10
Water (mL)	50	50	50	50
Physical properties	Transparent, difficult to peel	Transparent, difficult to peel	Transparent, peelable	Transparent, peelable
Handling	Low	Low	Satisfactory	Satisfactory
Folding endurance	150	300	> 400	> 400
Disintegration time (sec)	10	12	17	42

determined by folding the film sample at the same place till the film breaks or visible cracks are developed. It is expressed as the number of times the film can be folded without breaking (1).

Tensile strength and percent elongation

Tensile strength is the maximum stress applied to a point at which the film specimen ruptures. The tensile strength of the film was tested to assess the elasticity and strength of the film formulation (1). European Standard EN ISO 527-3 guidelines were followed to determine tensile strength (17). The film free from bubbles or imperfections was placed between two clamps held 50 mm apart using Tensile Strength Tester (Lloyd Instruments, UK) and pulled at a rate of 5 mm/min. The measurements were performed in triplicate and tensile strength was determined as per the following equation

$$\text{Tensile Strength} = \frac{\text{Force at break (N)}}{\text{Cross – sectional area (mm}^2\text{)}}$$

To determine percentage elongation, the distance between the grips of the tensile strength tester was measured before and after the fracture of the film on applying force (1). The percentage elongation of the film was calculated using the formula

$$\text{Percentage Elongation} = \frac{D_f - D_o}{D_o} \times 100$$

where,

D_o = Distance between the grips before fracture of the film.

D_f = Distance between the grips after fracture of the film

Uniformity of content

The uniformity of contents of the films (n = 10) was determined by immersing ODF in a 100 mL volumetric flask containing 2 mL of ethanol and 60 mL of 0.1 M HCl. The solution was sonicated for 15 min and volume was made up to 100 mL with 0.1 M HCl. After suitable dilutions with 0.1 M HCl, the absorbance was measured by UV/Visible spectrophotometer (U-2800 BMS, UK) at 254 nm. The percent drug content in each film was calculated by comparing the absorbance of the film with a standard solution of pure CPZ.

Drug content analysis

A sample of ODFs (2 x 2 cm²) equivalent to 250 mg of CPZ was placed in a 500 mL volumetric flask containing 10 mL of ethanol and 300 mL of 0.1 M HCl. The solution was shaken for 15 min and volume was made up to 500 mL with 0.1 M HCl. The solution was filtered followed by further dilution with 0.1 M HCl. Drug content was determined by comparing absorbance with a standard solution of the pure drug as described above (18).

In vitro dissolution study

In vitro drug release studies were performed in three media i.e., 0.1 M HCl, phosphate buffer pH 6.8, and distilled water (volume: 500 mL; temperature: 37 ± 0.5°C) in USP Type II (Paddle type) dissolution apparatus at 50 rpm. Sample aliquots (5 mL) were withdrawn at predetermined time intervals 0.5, 1, 2, 3, 4, 5, and 10 min, and the same volume of the medium was reinstated after each withdrawal to maintain

the sink conditions. Samples were analyzed by UV/Visible spectrophotometer at 254 nm after appropriate dilutions. Percent release of the drug was calculated from the standard curve (concentration range: 2-12 µg/mL). The drug release data were also fitted to various kinetic models like Zero order, First order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell using DD Solver free add-in extension for MS Excel® (19) to establish the best fit model (20, 21).

Fourier transform infrared (FT-IR) spectroscopy

Infrared spectra of CPZ, HPMC E5, and the drug-loaded film were obtained to determine the drug-polymer interactions if any by using FT-IR Spectrophotometer (Alpha Bruker, UK). The scanning range was 4000 to 400 cm⁻¹.

Differential scanning calorimetry (DSC)

DSC thermograms of pure drug, polymer, drug-polymer physical mixture, and film were obtained to get information about the thermal behavior and physical characteristics of the drug. Samples were placed in alumina crucibles in a nitrogen atmosphere. The differential scanning calorimeter (SDT Q-600, TA Instruments, USA) was run at a constant heating rate of 15°C/min with a nitrogen flow of 100 mL/min over a temperature range.

Taste evaluation of ODFs of CPZ

The taste evaluation study protocol was approved by the Institutional Ethical Review Committee, Lahore College for Women University, Lahore, Pakistan (Reference No. Dir/LCWU/157A). Film formulation was evaluated in twelve healthy human volunteers who were asked to gargle the mouth with 200 mL of water before the test. The volunteers were instructed to place the film (2 x 2 cm²) on the tongue until complete disintegration occurred and to score taste evaluation parameters of the film as per Table 4. Then the volunteers were asked to spit the sample and rinse the mouth with 200 mL of water (5, 22).

RESULTS AND DISCUSSION

In the current study, the solvent casting method was employed to form ODFs of CPZ. Literature has shown the solvent casting method as the most commonly used method for preparing ODFs because of certain advantages over other methods (13, 23).

Selection of placebo formulation

Seven placebo formulations were prepared using film formers and plasticizers either alone or in combination and assessed for peelability and physical appearance (Table 1). Previous studies have revealed that PVP K30 when used alone did not prove to be a good film former owing to the formation of films that were difficult to peel. Therefore, PVP K30 was used in combination with HPMC E5. Contrary, HPMC E5 alone gave better films compared to that made with a combination of HPMC E5 and PVP K30 in terms of peelability and transparency. This finding is consistent with the previous literature using HPMC E5 as a film former (14). It was also noticed that formulations employing PG and glycerin (plasticizers) in combination gave better film properties compared to the formulations in which either PG or glycerin was used as a plasticizer. Hence, formulation F4 containing 4.4% w/v HPMC E5 and 5.8% w/v total plasticizer concentration (2.8% w/v PG plus 3% w/v glycerin) was selected for drug loading.

Then different volumes (7, 8, 9, and 10 mL) of the formulation F4 were cast to select the most suitable volume resulting in desirable physical properties (Table 2). It was observed that films made by casting 7 mL volume were difficult to peel and handle. Casting 8 mL, 9 mL, and 10 mL volumes gave better physical properties but the disintegration time of the films was found to be increased (24, 42, and 55 sec respectively) with an increase in volume. Hence based on the physical properties and disintegration time, 8 mL volume was chosen for casting the drug-loaded films since disintegration time of less than 30 sec was a desirable film property (22).

Table 4. Taste evaluation score criteria.

Taste	After taste	Acceptability	Mouthfeel	Score
Very bitter	Very bitter	Very poor	Gritty, irritating	1
Bitter	Bitter	Poor	Gritty	2
Slightly bitter	Slightly bitter	Acceptable	Slightly gritty	3
Slightly sweet	Slightly sweet	Good	Smooth	4
Sweet	Sweet	Very good	Very smooth	5

Formulation selection of drug-loaded films

Four formulations of drug-loaded films (FA, FB, FC, FD) were made by varying the polymer concentration and keeping plasticizer concentration constant (Table 3) to select the polymer concentration that will impart the film a disintegration time of less than 30 sec and required folding endurance. The study disclosed that disintegration time and folding endurance increased with increasing polymer concentration and was found to be in line with previously reported literature (24). Formulations FA and FB gave films which were difficult to peel (Figure 2) and their folding endurance was also less. Formulations FC and FD appeared to have good physical properties, a folding endurance greater than 400, and a disintegration time of 17 and 42 sec (Table 3) respectively. Therefore, formulation FC (Figure 2) was picked for further investigation of the film properties and taste masking.

Figure 2. (i) Film (FB) not peelable in one piece; (ii) Film (FC) easily peeled from the Petri plate; (iii) ODF of CPZ (2 x 2 cm²) held between fingertips.

Characterization of drug-loaded ODFs

Table 5 represents the various physical and mechanical properties of CPZ film. On visual inspection, films were transparent, smooth, and flexible. The thickness of ODFs (n = 10) was determined at five locations. The thickness of individual locations ranged from 0.12-0.17 mm. The mean of five locations ranged from 0.13-0.16 mm (Table 5). Weight of ODFs (n = 20) ranged from 85-91 mg while the mean weight was 87.8 mg $\pm$ 1.64. Thickness and uniformity of weight of ODFs manifest the uniformity of dose distribution in the ODFs. The mean surface pH of ODFs (n = 3) was 6.44 $\pm$ 0.03. The pH of a buccal

mucosal surface is about 6.8. Too acidic or alkaline pH of film formulation can irritate the buccal mucosa. The mean surface pH of the ODFs was fairly close to the pH of buccal mucosa suggesting that the ODF of CPZ can be safely administered into the oral cavity without causing irritation (25). Mean disintegration time was 14.67 $\pm$ 1.53 sec. Disintegration time is directly related to the drug dissolution. An early disintegration of the film aids in faster dissolution. In CPZ film, a fast disintegration can be attributed to citric acid which acts as a saliva stimulating agent and can further improve the disintegration time of the film (26).

Folding endurance indicates the brittleness or flexibility of the film. The ability of the film to bear folding up to 300 times is considered satisfactory for good ODFs (1). ODFs of CPZ had a folding endurance of greater than 400 showing that the film was tough and had good flexibility (Table 5) and also in agreement with previously reported studies (4).

The tensile strength of ODFs is important to resist mechanical stress during production, storage, transportation, handling, and application. ODFs should ideally possess high percent elongation and moderate tensile strength (1). The ODFs of CPZ had a mean tensile strength of 1.54 N/mm² $\pm$ 0.10 and percent elongation of 18.7% $\pm$ 0.46. These findings were comparable with the previous studies (14). The prepared film had a content uniformity of 96.65-101.36% while the drug content was found to be 99.84% $\pm$ 1.55 based on the assay. These results indicated that the drug was uniformly distributed in the film (Table 5).

In vitro dissolution study

Figure 3 compares the *in vitro* drug release profile of the CPZ loaded ODFs in three media (phosphate buffer pH 6.8, 0.1 M HCl, and distilled water) at time intervals of 0.5, 1, 2, 3, 4, 5, and 10 min. It was

Table 5. Evaluation parameters of ODFs of CPZ.

Parameter	Mean $\pm$ SD	Min	Max
Thickness (mm)(n = 10)	0.15 $\pm$ 0.01	0.13	0.16
Weight variation (mg) (n = 20)	87.8 $\pm$ 1.64	85	91
Surface pH (n = 3)	6.44 $\pm$ 0.03	6.41	6.46
Disintegration time (sec) (n = 3)	14.67 $\pm$ 1.53	13	16
Folding endurance (n = 3)	> 400 $\pm$ 0	> 400	> 400
Percentage elongation (%) (n = 3)	18.7 $\pm$ 0.50	18.2	19.2
Tensile strength (N/mm ²) (n = 3)	1.54 $\pm$ 0.11	1.44	1.66
Content uniformity (drug content%) (n = 10)	99.33 $\pm$ 1.90	95.65	101.36
Assay (%) (n = 3)	98.84 $\pm$ 1.55	98.17	101.22

Table 6. Dissolution profile of ODFs of CPZ in different media.

Time (mins)	Drug release (%) in phosphate buffer pH 6.8			Drug release (%) in 0.1 M HCl			Drug release (%) in distilled water		
	Mean $\pm$ SD (n = 6)	Min	Max	Mean $\pm$ SD (n = 6)	Min	Max	Mean $\pm$ SD (n = 6)	Min	Max
0.5	9.67 $\pm$ 0.87	8.59	10.68	16.77 $\pm$ 0.93	15.70	18.01	22.56 $\pm$ 1.80	19.82	24.82
1	25.51 $\pm$ 1.21	23.96	27.53	78.73 $\pm$ 2.38	75.60	81.68	73.20 $\pm$ 2.89	68.27	76.72
2	85.21 $\pm$ 2.90	80.34	88.12	96.67 $\pm$ 1.03	95.49	98.19	84.74 $\pm$ 1.87	81.56	86.85
3	99.26 $\pm$ 1.12	97.55	100.51	98.37 $\pm$ 0.83	97.33	99.70	90.68 $\pm$ 1.91	87.37	92.33
4	100.87 $\pm$ 1.12	98.93	102.07	99.99 $\pm$ 0.99	98.27	101.03	98.58 $\pm$ 1.46	96.78	100.64
5	100.49 $\pm$ 1.11	98.43	101.60	99.80 $\pm$ 0.96	98.15	100.76	99.44 $\pm$ 1.21	97.78	100.77
10	100.04 $\pm$ 1.05	98.34	101.18	99.30 $\pm$ 0.91	98.03	100.30	99.09 $\pm$ 1.06	97.52	100.34

Table 7. Release kinetics modeling of ODFs of CPZ.

Medium	R ² - value				
	Zero Order	First Order	Higuchi	Hixon-Crowell	Korsmeyer-Peppas
Phosphate buffer pH 6.8	0.8476	0.8362	0.7816	0.8905	0.8759
0.1 M HCl	0.1900	0.8277	0.7026	0.8675	0.7098
Distilled water	0.1769	0.8931	0.7846	0.8865	0.7966

found that more than 95% drug release was obtained within 3 min in all three media (Table 6). The salivary pH of normal individuals ranges from 6.2 to 7.4. The drug release profile in the phosphate buffer pH 6.8 was of prime interest since it depicts the drug release from ODF in the oral cavity. It can be seen that the initial drug release from the ODF was slow i.e. 9.67% $\pm$ 0.87 in 30 sec and 25.51% $\pm$ 1.21 within 1 min which is possibly due to the time taken by the polymer to get hydrated followed by subsequent dissolution and release of the drug from the ODF in phosphate buffer pH 6.8 (25).

Hixon-Crowell model best fitted in phosphate buffer pH 6.8 and 0.1 M HCl suggesting that drug diffusion depends on the surface area of the ODF (Table 7). Results have shown a change in surface

area with the progressive dissolution of matrix as a function of time. It can be attributed to the fact that on coming in contact with the dissolution medium the film polymer first hydrates and subsequently the drug dissolves as a result of film disintegrations in the medium (25). It further suggested that the drug release rate from the ODF is dependent on the dissolution of drug particles and not on drug diffusion from the film (20). In distilled water, the film followed the first order kinetic model which means that drug release from ODF is concentration-dependent (Table 7).

Fourier Transform Infrared (FT-IR) spectroscopy

The possible interaction between CPZ and HPMC E5 was investigated by infrared spectroscopy. Infrared spectra of pure CPZ, HPMC E5, and drug-loaded film are shown in Figure 4. Drug spectrum

Figure 3. Comparison of *in vitro* drug release profile of ODFs of CPZ in different media.

Figure 4. FT-IR spectrum of CPZ pure drug, HPMC E5 and CPZ film.

Figure 5. DSC thermograms of CPZ pure drug, HPMC E5, physical mixture and CPZ film.

shows characteristic absorption peaks at 2933.62 cm^{-1} (aliphatic C–H stretching), 2394.12 cm^{-1} (indicating $\text{H}_3\text{C}-\text{NH}^+$ stretching and combination mode), 1564.21 cm^{-1} (indicating phenyl ring vibrational mode), 1456.31 cm^{-1} (C–H deformational mode) and 750.37 cm^{-1} (aromatic C–H bending mode) (27, 28). HPMC E5 exhibits principal peaks at $3500\text{--}3400\text{ cm}^{-1}$ (OH stretching), 2990 cm^{-1} (methyl and hydroxypropyl group stretching), $2550\text{--}2500\text{ cm}^{-1}$ (OH stretching), $1300\text{--}1250\text{ cm}^{-1}$ epoxide (cyclic C–O–C), $1100\text{--}1000\text{ cm}^{-1}$ (stretching vibrations of C–O–C group), $1000\text{--}950\text{ cm}^{-1}$ (pyranose ring). Approximately the same absorption peaks of CPZ and HPMC E5 are present in the spectrum of the film suggesting no significant interactions between drug and polymer (29, 30).

Differential Scanning Calorimetry

Figure 5 shows DSC thermograms of pure CPZ, HPMC E5, drug-polymer physical mixture, and film. A broad shoulder endotherm with a peak temperature at 198°C is shown for both pure CPZ and its physical mixture with HPMC E5 indicating that the pure drug was in a crystalline state. On the other hand, no melting peak was observed for the drug-loaded film. This disappearance of the endothermic peak indicated that CPZ is present in an amorphous or a dissolved state in the prepared film due to crystallization inhibition by HPMC E5 (22, 30, 31).

Taste evaluation

Results of taste evaluation parameters including taste, after taste, mouthfeel, and overall acceptability are depicted in Figure 6. Taste evaluation parameters were scored based on the scoring criteria given in Table 4 and taste evaluation was performed according to the protocol approved by the Institutional Ethical Review Committee. Results showed that the

Figure 6. Taste evaluation of ODFs of CPZ by human volunteers (n = 12).

mean score for the taste of ODF was 5 signifying that the taste sensed by human volunteers was sweet. Mouthfeel and after taste got scores of 4.6 and 4 and found to be smooth and slightly sweet. In terms of overall acceptability, the ODFs were scored between acceptable and good.

Hence CPZ was successfully developed in ODF by solvent casting technique employing HPMC E5 as polymer and PG and glycerin as plasticizers. The prepared ODFs showed desirable physical and mechanical properties (like folding endurance, tensile strength, and percent elongation), uniformity of drug content, and *in vitro* drug release. A disintegration time of less than half a minute was successfully achieved. Moreover, ODFs were found to be palatable and acceptable by the majority of volunteers crediting to the selected polymer-plasticizer combination, sucralose, and menthol.

CONCLUSION

It can be concluded that CPZ ODF can prove a potential drug dosage form in the pharmaceutical market because it can enhance the onset of action for CPZ in the treatment of emesis and schizophrenia. It can also increase compliance among the patient population.

Conflicts of interest

The authors declare no conflict of interest.

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