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Formulation and characterization of orodispersible film containing diltiazem hydrochloride with taste masked effects

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Abstract: Orodispersible film (ODF) is a better alternate to oral disintegrating tablets owing to its ease in application and subsequent patient compliance. This study investigates an improvement in physico-mechanical properties and palatability of Diltiazem Hydrochloride (DTZ) by formulating ODF employing solvent casting method. DTZ, used in the treatment of angina and hypertension, undergoes extensive presystemic metabolism and gives an incomplete bioavailability of 35-40%. DTZ also manifests a very bitter taste and after taste. DTZ was formulated into films using different polymer concentrations of Hydroxypropyl methylcellulose ethocel5 and Carboxymethyl cellulose and plasticizer levels of Propylene glycol and Glycerin to screen appropriate polymer-plasticizer combination. Optimized film disintegrated in 10.0±1.53 sec and appeared to be clear and smooth, and almost 100% of the drug release was achieved within 4min from the ODF. Film revealed a good mechanical strength with folding endurance of >260, tensile strength of 1.36±0.11 N/mm^2 and %elongation of 15.47±0.47 %. FTIR and DSC showed compatibility between the drug and polymer. Film demonstrated a slightly sweet taste and after taste as well as an acceptability by the human volunteers. In conclusion DTZ was successfully formulated into film with improved physical properties and taste and could be beneficial to patients with cardiovascular disorders.

Keywords: Diltiazem HCl, ODF, HPMC E5, propylene glycol, solvent casting, saccharin Na, taste concealing, taste evaluation, patient compliance.

INTRODUCTION

The oral route, despite of a preferable method of drug administration, has certain challenges including first pass metabolism, dysphagia and fear of obstruction (Barkat *et al.,* 2021). According to an estimation, a large percentage of general population, elderly home patients and hospitalized patients have dysphagia, a result of several diseases including cardiovascular disorders (Visser *et al.*, 2020). Dysphagia compels caregivers to crush pills and blend with food to ease ingestion. However, as a result of these practices, dosing errors may occur leading to reduced therapeutic efficacy or even toxicity. Furthermore oral solid dosage forms are not regarded ultimate for bedridden, nauseated, insensible as well as for young and older patients (Karki *et al.,* 2016).

Additionally, another major barrier preventing patients to get adhered to a recommended drug regime has been documented as the obnoxious taste of active pharmaceutical ingredients (APIs) in oral formulations. Patient acceptability and compliance are dictated by the taste, which plays a fundamental role in defining the market penetration and commercial realization of oral products, specifically in pediatric population (Scarpa *et al.,* 2017).

Development of Oral Strip or orodispersible film (ODF) composed of hydrophilic polymers has gained much attention owing to their potential to enhance patient compliance, safety and efficacy of a drug molecule (Gupta and Kumar, 2020). This delivery system comprises a thin film usually of the size of a postage stamp which disintegrates and dissolves within few sec, after it is placed on the tongue or any oral mucosal tissue. When film comes in contact with saliva, it releases the drug to undergo absorption in the oromucosal region (Wasilewska and Winnicka, 2019). ODFs have been reported to overcome some of the therapeutic obstacles such as impaired swallowing and bitter taste of drugs (Musazzi *et al.,* 2020). They also offer benefits like an easy application, a rapid onset of action, avoidance of degradation of drug by gastrointestinal (GI) fluids, bypassing the pre systemic metabolism, possibility to adapt the dosing requirements for a subset of patients and lack of requirement for drinking water (Wasilewska and Winnicka, 2019).

Diltiazem Hydrochloride (DTZ) was selected as a model drug for the current study. It is a calcium channel blocker

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and has been widely prescribed in the treatment of various cardiovascular conditions including angina, hypertension and certain heart rhythm disorders. DTZ is marketed as immediate sustained-release tablets, extended sustained-release capsules and injections. DTZ is vulnerable to hepatic metabolism on oral administration and gives an incomplete bioavailability of 35-40%. It also has been reported to cause GI discomfort (Wang *et al.*, 2016). Moreover DTZ is very bitter and has after taste.

Oromucosal route of drug administration may prove promising to address the above drawbacks. Hence, the present study was designed to formulate ODF of DTZ by solvent casting method in an attempt to improve absorption, resulting in a faster onset of action and improved bioavailability and to enhance its palatability. Previously, fast dissolving tablets of DTZ have been reported (Jagdale *et al.*, 2011) but no literature is available regarding film formulation of DTZ. Hence a new ODF containing DTZ has been developed and characterized for physico-mechanical characteristics and *in vitro* release studies. Newly developed DTZ film was also assessed for taste concealing using the human volunteers.

MATERIALS AND METHODS

Materials

Diltiazem HCl (DTZ) was provided by Mass Pharma Pvt. Ltd. Lahore Pakistan as a gift sample. All other chemicals including hydroxypropyl methylcellulose ethocel 5 (HPMC E5), carboxymethyl cellulose (CMC), propylene glycol, glycerin, citric acid and saccharin sodium, potassium dihydrogen phosphate and disodium hydrogen phosphate were of analytical grade.

Optimized film preparation

Twelve DTZ film formulations (F1-F12) were made with varying quantities of film forming polymer HPMC E5 and CMC and plasticizers propylene glycol and glycerin (table I) by solvent casting method (Scarpa *et al.*, 2018). Briefly, polymer was dissolved in water by sonication with subsequent addition of plasticizer and drug. Film solution volume was made up as shown in table 1 and entrapped air bubbles were removed by de-aeration. Appropriate volume (10mL) was poured into glass petri dishes of uniform dimensions and dried in oven at 45˚C for sufficient time to obtain a dry film. Physical appearance, peelability and disintegration time were taken as parameters to choose the best film as shown in table 1. In order to identify the most suitable volume to prepare films with desired physical properties, different volumes of chosen film formulation were cast into petri dishes and allowed to dry. Films were observed for appearance, peelability, smoothness, handling and disintegration time and the suitable volume was selected (table 2).

To prepare optimized DTZ film, selected polymer was immersed in 20 ml of water with constant spinning for 30 min followed by addition of plasticizer and DTZ. Then accurately weighed quantities of citric acid (20mg), saccharin sodium (200mg) and mint flavour were added to above solution. Sufficient water was added to produce a volume of 40ml. The resulting clear solution was subjected to stirring for half an hr to eliminate entrapped gas bubbles. Lastly the designated volume of the solution was cast into glass petri dishes of area 58.059cm^2 (the amount of the DTZ was calculated to incorporate 30mg CPZ/film/6cm^2) and dried in the oven at 40^{o}C for a period of 5 hr. The prepared films were carefully detached from the petri dishes, examined for any defects and cut as per the dimensions (3 cm length, 2 cm width). Finally, DTZ film was explored for various physico-mechanical characters, release rate and taste concealing.

Characterization of ODFs of DTZ

Visual inspection and thickness

Films were visually inspected (n=10) for appearance, transparency and surface texture (Barkat *et al.*, 2021). Film thickness was measured at five different locations (four corners and center) using micrometer screw gauge.

Uniformity of mass and Surface pH

The uniformity of mass of DTZ loaded film was executed by weighing twenty films (3 x 2 cm^2) individually using an electronic balance and calculating the average mass. The surface pH was determined by placing the film sample (n=6) in a petri dish holding 4 ml distilled water. After the film disintegrated completely, pH was checked using pH meter (Loys *et al.*, 2017).

Disintegration test

Disintegration time of the ODF (3x2cm^2) was determined by a previously reported method (Kumar and Yagnesh, 2019). Film (n=6) was placed in a glass petri dish and 10 ml distilled water was instilled on its surface with swirling every 10 sec Time was measured until the film disintegrated completely.

Mechanical properties (Tensile strength, percent elongation and folding endurance) of the DTZ film

Tensile strength and percent elongation of DTZ film were determined using Tensile Strength Tester (Lloyd Instruments, UK) as per the European Standard EN ISO 527-3 guidelines (Wang *et al.*, 2021). Tensile strength is a maximally applied stress right before the film sample breaks and is an indicator of film elasticity. The film free of any physical defects was placed between two clamps held 50mm apart and pulled by clamp at a rate of 5mm/min. The tensile strength was calculated by formula:

$$\text{Tensile strength} = \frac{\text{Load at failure (N)}}{\text{Film thickness (mm) x film width (mm)}}$$

To measure the percent elongation, distance between the tensile grips of the testing machine was noted before (D_O)

and after the fracture of the film (D_F). The Percent Elongation (%E) was computed using the following formula:

$$\text{Percent Elongation (\%E)} \frac{D_o - D_f}{D_o}$$

The number of times, the film sample can be subjected to twisting without being broken, is regarded as the folding endurance value. It was measured by repeatedly twisting each of the randomly selected film (n=6) up and down at a similar position till it breaks or tears (Khalid *et al.*, 2020).

Water sorption Study

As the HPME E5 is a hydrophilic polymer, water sorption may pose problems while packaging and storage. To measure water sorption, DTZ film (n=3) was weighed. Then, the film fragments were held in a pinch, kept at room temperature, and reweighed every five min until a constant weight achieved. (Zayed *et al.*, 2020)

Content uniformity

Content uniformity was worked out for estimating drug content in individual film (n=10) Each ODF measuring 3 x 2cm^2 was dissolved in 50ml of 0.1N HCl. After appropriate dilutions, absorbance of the solution was measured at 237 nm by UV-visible spectrophotometer (U-2800 BMS, UK). Percent content of drug in each film was calculated using standard curve (concentration range: 6-16µg/ml).

Drug content analysis (Assay)

Film sample equivalent to 180mg DTZ was placed in a 200ml volumetric flask holding 0.1N HCl and was dissolved with constant stirring. Volume was made up to 200ml with the same solvent. 1ml of this solution was further diluted to 100 ml with 0.1 N HCl. Absorbance of test preparation was taken by UV-visible spectro-photometer at 237nm. Drug content was calculated from standard curve of drug (concentration range: 6-16µg/ml).

Thermal analysis

DSC thermograms were obtained for DTZ, polymer, drug-polymer physical mixture (PM) and DTZ film using Q-600, TA Instrument, USA. Samples were loaded in alumina crucibles to know about the physical state of the DTZ. Analysis was done in nitrogen atmosphere with a nitrogen flow of 100 ml/min and heating rate of 15˚C/min over a temperature range of room temperature to 300ºC.

Fourier transform infrared spectroscopy (FTIR)

Infrared spectra of pure DTZ, polymer and prepared film were obtained using FT-IR Spectrophotometer (Alpha Bruker, UK) to determine any drug-polymer interactions over a scanning range of 4000 to 400cm^{-1}.

In vitro drug release study

In vitro release of DTZ from the film was studied on USP type II (Paddle) apparatus operated at 50 rpm. The study was conducted in 500ml each of distilled water, phosphate buffer pH 6.8 and 0.1N HCl maintained at 37 ±0.5°C. Liquid aliquots (5ml) were removed at fixed time intervals ranging from 0.5-10 min and analyzed at 237 nm to determine cumulative drug release. Sink condition was maintained throughout the experiment by reinstating the same volume of the dissolution medium. The *in vitro* release data was analyzed by zero and first order kinetics as well as Higuchi, Korsmeyer-Peppas and Hixson-Crowell models (Zhang *et al*., 2010). The model with the highest correlation coefficient (R^2) was considered as the best one.

Taste evaluation

Approval for the taste evaluation study was obtained from the Institutional Ethical Review Committee, Lahore College for Women University, Lahore (ref no. Dir/LCWU/157A). To determine *in vivo* disintegration time and palatability of DTZ film, twelve healthy human volunteers were given 200 ml of water to gargle mouth before taste evaluation. Then they were given one ODF each to be kept on tongue. The time at which film undergoes complete dissolution in the oral cavity was recorded. The volunteers were asked to score taste of films according to scale as given in table 3. Then volunteers were asked to spit out sample and rinse their mouth with 200 ml water (ElMeshad and El Hagrasy, 2011). Volunteers were asked to rate the initial taste, after taste, mouth feel and overall acceptability of film as per the rating system (table III) that was scaled from 1-5.

STATISTICAL ANALYSIS

Physico-mechanical, *in vitro* release testing and taste evaluation studies were executed in triplicate. All data was expressed as mean $\pm$ SD using Microsoft Excel 2010 (v 14.0)

RESULTS

Screening the suitable film formulation

Varying amounts of film forming polymers (HPMC E5 and CMC) and plasticizers (Propylene glycol and glycerin) were tested either alone or in combination to screen out the most suitable film formulation based on the film attributes as shown in table 1. As CMC alone is known to produce brittle and sticky films, it was used in combination with HPMC E5. But the film formulations entailing CMC and HPMC E5 in combination (F1-F3, F5, F6) produced opaque films (table 1). Films comprising HPMC E5 alone (F4, F7-F12) exhibited different characters in terms of peelability and surface texture (Serrano *et al.*, 2019) as illustrated in table 1. Likewise, when plasticizers PG and glycerin were employed in

combination, they produced sticky films (F5, F6). Contrary, PG alone gave smooth and peelable films (F11, F12). Hence, based on transparency and peelability, formulation F12 was chosen to prepare the final film. Then different volumes (7ml, 8ml, 9ml, 10ml & 11ml) of the formulation F12 were cast into petri plates to select the suitable volume imparting film the desirable physical properties. Casting 6ml volume produced film which was rough as well as difficult to peel. An increase in casting volume from 8-11ml imparted films peelability, smooth surface and satisfactory handling but disintegration time was observed to be exceeded (table II). Based on the disintegration time, 8ml volume was picked for casting. Hence final DTZ loaded film was prepared from formulation F12 containing 3.625% of DTZ, 4.5% w/v HPMC E5 as film forming polymer, 5% w/v propylene glycol as plasticizer, saccharin sodium as sweetener and citric acid as saliva stimulating agent and characterized.

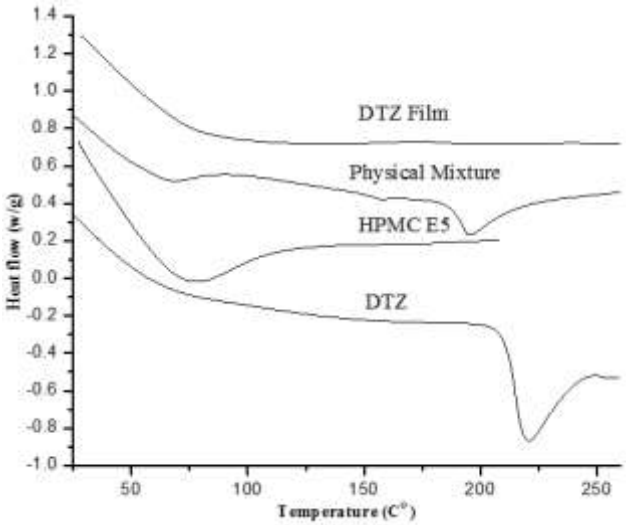

Fig. 1: DSC thermograms of individual components, PM and DTZ film

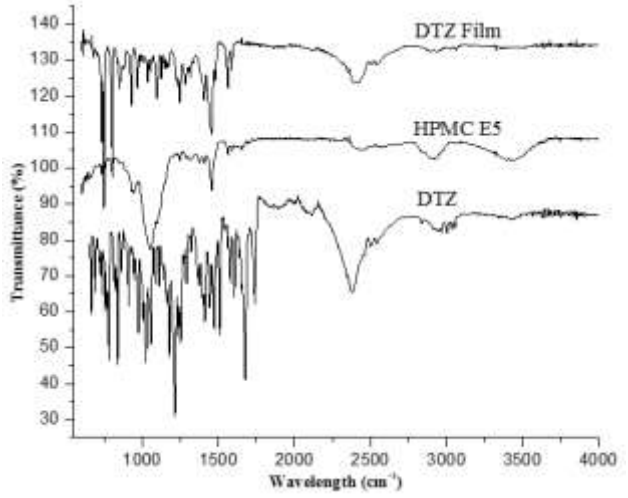

Fig. 2: FTIR spectra of individual components and DTZ film

Physico-mechanical investigation of DTZ loaded film

When films were visually observed, they were transparent, smooth, easy to peel and free from bubbles. Film thickness alternated between 0.15-0.17 mm and mean thickness was 0.16±0.01mm. It is essential to ascertain uniformity in the thickness of film since accuracy of dose distribution can be maintained if the film is made of uniform thickness. The weight variation ranged from 102-106 mg (mean: 104.4±1.64mg). The surface pH of film ranged from 6.1-6.36 (Mean: 6.43±0.03). Surface pH was evaluated because oral mucosa is pH sensitive and mucosal irritation can be caused if the pH of the film is not appropriate (Prabhu *et al.,* 2015). Hence the pH of the DTZ film is compatible to oral mucosa expecting not to cause any irritation to oral mucosa. The mean disintegration time of DTZ film was appeared to be 14.0±1.53 sec. The drug content in film was found to be 98.84±1.55% and content uniformity was within the range of 99.9-100.9% (Mean: 100.5±0.3).

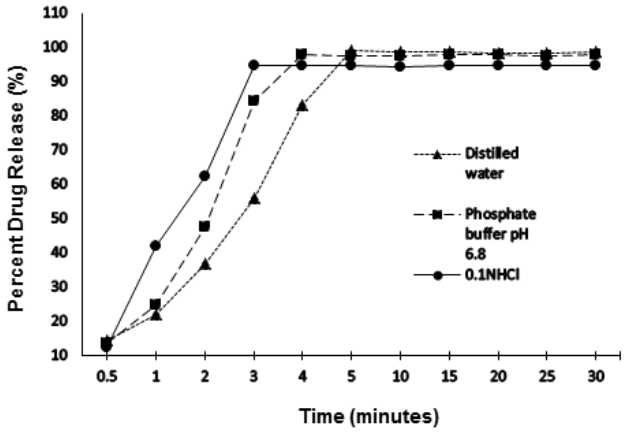

Fig. 3: Release of DTZ from DTZ film in 0.1N HCl, phosphate buffer pH 6.8 and water

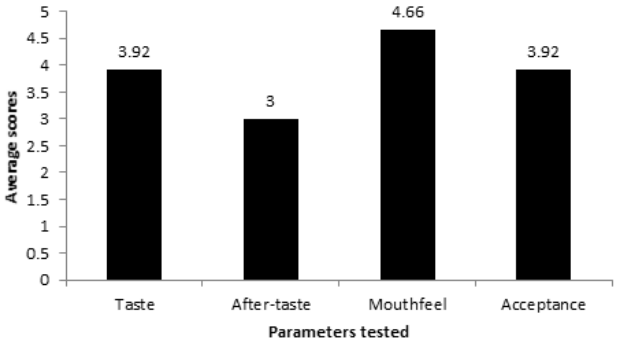

Fig. 4: Taste Evaluation of DTZ Film

Mechanical properties dictate that ODFs are strong enough and ductile to avoid any damage signifying their stability during processing and shipment. It was observed that DTZ film can be folded approximately 260 times without breaking or any visible cracks attributing to plasticizer (propylene glycol) and suggesting the non brittle nature of film.

Table 1: Screening the suitable formulation to prepare final ODF

Variables	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diltiazem HCl (g)	1.08	1.45	1.45	0.72	1.08	1.45	0.91	1.26	1.45	0.91	1.26	1.45
HPMC E5 (g)	0.5	0.6	0.7	3	2	2	2	2	2	1.8	1.8	1.8
CMC (g)	0.3	0.2	0.1	-	0.2	0.4	-	-	-			
Propylene glycol (ml)	8	9	10	6	4	3	2.75	2.75	2.5	2.5	2	2
Glycerin (ml)	-	0.5	0.4	-	1	1	-	0.8	-			
Final volume (ml) to be prepared	30	40	40	20	30	40	25	35	40	25	35	40
Physical evaluation	Opaque, rough	Bubbles after drying	Opaque, rough	Difficult to peel, rough	Sticky, not peelable	Sticky, not peelable	Opaque	Opaque	Brittle rough	Semi transparent difficult to peel	Clear, smooth but a bit difficult to peel	Clear, smooth, easy to peel
Disintegration time (sec)	25	27	24	30	37	30	42	28	32	28	25	20

Table 2: Physical properties of films after casting various volumes of optimized formulation

	Volume poured (ml)				
Physical properties	7	8	9	10	11
Peelability	Not Peelable	Peelable	Peelable	Peelable	Peelable
Surface texture	Rough	Smooth	Smooth	Smooth	Smooth
Handling	Poor	Satisfactory	Satisfactory	Satisfactory	Satisfactory
Disintegration time (Sec)	14	15	20	25	25

Table 3: Five point scale for taste evaluation

Taste	After taste	Acceptability	Mouth feel	Score
Very bitter	Very bitter	Very poor	Very gritty	1
Slightly bitter	Slightly bitter	Poor	Gritty	2
Acceptable	Acceptable	Acceptable	Acceptable	3
Slightly sweet	Slightly sweet	Good	Creamy	4
Sweet	Sweet	Very good	Very creamy	5

Table 4: Release kinetic models for DTZ film+

Medium	R^2- value					Value of 'n'
	Zero Order	First Order	Higuchi	Hixon- Crowell	Korsemeyer- Peppas	
Phosphate buffer pH 6.8	0.2488	0.9370	0.7702	0.8905	0.7327	0.3614
0.1N HCl	0.0700	0.9407	0.6701	0.8851	0.7098	0.370
Distilled water	0.5641	0.9231	0.8445	0.8865	0.8966	0.3340

Preferably, ideal films should exhibit high % elongation and moderate tensile strength (Barkat *et al.*, 2021). Tensile strength of DTZ film ranged from 1.27-1.45 N/mm^2 with a mean value of 1.36±0.11 (Chinnala *et al.*, 2015) and Percent elongation ranged from 14.7-16.2% (Mean: 15.47±0.50). Overall improvement in mechanical properties can be endorsed to the insertion of the plasticizer between the strands of polymer, thereby decreasing the polymer-polymer interaction with a consequent decrease in film stiffness and increase in film ductility (ElMeshad and El Hagrasy, 2011).

Water sorption

DTZ film expressed a minimum value (1.78%) for water sorption specifying the less hygroscopic nature of the prepared film which may impart mare stability to the film.

Differential scanning calorimetry

Thermal behavior of the starting components and the DTZ film was inspected by DSC to evaluate the physical state of the drug in the film formulation. The DSC thermograms (fig. 1) revealed the endothermic peaks for pure DTZ and HPMC E5 at 212 and 77.11°C respectively. The aforementioned peaks can be detected for physical mixture (PM) but the thermogram of the film showed complete loss of peak of DTZ suggesting the possible amorphization of DTZ due to fast solvent drying and further manifesting decreased drug mobility in the solidified film matrix (Chachlioutaki *et al.*, 2020).

Fourier transform infrared spectroscopy (FTIR)

Fig. 2. displays the IR spectra for pure DPZ, HPMC E5 and DPZ film. The characteristic peaks of the DTZ at 2966, 2837, 2393,1740 and 1679 cm^{-1} can be attributed to Aromatic C-H stretch, O-CH3 C-H stretch, Amine HCl N-H stretch, Acetate C=O stretch and Lactam C=O stretch . Similarly for HPMC E5 absorption peaks at 3500-3400, 2990, 2550-2500,1300-1250 and 1100-1000 and 1000-950 cm^{-1} can be assigned to OH stretching, methyl and hydroxypropyl group stretching, OH stretching, epoxide (cyclic C-O-C), (stretching vibrations of C-O-C group) and pyranose ring. DTZ film showed almost all characteristic peaks for pure drug and the polymer indicating no interaction between DTZ and HPM E5 (Zayed *et al.*, 2020).

Dissolution study

Fig. 3. describes the percent release of DTZ from film formulation (n=6) in 0.1 N HCl pH 1.2, distilled water and phosphate buffer pH 6.8. DTZ film presented more than 95% release within 4 min in all media. This rapid release could be attributed to the DTZ being present in an amorphous state within the film as already shown with DSC analysis. As salivary pH of an individual varies from 6.2 to 7.4 (Suryawanshi *et al.*, 2021), release of drug in basic medium (phosphate buffer pH 6.8) will be of utmost importance since it defines the drug release from film in the oral cavity. On the basis of coefficient of regression (R^2), first-order kinetic model was seen to be best fit model for DTZ loaded ODFs showing concentration dependent release of the drug from the film. The drug release mechanism was found fickian diffusion based on n value (table 4).

Taste assessment of DTZ film

DTZ film dissolved within 10±1.53 sec in the oral cavity. Hence *in vivo* disintegration time was appeared shorted than the *in vitro* disintegration time and could be attributed to the extra agitation effect imparted by tongue. Fig. 4 shows the results for taste evaluation parameters including taste, after taste, mouth feel and overall acceptability. The developed ODF got a score of 4.2 by human volunteers and found to be slightly sweet (Table 3). Similarly the mean scores for after taste and mouth feel were 3 and 4.66 respectively suggesting an acceptable after taste and creamy mouth feel. Overall acceptability of ODFs of DTZ was good scoring 3.92. Thus the taste masking of DTZ could be achieved by the selected polymer-plasticizer combination and saccharin sodium.

DISCUSSION

DTZ, a very bitter drug, is widely prescribed in the treatment of various cardiovascular conditions. It has shown extensive metabolism in the liver on oral administration (Wang *et al.*, 2016) and also demonstrates a bitter taste. These shortcomings render oral strip technology a convenient dosage form ensuring safety, stability and acceptability of a drug as well as offering improved patient compliance and easing the patients suffering from dysphagia.

The present study describes the development of DTZ into orodispersible film, comprising 4.5% w/v HPMC E5 as film former, 5% w/v propylene glycol as plasticizer and saccharin sodium as sweetening agent, by solvent casting technique. Prepared film displayed the acceptable physical and mechanical properties. A disintegration time of 14.0±1.53 sec presented by the DTZ film meets the nonbinding recommendations of the FDA for drug products meant to be administered without chewing or liquids (<30 s) (Chachlioutaki *et al.*, 2020). This fast disintegration may improve the release of the DTZ for both oromucosal and gastrointestinal absorption on swallowing of the film residues. HPMC E5 and propylene glycol imparted necessary tensile strength and % elongation to oral strip. Folding endurance was quite high (~260) proposing integrity of DTZ film to bear handling, insertion, storage or shipment stresses. Literature also supports the better performance of hydroxyl containing plasticizer i-e propylene glycol with cellulose containing polymer i-e HPMC E5. DSC confirmed the presence of DTZ in ODF in amorphous state allowing the

improvement of drug dissolution (Olechno *et al.*, 2022). FTIR revealed no interaction between DTZ and HPMC E5. *In vitro* dissolution testing presented 95% release of DTZ from the film within 4 min attributing to less viscous nature of the HPMC E5. Moreover, DTZ film showed a faster release in phosphate buffer pH 6.8 in comparison to DTZ orodispersible tablets (Jagdale *et al.*, 2011) and may lead to a faster onset of action of DTZ in the management of various cardiovascular disorders. Bitter taste of DTZ was also masked by the selected polymer-plasticizer combination. After taste and mouth feel were appeared acceptable by the human volunteers.

CONCLUSION

DTZ, a bitter drug, could be successfully developed with improved physico-mechanical properties and taste masked effects by orodispersible film technology. DTZ film can have a potential to augment onset of action for DTZ in the treatment of angina and cardiac arrhythmias. Furthermore, it can offer adherence to treatment within patient population.

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