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Formulation design, characterization and *in vitro* drug release study of orodispersible film comprising BCS class II drugs

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Abstract: Fast dissolving orodispersible film (ODF) was prepared for concurrent administration of biopharmaceutical classification system (BCS) class II drugs, i.e., meloxicam (MX) and tizanidine (TZ), using natural (xanthan gum), semisynthetic (hydroxypropyl methylcellulose and hydroxyethyl cellulose) and synthetic (polyvinyl alcohol) polymers. Compatibility of the ingredients of ODFs was ascertained through Fourier transform infra-red spectroscopy and differential scanning calorimetry. ODFs were characterized through disintegration time, pH of the surface of film, tensile strength, folding endurance, % elongation and content uniformity (MX and TZ) which were found in the range between 17±1.3–56±3.1 s, 5.11±0.07–6.28±0.05, 14.721±1.2–33.084±3.1 N/m^2, > 100, 3.33±0.53–10.04±0.77 % and 98.01–99.34 % (MX) and 97.48–99.03 % (TZ), respectively. The values of moisture uptake, moisture loss and loss on drying of all formulations were in the range from 1.06±0.09–7.51±0.93 %, 0.06±0.01–2.3±0.08 % and 0.008±0.002–0.03±0.03 %, respectively. *In vitro* drug release study in simulated saliva fluid of pH 7.4 has shown that > 90 % MX and TZ was released within 5 min. Visual inspection, scanning electron microscope and X-ray diffraction analysis of all ODFs expressed their smooth surfaces. ODF prepared from xanthan gum (F5) exhibited better physicochemical and mechanical properties as compared to other formulations.

Keywords: Orodispersible film, meloxicam, tizanidine, immediate release, fast dissolving film.

INTRODUCTION

Oral route of drug administration is considered as the safest route owing to many advantages. However, it has been observed that almost 26-50% of the population find problems in the swallowing of conventional solid oral dosage forms, i.e., tablets and hard gelatin capsules due to dysphagia, tremors and afraid of taking solid oral dosage forms due to underdeveloped nervous and muscular systems (Andersen *et al.*, 1995; Slowson and Slowson, 1985). Additionally, patients who are disabled/ handicapped, mentally ill, nauseated, on scheduled less liquid intake and the travelers as they may not have enough access to purify water can face swallowing issues (Lindgren and Janzon, 1991). The traditional substitute to the swallowing difficulties is the manufacturing of liquid dosage form. Nonetheless, liquid dosage forms have its own limitations, i.e., physical, microbial and chemical stability problems, drug and its formulation's organoleptic properties, wastage, precise dosing, etc. (Shahiwala, 2011).

Recently, fast dissolving orodispersible formulations (orodispersible tablet (ODT) and orodispersible film (ODF)) have gained importance in geriatrics and patients suffering from stroke, dysphagia, Parkinson's disease, thyroid disorder, cerebral palsy and multiple sclerosis (Dave *et al.*, 2015; Scarpa *et al.*, 2017; Manda *et al.*, 2018). Such formulations are capable to disperse/dissolve immediately in oral cavity and provide great comfort to the patients facing swallowing difficulties (Sjoholm and Sandler, 2019; Slavkova and Breitkreutz, 2015; Orlu *et al.*, 2017). The ODFs are flexible and less fragile than ODTs, therefore, ODFs provide ease in customer handling, storage and transportation (Dahiya, 2009). There are many methods to prepare ODF (Musazzi *et al.*, 2019) and among them, solvent casting is the most commonly used method to prepare the ODFs due to its low cost and easy procedure (Dixit and Puthli, 2009; Shahzad *et al.*, 2020; Khadra *et al.*, 2019).

Meloxicam (MX), an oxicam derivative is usually prescribed for the treatment of osteoarthritis and rheumatoid arthritis. Tizanidine (TZ) is myotonolytic agent and considered as an effective drug for the management of spasticity (Coward and White, 1989). TZ has to face hepatic metabolism after oral administration which decreases its bioavailability. Recently, a sustained release mucoadhesive buccal film was developed for the administration of MX and TZ (Zaman *et al.*, 2018). However, for quick relief of musculoskeletal pain, an

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immediate release formulation is more beneficial than sustained release formulation. Therefore, our aim was to prepare fast dissolving oral film using natural, semisynthetic and synthetic polymers for simultaneous administration of biopharmaceutical classification system (BCS) class II drugs, i.e., MX and TZ. We are focused on the preparation of ODF using solvent casting method in which both drugs are solubilized in their respective solvents to get a homogenized, smooth and transparent film.

MATERIALS AND METHODS

Hydroxyethyl cellulose (HEC), polyvinyl alcohol (PVA), Hydroxypropyl methylcellulose (HPMC) E5, HPMC E50 and NaOH were acquired from Sigma-Aldrich, Germany. Croscarmellose sodium, xanthan gum, polyvinyl pyrrolidone (PVP) K30, aspartame, polyethylene glycol (PEG) 400, and methanol were purchased from the Riedel-de Haen, Germany. United States Pharmacopeia (USP) specified meloxicam (MX) and tizanidine (TZ) were gifted by the Wilshire Laboratories, Lahore, Pakistan.

Preparation of ODF

MX and TZ loaded ODF was prepared using solvent casting method in two steps. Five formulations were prepared using natural (xanthan gum), synthetic (PVA) and semisynthetic (HEC, HPMC E5 and HPMC E50) polymers (table 1). In a typical formulation, polymer was dissolved/suspended in distilled water at 60 °C for 1 h under continuous stirring. After that, TZ was added and mixed for 30 min followed by the addition of croscarmellose sodium, aspartame and PEG 400. All ingredients were allowed to mix under continuous stirring keeping the temperature at 60 °C for another 2 h. Final mixture was poured in petri dish and dried in hot air oven at 60 °C for 8 h. MX was dissolved in a mixture of methanol and 0.1 N NaOH and poured on the dried film of TZ followed by drying at 50 °C for 6 h. After complete drying of the film, the prepared film was peeled off and stored in desiccator until further use. Same procedure was adopted for other polymers. It was observed that the film prepared with xanthan gum was slightly rough in nature and difficult to detach from glass petri dish. Therefore, PVP K30 was used in the preparation of formulation F5 for easy removal of film from petri dish.

Characterization of ODF

ODFs were evaluated through different analytical techniques, i.e., Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and X-ray diffraction (XRD) to ascertain the physical compatibility of the ingredients and the quality of the prepared formulation.

FTIR

This study was carried out to observe any possible drug-excipient interaction (Pimparade *et al.*, 2017). FTIR was performed using KBr pellet technique. Each ingredient of the formulation and final formulation was separately mixed and ground with KBr followed by compression into pellet. FTIR spectrum was recorded from the range of 400 to 4000 cm^{-1}.

DSC

DSC was performed to examine the drug-excipient compatibility of the formulations (Pimparade *et al.*, 2017). Samples were heated from 25 to 600 °C at the rate of 20 °C/min under nitrogen. DSC was performed on SDT Q 600 (TA Instruments, USA) thermal analyzer.

SEM

Surface morphology of the ODF was observed using SEM (S-2380N, Hitachi, Japan) which was operated at voltage of 8 kV. The sample of the film was mounted on adhesive pads and then placed on aluminum stub. Hummer sputtering system was used for gold sputtering in high vacuum evaporating system. Visual inspection of ODF was also performed to observe the transparency, color and homogeneity of the ingredients.

XRD

XRD measurement of the prepared film formulation was carried out from 10-90° (2θ) on an Xpert Pro MPD, (PANalytical, The Netherlands) diffractometer equipped with monochromatic X-rays and operated at 40 mA and 40 kV.

Physicochemical and mechanical properties

Physicochemical and mechanical properties of ODFs were determined to observe the physical strength and integrity of the formulations.

Film thickness and weight

The thickness of the film was evaluated at three different points by micrometer screw gauge and average value was calculated. Prepared film was cut into 3×2 cm^2, accurately weighed on analytical balance and weight variation was calculated. Thickness and weight uniformity of each film is important to ensure the content uniformity. Film thickness and weight of each film was noted in triplicate and expressed the mean value.

Disintegration time of ODF

Two methods were performed in order to evaluate the disintegration time of ODF (Preis *et al.*, 2012; Garsuch and Breitkreutz, 2012; Woertz *et al.*, 2011).

Method 1 (petri dish method): In this method, prepared film was cut in standard size and placed on a clean dry glass petri dish. Distilled water (2 mL) was carefully added along the side of petri dish. Film was completely

immersed in distilled water. Petri dish was oscillated until the film was completely disintegrated. Time required to fully disintegrate the film was noted.

Method 2 (drop method): In this method, ODF was placed in a glass beaker and then carefully added one drop of distilled water (0.2 mL) on the film. Time required to generate the hole in ODF at the site of drop was observed. Both of the above methods were performed thrice and mean value was calculated along with standard deviation.

Surface pH of the film

The pH of the film was examined by dropping the distilled water (5 µL) over the surface of each film. The pH was observed by touching the electrode of pH meter to the surface of the wet film. Three readings were taken and mean value of pH was reported (Patel and Poddar, 2009).

Tensile strength

Tensile strength is defined as the maximum stress needed to break/disrupt the sample. Tensile strength was used to examine the mechanical strength of the prepared film (Nagar *et al.*, 2011). Tensile strength can be calculated by determining the applied force at rupture on cross-sectional area of the film using eq. (1).

$$TS = \left(\frac{L}{T} \times W_d\right) \quad (1)$$

where, TS is the tensile strength, L is load at failure, T is strip thickness and W_d is strip width.

Percent elongation

Stretching of the sample on exerting a stress/load is defined as strain and expressed as the ratio of change in length of the sample to its original/initial length. Percent elongation is a quantitative value used to determine the concentration of the plasticizer in each film formulation. Improved percent elongation was observed by increasing the concentration of the plasticizer. Percent elongation is calculated using eq. (2) (Liew *et al.*, 2012).

$$E = \left(\frac{L_f}{L_i}\right) \times 100 \quad (2)$$

where, E is percentage elongation, L_f is the change in length and L_i is initial length of the film.

Folding endurance

Folding endurance is the number of times in which film is folded without breaking and is used to determine the mechanical strength of the film. Good mechanical strength of the film is exhibited from high value of folding endurance (Irfan *et al.*, 2016). Mechanical strength of the film can be controlled by the concentration of the plasticizer. Therefore, mechanical strength of the film is directly proportional to the amount of plasticizer.

Content uniformity

Content uniformity of MX and TZ in the prepared film formulations was performed to ascertain the uniform distribution of active ingredients in the formulation. Twenty samples of film were dissolved in methanol and filtrate was analyzed through UV spectrophotometer. Concentration of active ingredients was calculated after comparing with standard drug. According to USP 27, the contents should be within the range of 85-115% with standard deviation (SD) of either equal or less than 6% (Chaudhary *et al.*, 2013).

Moisture uptake

The film was evaluated for moisture uptake with a dimension of 2×3 cm^2. Films were placed in an area maintain the relative humidity about 75% and temperature at 25 °C for the span of 7 days. Increase in weight of films was calculated using eq. (3) (Gorle and Gattani, 2009).

$$M_u = \left(\frac{W_f - W_i}{W_i} \times 100\right) \quad (3)$$

where, M_u is the percentage moisture uptake, W_f is final weight and W_i is initial weight of the film.

Moisture loss

Hygroscopic nature of the film was evaluated by determining the moisture loss of the film. For this purpose, weighed sample of film was placed in a desiccator for the period of three days. Moisture loss was calculated using eq. (4) (Yellanki *et al.*, 2011).

$$M_l = \left(\frac{W_i - W_f}{W_i} \times 100\right) \quad (4)$$

where, M_l is the percentage moisture loss, W_f is final weight and W_i is initial weight of the film.

Loss on drying

Loss on drying (LOD) was calculated by placing the weighed sample of film in a hot air oven for 1 h at 105 °C. The difference in weight of the film before and after placing in oven was calculated and loss on drying was determined using eq. (5).

$$LOD = \frac{W_f - W_i}{W_f} \times 100 \quad (5)$$

where, LOD is loss on drying, W_f is final weight and W_i is the initial weight of the film.

In vitro drug release study

Drug release study was performed in USP dissolution apparatus II. Simulated saliva of pH 7.4 was used as dissolution media. Simulated saliva (1 L) was prepared using NaCl (40 mM), KH_2PO_4 (12mM) and $CaCl_2$ (1.5 mM), and adjusted to pH 7.4 with NaOH as described elsewhere (Gittings *et al.*, 2014). During the dissolution study, speed of the paddles was maintained at 100 rpm and temperature was kept at 37°C (Vijayanand *et al.*, 2015). Samples were withdrawn at specific time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 min), filtered, suitable diluted (if necessary) and analyzed through UV-visible spectrophotometer at 228 and 355 for TZ and MX, respectively. After taking the sample, dissolution media was immediately replenished with equal volume of fresh media to maintain the sink conditions.

Table 1: Composition (mg) of different formulations of ODF

Ingredients	F1	F2	F3	F4	F5
Meloxicam (MX)	7.5	7.5	7.5	7.5	7.5
Tizanidine (TZ)	2	2	2	2	2
HPMC E5	49.8	-	-	-	-
HPMC E50	-	47.7	-	-	-
HEC	-	-	47.1	-	-
PVA	-	-		49.8	-
Xanthan gum	-	-	-	-	21
Croscarmellose sodium	17.3	20.7	27.7	31.1	27.2
Aspartame	19.4	19.4	19.4	19.4	19.4
PEG 400	20.7	20.7	19.9	15.7	18.3
PVP K30	-	-	-	-	5.5
Total	116.6	117.8	123.6	125.5	100.9

Table 2: Different physicochemical parameters of prepared ODF

Parameters		F1	F2	F3	F4	F5
Weight (mg)		122.8±2.9	125.2±3.8	129.9±4.1	129.8±3.3	105.8±2.9
Thickness (mm)		0.190±0.005	0.127± 0.003	0.101±0.002	0.130±0.003	0.121±0.003
Disintegration time (s)	Drop method	56±3.1	51±2.5	47±1.9	53±3.7	27±1.7
	Plate method	41±2.3	33±1.3	36±2.2	44±2.7	17±1.3
pH of film surface		5.11±0.07	5.74±0.09	5.62±0.04	6.03±0.03	6.28±0.05

All values are expressed as mean ± SD.

Drug release kinetics and release mechanism

MX and TZ release studies from ODF were performed in simulated saliva of pH 7.4 and release data were used to determine rate and kinetics of drug release through different kinetics models. Zero order (eq. (6)), first order (eq. (7)), Higuchi (eq. (8)) and Hixson-Crowell (eq. (9)) models were applied on MX and TZ release data. Coefficient of determination (R^2) was calculated for each model. Drug release kinetics model having the highest value (~1) of coefficient of determination was considered the most appropriate and best fitted model.

$$Q_t = K_0 t \quad (6)$$

Where, K_0 is zero order rate constant and Q_t is the amount of drug released at time t (Gibaldi and Feldman, 1967).

$$log\ Q = log\ Q_0 - \left(\frac{K_1 t}{2.303}\right) \quad (7)$$

Where, Q is the remaining drug in the formulation after time t, Q_0 is the concentration of drug at time t = 0 and K_1 is first order rate constant (Wagner, 1969).

$$Q_t = K_H (t)^{1/2} \quad (8)$$

where, , K_H is Higuchi rate constant and Q_t is the amount of drug released at time t (Higuchi, 1961: Higuchi, 1963).

$$Q_0{}^{1/3} - Q_t{}^{1/3} = -K_{HC} t \quad (9)$$

Where, K_{HC} is the Hixson-Crowell rate constant. Q_0 and Q_t is amount of drug present in the formulation at t = 0 and amount of drug released at time t, respectively (Hixson and Crowell, 1931).

For determination of drug release mechanism, Korsmeyer-Peppas model was used (eq. (10)) (Korsmeyer *et al.*, 1983).

$$\frac{M_t}{M_\infty} = k_p t^n \quad (10)$$

Where, M_t/M_∞ indicated the fraction of drug released in time t, k_p is Korsmeyer-Peppas model constant and n is the diffusion coefficient which explained the drug release mechanism. Drug release followed the Fickian diffusion, non-Fickian diffusion and supercase-II transport mechanism when the value of n is <0.45, between 0.45 and 0.89 and n>0.89, respectively (Ritger and Peppas, 1987).

Stability study

Stability studies (ICH Q1-R2) of the prepared films were performed to determine the quality of ODFs under the influence of various environmental factors. ODFs from each formulation were carefully packed in aluminum strip before placing in the stability chamber which was maintained at 40±2°C and 75±5% RH for 6 months (accelerated storage conditions). After predetermined time intervals (1, 2, 3 and 6 months), films sample were analyzed through physicochemical and mechanical properties (Shen *et al.*, 2013).

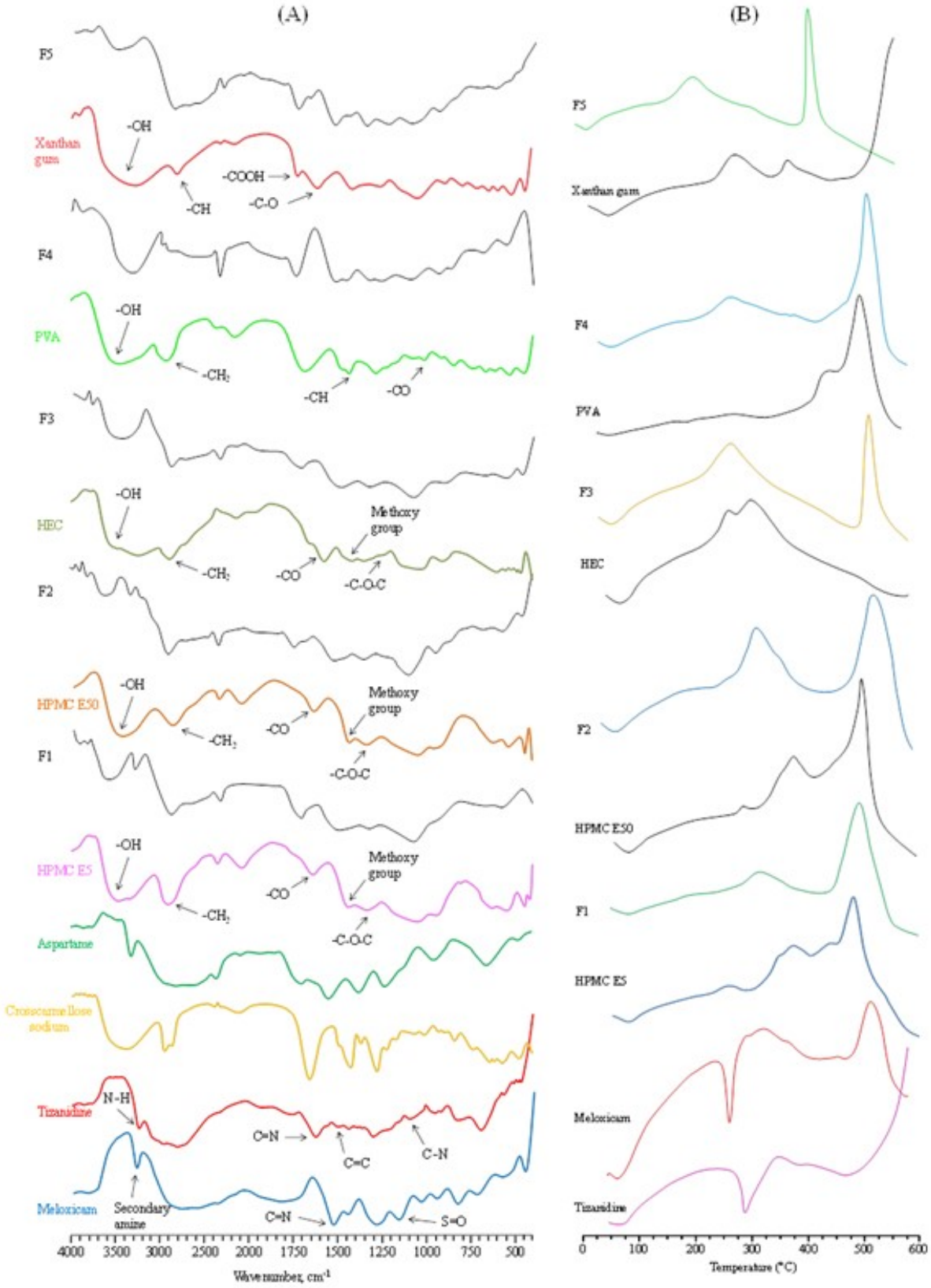

Fig. 1: FTIR spectra (A) and DSC thermograms (B) of active ingredients (MX and TZ), excipients (HPMC E5, HPMC E50 croscarmellose sodium and aspartame) and orodispersible film formulations (F1, F2, F3, F4 and F5)

Table 3: Mechanical properties and other parameters of ODF

Parameters		F1	F2	F3	F4	F5
Tensile strength (N/m^2)		18.534±1.9	23.239 ± 2.5	33.084±3.1	14.721±1.2	18.783±1.5
Percent elongation (%)		3.33±0.61	3.33±0.53	15.93 ± 1.4	6.66 ± 0.31	10.04±0.77
Folding endurance		More than 100 times				
Content uniformity (%)	MX	98.59	99.27	98.11	98.01	99.34
	TZ	97.81	98.79	98.37	97.48	99.03
Moisture uptake (%)		2.09±0.11	1.14 ± 0.37	7.51 ± 0.93	1.06 ± 0.09	1.14 ± 0.17
Moisture loss (%)		0.06±0.01	1.51 ± 0.09	2.3 ± 0.08	0.09 ± 0.02	0.17 ± 0.07
Loss on drying (%)		0.03±0.01	0.008±0.002	0.030±0.03	0.02 ± 0.01	0.02 ± 0.01

MX: Meloxicam, TZ: Tizanidine. All values are expressed as mean ± SD.

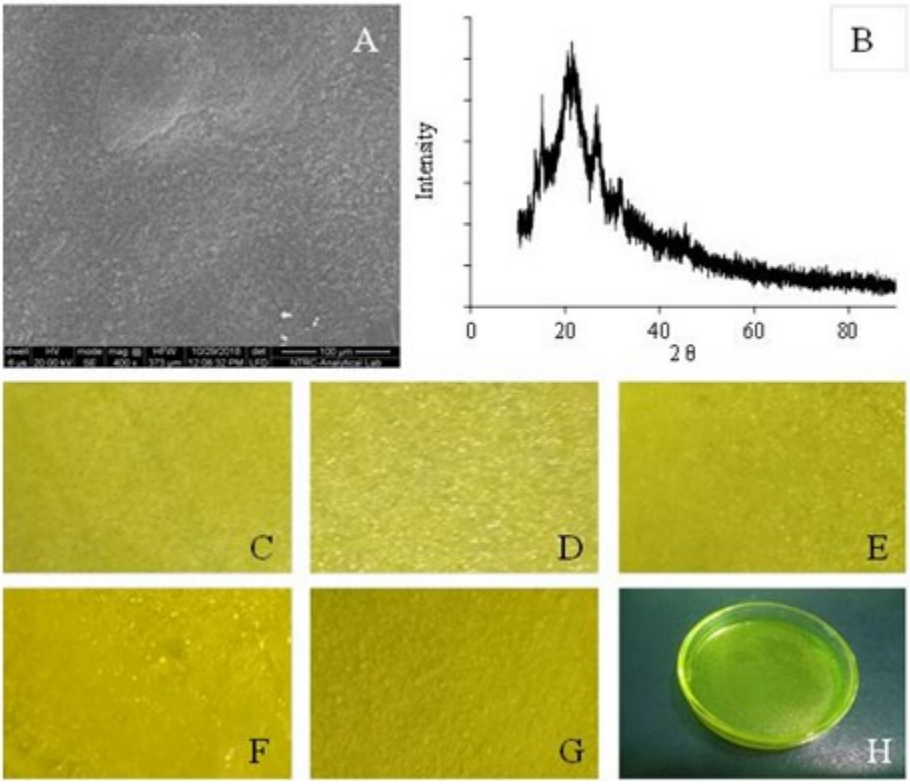

Fig. 2: SEM image (A) and XRD spectrum (B) of ODF (formulation F5), photographs of formulations: F1 (C), F2 (D), F3 (E), F4 (F) and F5 (G) and dried ODF (formulation F5) placed in petri dish.

STATISTICAL ANALYSIS

Experimental data was expressed as mean ± standard deviation (SD) and calculated by using MS Excel 2010 software.

RESULTS

Preparation of ODF

ODF was prepared by modified solvent casting method in which TZ loaded polymeric film was prepared by dissolving the TZ in aqueous polymeric solution followed by the addition of other excipients. After drying the TZ film, MX solution in methanol and 0.1 N NaOH was evenly poured on TZ film and dried in hot air oven.

Characterization of ODF

FTIR spectra of drugs, polymers and physical mixture of different formulations are shown in fig. 1A. In FTIR spectrum of MX, absorption peaks are appeared at 1166 cm^{-1} (S=O), 1533 cm^{-1} (C=N) and 3284 cm^{-1} (secondary amine). FTIR spectrum of TZ has shown the peaks at 3236 cm^{-1} (N–H stretching, primary amines), 1614 cm^{-1} (C=N stretching, ring form), 1520 cm^{-1} (C=C stretching) and 1083 cm^{-1} (C–N stretching in amines). The FTIR spectra of HPMC E5 and E50 have shown the bands of –OH between 3500 to 3400 cm^{-1}, $–CH_2$ at 2900 cm^{-1}, –CO between 1650 to 1600 cm^{-1}, methoxy group between 1500-1450 cm^{-1} and –C–O–C between 1300 to 1250 cm^{-1}. Absorption bands in FTIR of PVA can be seen between 3500-3300 cm-1 for –OH stretching, at 2900 cm^{-1} for

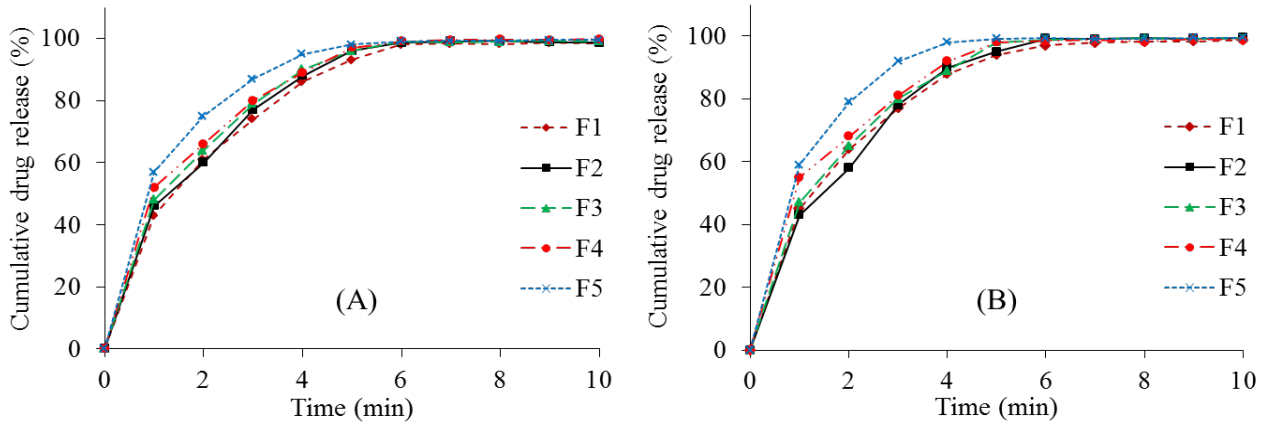

Fig. 3: Drug release study of MX (A) and TZ (B) from different formulations in simulated saliva of pH 7.4

Table 4: Mathematical data of meloxicam and tizanidine release kinetics and release mechanism from different formulations

		Meloxicam					Tizanidine				
		F1	F2	F3	F4	F5	F1	F2	F3	F4	F5
Zero order	R^2	0.8148	0.8144	0.8336	0.7756	0.7394	0.8446	0.8991	0.8313	0.7605	0.8336
	K_0	21.745	22.345	25.767	26.000	28.267	25.200	25.100	25.767	26.733	35.214
First order	R^2	0.9945	0.9891	0.9912	0.9843	0.9946	0.9951	0.9892	0.9950	0.9813	0.9979
	K_1	0.491	0.521	0.557	0.590	0.750	0.528	0.503	0.559	0.637	0.842
Higuchi	R^2	0.9989	0.9978	0.9985	0.9907	0.9841	0.9995	0.9947	0.9984	0.9869	0.9943
	K_H	42.493	43.659	45.534	46.190	50.375	44.488	44.012	45.549	47.546	55.012
Hixson-Crowell	R^2	0.9816	0.9799	0.9752	0.9581	0.9758	0.9792	0.9858	0.9791	0.9550	0.9859
	K_{HC}	0.130	0.138	0.149	0.156	0.196	0.142	0.136	0.149	0.167	0.222
Korsmeyer-Peppas	R^2	0.9994	0.9983	0.9996	0.9993	0.9996	0.9998	0.9972	0.9995	0.9987	0.9999
	K_{KP}	43.641	44.922	47.309	51.236	57.671	45.472	41.349	47.320	59.292	62.000
	n	0.478	0.477	0.462	0.398	0.366	0.479	0.561	0.463	0.403	0.472

alkyl stretching, at 1430 cm^{-1} for –CH bending, at 1090 cm^{-1} for –CO deformation and 918 cm^{-1} for out of plane hydrogen bonding. In FTIR spectrum of xanthan gum, intermolecular hydrogen bonding can be evident from the absorption bands around 3300 cm^{-1} (–OH), 2903 cm^{-1} (–C–H), 1732 cm^{-1} (–COOH) and 1632 cm^{-1} (–C–O). DSC thermograms of active ingredients, polymers and different formulations are expressed in fig. 1B.

SEM image of formulation (F5) is shown in fig. 2A exhibiting the smooth surface of ODF. The XRD spectrum of ODF formulation (F5) is expressed in fig. 2B and has shown peaks at 15°, 20° and 26°. Photographs of different formulations (F1-F5) are also shown in fig. 2C-G and fig. 2H represented the dried film in petri dish.

Physicochemical and mechanical properties of ODF

ODF was characterized through weight, thickness, disintegration time and pH of surface of film and results are depicted in table 2. Weight and thickness of formulations (F1-F5) are in the range from 105.8±2.9–129.9±4.1mg and 0.101±0.002–0.190±0.005 mm, respectively. Disintegration time was recorded by drop method and plate method and the values are in the range from 27±1.7–56±3.1 s and 17±1.3–44±2.7 s, respectively. pH of the surface of ODF is ranged from 5.11±0.07–6.28±0.05. The values of tensile strength, percent elongation, folding endurance, content uniformity, moisture uptake, moisture loss and loss on drying of all formulations are expressed in table 3.

Drug release study

The release study of MX and TZ is shown in fig. 3A and B, respectively. It can be seen that almost complete release of drugs from all formulations were accomplished within 5 min. However, as compared to other formulations, relative fast release of both drugs from formulation F5 was observed.

Drug release kinetics and release mechanism

The data of drug release kinetics models and release mechanism for MX and TZ are depicted in table 4. Higuchi and Korsmeyer-Peppas models exhibited the highest values of R^2. For MX, the values of diffusion coefficient (*n*) calculated from Korsmeyer-Peppas equation for formulations F1, F2, F3, F4 and F5 are 0.478, 0.477, 0.462, 0.398 and 0.366, respectively. For TZ, the values of *n* are calculated as 0.479, 0.561, 0.463, 0.403 and 0.472 for formulations F1, F2, F3, F4 and F5, respectively.

Stability study

For stability study, ODFs were evaluated through physicochemical and mechanical parameters after specific time intervals, i.e., 1, 2, 3 and 6 months. It was observed that slight difference in term of smoothness of ODFs was observed at 40±2°C and 75±5% RH in all formulations. The values of all other parameters are almost same and did not observe any significant difference. Content uniformity of all formulations remained the same at the end of 6 months.

DISCUSSION

Solvent casting method was used to prepare ODF loaded with TZ and MX. NaOH solution was selected to dissolve MX and also to maintain the pH of the resultant film as close to the pH of the saliva. Therefore, at the pH of saliva, ODF disintegrated more rapidly to release the maximum drug and made available for absorption from oral cavity.

FTIR spectra of the drugs, polymers and physical mixture of different formulations indicated some distinctive and characteristic peaks pertaining to specific functional groups of polymers and drugs. FTIR spectrum of MX displayed its characteristic absorption peaks of S=O, C=N and secondary amine (Issa *et al.*, 2013). Distinctive peaks in FTIR spectrum of TZ has assigned for N-H stretching of primary amines, C=N stretching of ring form, C=C stretching and C–N stretching in amines (Zaman *et al.*, 2018). All peaks appeared in the spectra of HPMC E5, HPMC E50 and HEC are in good agreement with carbohydrate region, i.e., polysaccharide (Nabarawi *et al.*, 2016; Wang and Ye, 2010). The chemical composition of HPMC E5 and E50 are similar but vary with respect to their hydroxypropyl, methoxy and ethoxy moieties. Therefore, these moieties have particular peaks between 1500–1450 cm^{-1}. Similarly, absorption bands in FTIR spectra of PVA and xanthan gum are similar as reported in the literature (Hu *et al.*, 2013; Basavaraju *et al.*, 2007). FTIR spectra of aspartame and croscarmellose sodium are in accordance to already reported literature (Szakonyi and Zelko, 2012; Lin and Cheng, 2000). After evaluating the spectra of all formulations, it is indicated that all components of a formulation are compatible with each other as the distinctive peaks of each ingredient are prominent in the FTIR spectra of all formulations. Furthermore, presence of any new peak or shifting of existing peaks is not evident from these spectra which indicated a physical compatibility of the ingredients of these formulations.

DSC thermograms of active ingredients, polymers and different formulations indicated that in each formulation, all components are compatible with each other as evident from the characteristic endothermic peaks present in the formulations (Issa *et al.*, 2013; Masareddy *et al.*, 2011).

Smooth surface of the ODF is obvious in SEM image of the formulation (F5) which indicated the homogenous distribution of the contents of the formulation. The peaks in XRD spectrum of the formulation F5 indicated the crystalline nature of the prepared film which is considered due to the presence of crystalline active ingredients. XRD spectrum also confirmed that the crystalline nature of active ingredient has not changed even after the film formation which indicated the compatibility of the ingredients even during and after the preparation procedure.

Photographs of different formulations (F1–F5) also showed that all formulations are good in appearance, transparency, color and homogeneity (Raju *et al.*, 2011).

Weight variation, thickness, disintegration time and pH of the surface of film are in standard range. Disintegration time was recorded by drop method and plate method, and the values are noted as less than 60 s which are considered as good values. The value of disintegration time measured through plate method (17 s) was less as compared to drop method (27 s) which may be due to the difference in the contact area of the disintegration media which is more in case of plate method. pH of the surface of ODF is noted as close to the values of the saliva. pH of the saliva is considered as 6.2 to 7.6 and any ODF formulation having pH close to saliva pH is advantageous with respect to disintegration and ultimately increase the absorption of active ingredient. The values of tensile strength, percent elongation, folding endurance, content uniformity, moisture uptake, moisture loss and loss on drying of all formulations are also in accordance to the standard values or already reported in the literature (Alhayali et al., 2019).

In the release study of MX and TZ, It was observed that maximum drug was released within 5 min which is due to the presence of swellable polymer and superdisintegrant. Furthermore, the release of TZ was fast as compared to MX which may be due to high solubility of TZ in the dissolution media. Relatively rapid drug release from formulation F5 was observed due to the presence of Xanthan gum in the formulation which had the capacity to absorb the drug release media more rapidly. Hence, the release of drug from F5 was quick as compared to other formulations.

The data of drug release kinetics and release mechanism of MX and TZ expressed the rate and extent of drug release after specific time intervals. A model having highest value of regression coefficient (R^2) was considered as the best fit model to explain the release of drugs from ODF. Higuchi and Korsmeyer-Peppas models have the highest values of R^2. Higuchi equation explained the drug release from a planar surface, i.e., film (Siepmann and Peppas, 2011) which indicated that the

diffusion of drug from ODF is constant. The values of diffusion coefficient (*n*) calculated from Korsmeyer-Peppas equation indicated that the release of MX from F1, F2 and F3 followed non-Fickian diffusion, i.e., swelling and diffusion mechanism, whereas, from F4 and F5, MX release was controlled by Fickian diffusion, i.e., diffusion controlled mechanism (Korsmeyer *et al.*, 1983; Ritger and Peppas, 1987). TZ release from all formulations was governed by non-Fickian diffusion as the value of $n > 0.45$.

In stability study of ODFs, slight roughness on the surface of ODFs was observed which may be due to high humidity of the environment and hygroscopic nature of the polymers. The values of all other parameters observed after 6 months storage of ODFs remained the same and did not show any significant difference. Content uniformity of all formulations at both storage conditions remained the same at the end of 6 months. Due to the absorbance of moisture by ODFs, slight change in the values of disintegration time was observed. Therefore, to protect from humidity and maintaining physicochemical and mechanical properties, a proper packing of these ODFs is required.

CONCLUSION

ODF of MX and TZ was formulated with different polymers for immediate relief of these drugs for musculoskeletal disorder. The nature of polymers affects the physicochemical and mechanical properties of the films. ODF prepared with xanthan gum (F5) has shown better physicochemical properties and immediate release of drugs as compared to other polymers. Using current method, both hydrophilic and hydrophobic drugs can be incorporated in a single film without using any surfactant.

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