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Formulation of instant disintegrating buccal films without using disintegrant: An *in-vitro* study

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Abstract: The current study was conducted to fabricate Metoclopramide HCL (MCH) and Sumatriptan succinate (SS) instant release buccal films (IRBF) without using any super disintegrant. The solvent casting method was used for the preparation of IRBFs and prepared IRBFs were physicochemically evaluated. Spectrophotometric analysis was done to determine the lambda max followed by the linearity determination of both drugs. Different concentrations such as 100, 125, and 150mg of hydrophilic polymer (HPMC E5) were employed but the concentration of glycerol was variable. Comparatively better results were observed for the formulation with 150mg of HPMC E5 and 30% glycerol. Formulated IRBFs showed good tensile strength with a mean disintegration time of 12.4-28.4 seconds and rapid dissolution with more than 50% drug release within 2 minutes. It was concluded that the chosen combination of polymers was appropriate for the fabrication of MCH and SS buccal strips.

Keywords: Buccal films, HPMC E5, dissolution studies, disintegration studies, UV-spectrophotometric analysis.

INTRODUCTION

Migraine is an episodic headache that becomes a disorder, involves the trigeminovascular system and the cerebral cortex, it may last for several days and is associated with many other complications such as photalgia and stomach revulsions (Ahmad *et al*., 2020). Serotonin and its 5-HT_{1B} and 5-HT_{1D} receptors have a role in migraine pathophysiology (Jhee *et al*., 2001). Furthermore, and even surprisingly, the autonomic nervous system can have an essential part in migraine (Brennan and Pietrobon, 2018). It is believed that reduce the level of nor epinephrine cause increased activity of the sympathetic nervous system and impaired parasympathetic baroreflex response, indicating its role in migraine (Sanya *et al*., 2005). This disorder significantly affects routine life owing to unbearable nausea, vomiting, and pain. The selective treatment choices in migraine are prophylactic ally NSAID, triptans, serotonin antagonists, β- blocker, ergot derivatives, selective serotonin reuptake inhibitors (SSRIs) and valproate. Ergot derivatives and triptans, agonists of 5-HT_{1B} and 5-HT_{1D} have significant vaso-constrictive effect (Wood *et al*., 2002). Sumatriptan is an effective option for migraine treatment due to its vasoconstriction action on extra-cranial blood vessels and neuropeptides release inhibition (Jhee *et al*., 2001).

The concomitant symptoms of vomiting and nausea demand the use of anti-emetic drugs. Studies have reviled that the use of Metoclopramide HCL (MCH) is an effective treatment option in such conditions. MCH is a prokinetic agent employed for the treatment of GIT motility disorders, nausea, gastroesophageal reflux disease, and vomiting (Shakhatreh *et al*., 2019). During migraine attacks, the gastric status may affect drug absorption that leading to therapy failure. Considering this issue, the buccal route is one of the preferred options, as it allows the drugs to penetrate directly into the blood circulation system by buccal mucosa. The oral cavity has a large surface area that is adequate for the rapid dissolution and disintegration of instant release buccal films (IRBFs) to deliver the active drugs effectively. The highly vascularized oral mucosal lining is a suitable route for drug administration that offers rapid action. Conventional dosage forms of MCH and Sumatriptan succinate (SS) i.e. capsules and tablets used in controlling pain threshold, but owing to frequent dosing and inadequate dose enhance noncompliance. Therefore, the preparation of IRBFs is a considerable alternative to cope with the problems, encounter by a conventional dosage form during migraine attacks. The IRBF is advantageous to fast dissolving tablets because it does not require disintegrant to dissolve. The onset of action of oral liquid

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formulations is higher as compared to conventional solid dosage forms but the dose can be defined. IRBFs are easily swallow in the mouth cavity without requiring water. IRBFs are thin in size while shape and size are practically similar to the postage stamp. They are placed on the buccal mucosa or simply tongue followed by hydration with saliva and rapid drug release (Ketul *et al*., 2013). The structural unit of the film is a polymer that comprises 20-75% w/w of total dry weight (Kulkarni *et al*., 2003).

IRBFs include cellulose derivatives, starch derivatives, polysaccharides, natural gums, and peptides, polyethylene glycols, polyvinyl alcohol, polyvinyl pyrrolidone, carboxy vinyl polymers, and polyacrylic acids (Leung *et al*., 2005). Amongst all these low viscosity cellulose derivatives like Hydroxypropylmethycelulose (HPMC) E4, HPMC E5 and HMPC E15, etc., have been used more frequently (Smith, 2005).

The current study was aimed to improve patient compliance during migraine attacks by formulating IRBFs containing a combination of anti-emetic and anti-migraine drug. Commonly available and frequently used film former (HPMC E5) and plasticizer (glycerol) were employed to formulate the buccal film dosage form by employing solvent casting technique.

MATERIALS AND METHODS

SS was gifted by ATCO Laboratories (Karachi, Pakistan), MTH was gifted by Unexo Laboratories (Lahore, Pakistan), Ethanol was taken from The University of Lahore. *Polyvinylpyrrolidone* (PVP) K30, HPMC E5, Saccharin Sodium as sweetener, Menthol as flavorant, and Glycerol as a plasticizer were gifted from Harmann pharmaceuticals (Lahore, Pakistan).

Formulation of IRBFs

The stock solutions were prepared for the formulation of IRBFs, except for saccharin sodium. Solutions of glycerol (100mg/ml), HPMC E5 (100mg/ml), SS (25mg/ml), PVP K30 (30mg/ml), MCH (5mg/ml), and menthol (10mg/ml) were prepared. The ratio of plasticizer and polymer is important in film formation so different concentrations (20%, 30% and 40%) of plasticizer were used for film formulation having a constant quantity of HPMC E5 and similarly, for particular concentration glycerol, 3 different polymer concentrations (100mg, 125mg & 150mg) were employed. Films were formulated by mixing each ingredient's respective solution and sodium saccharin was added accordingly (table 1). All solutions were mixed by magnetic stirring followed by pouring the film homogenous mixture into a petri dish and dried for 24 hours at 40^{o}C. Then, they were easily peeled off, packed in aluminum foil for storage until further use.

Preformulation Studies

Preformulation studies including determination of compatibility of ingredients and maximum absorption and linearity of both drugs were performed. FTIR was done to evaluate chemical interactions between SS and MCH. ASTM was followed to obtain infra-red (IR) spectra for the qualitative analysis of materials. Thus, the alkali halide pressed pellet method was employed according to ASTM standards. The sample is to be mixed with KBr in a ratio of 1:50 to 1:1000. 4 pallets were formulated in this way, one with MCH, one with SS, one only KBr (blank), one with SS and MCH in an equal ratio by crushing KBr and sample together in mortar and pestle. Die was filled with individual powder (approximately 10mm) and a pressure of 20 megapascals was provided and the die was connected for 10 min to the vacuum pump for removal of moisture. The formed pellets were separately packed and put in the desiccator until further use. The FTIR spectra for all three samples were in the range of 400cm^{-1}-4000cm^{-1}.

To determine λmax, a solution of concentration 10µg/ml of MCH and SS and their mixture was formulated separately. Then these solutions were scanned using UV-Spectrophotometer over the range of 190 to 400 nm. Standard curves of both drugs were prepared by analyzing the serial dilutions of concentration ranging from 2-10 µg/ml on selected wavelengths.

Evaluation of prepared IRBFs

Optical Microscopy

It was performed to evaluate the film at the micro-level. For this purpose, Optika microscope 4083B3, Italy was employed. A small part from each strip was taken and mounted on a slide and observed under the microscope (40X power lens)

Thickness

The thickness test was performed by employing a digital vernier caliper. From each batch single strip was selected and thickness at different points was noticed with mean and standard deviation (Bhupinder and Sarita, 2012).

Tack test

Tack is the characteristic of adhesion to a surface. To evaluate this strip was pressed between an aluminum foil layer. Observations were noted as tack free, slightly tacky, tacky and very tacky according to the strips adhesion to the aluminum foil (Chaudhary *et al*., 2013).

Tensile strength

For film formation, the primary test is tensile strength (TS). It was done using Universal Testing Machine (TIRA test 2810 E6, Germany), employing TIRA test software. Specimen cutter was employed to cut strips of 80- and 10-mm length and width respectively to avoid imperfections along the edges and length. Initial grip separation of

50mm was employed and the test was done by 50mm/min crosshead speed. At both sides of the film strip, a thin sheet of polystyrene thermoform was put for strong gripping to avoid slippage (Intl, 2001). The following characteristics were determined in the tensile testing.

Stress

Stress testing was executed to check the mechanical strength of IRBF. It is the highest stress that can be tolerated by a film strip before the break. It is calculated by the Equation (Eq) 1 given below (Irfan *et al*., 2016):

$$\text{T.S} = \frac{\text{Force required to break (N)}}{\text{Strip cross} - \text{sectional area (mm}^2\text{)}} \qquad \text{Eq.1}$$

Strain

Applying the force on the film causes the stretching of the film strip, this is known as strain and can be determined by the following given expression:

$$\text{Strain} = \frac{(1l_f - l_i)}{l_1} \qquad \text{Eq.2}$$

In Eq.2 l_i and l_f are the initial and final length at break respectively. Strain points to the overall mechanical level of the films (Zaman and Hanif, 2018).

Percentage Elongation at break (EB)

Variation in length of film strip before the break is measured in percentage is called as %age elongation at break that was calculated by the Eq. 3 (Koland *et al*., 2010):

$$\text{EB} = \frac{\text{Variation in strip length at break}}{\text{Strip initial length}} \times 100 \qquad \text{Eq.3}$$

Young's modulus of elasticity (YM)

It is measured to determine film stiffness. Elastic deformation is increased proportionally in the linear region of strain versus stress graph of tensile testing, the slope of that linear region is known as young's modulus (YM) of elasticity. This is measured by Eq. 4 (Mashru *et al*., 2005):

$$\text{YM} = \frac{\text{Force at specific strain (N)}}{\text{Strip area (mm}^2\text{)} \times \text{analogous strain}} \times 100 \qquad \text{Eq.4}$$

Folding fortitude (F.F)

It is resistance of a film to crack at one point, generally known as folding endurance. It is measured by repeatedly folding the strip manually at one point until there appears the crack at that point. The number at which the strip showed the crack was the folding fortitude (Prabhu *et al*., 2011).

Weight Uniformity

Weight uniformity is an important parameter to calculate dose in film preparations. Drug dose in film preparation is generally calculated with a surface area of developed film. To determine the weight uniformity, 6 strips from each film were weighed individually with mean weight and standard deviation of each film (Ahmad *et al*., 2020).

pH determination

The pH of IRBFs should be in the range of pH of the buccal cavity because they have to dissolve in the oral cavity. For pH determination, one strip from each formulation was selected and was dissolved in distilled water of volume 2ml. The pH of IRBF was noted using pH meter after dipping electrode in the strip solution and pH value was recorded after waiting for ten minutes till the reading was stabilized (Ahmad *et al*., 2020).

Percent moisture content (%MC)

It was calculated by drying the strips till constant weight (Bajdik *et al*., 2009). The film was dried using hot air. The weight of films from each batch was noted and then to achieve constant weight films were placed at 50^{o}C in a hot air oven for 24h.% moisture contents were determined using the Eq. 5:

$$\%\text{ moisture content} = \frac{W_i - W_f}{W_i} \times 100 \qquad \text{Eq.5}$$

In Eq 5; W_i and W_f are initial weight and strip dried weight, respectively.

In-vitro disintegration time (DT) and total dissolution time (T.D)

IRBFs exhibit a fast disintegration time of < 1 min. The film of 1x1 cm^2 was put on the surface of 10 ml distilled water pre-warmed at 37 ^{o}C in such a way that it floats on the water surface and neither stick to the petri dish walls nor sink. Time was noted while putting the strip then the dish was slightly shaken and the time was again noted. The time at which the strip began to disintegrate was recorded as the DT (El-Setouhy and El-Malak, 2010, Ahmad *et al*., 2020). The DT was recorded for three cut strips from each formulation.

Drug contents (%)

The drug content uniformity of the individual IRBF by standard assay method was determined after dissolving in 250 ml solution. Take 2ml solution and diluted to 10ml (S1) and again take 2ml solution from S1 and further diluted into 10ml (S2). For MCH the absorbance of S1 was measured at 315nm and for SS the absorbance of S2 was measured at 226nm. The % drug contents were measured by comparing them with standard dilutions of SS and MCH respectively.

In-vitro drug release

The magnetic stirrer method was commonly used to calculate the *in-vitro* drug release (Nalluri *et al*., 2013). The dissolution media used was 37^{o}C pre-warmed 250ml distilled water. Strip having one dose was attached to the inside wet wall of a beaker of volume 250ml that was preheated to 37°C and the distilled water was immediately added to the beaker and magnetically stirred at 500 rmp. A sample of volume 2ml was taken at fixed time intervals and was analyzed for MCH and SS after dilution.

Kinetic analysis

The drug release data obtained from all formulations were fitted to kinetic models such as Hixon Crowell, Higuchi, first order and zero-order, etc. to evaluate the model that best explained the data.

RESULTS

Pre-formulation studies

Fig. 1 shows the FTIR spectra of MCH, SS and mixture which reveals drug characteristics i.e. N-H bend ($1563.99cm^{-1}$), O-H stretch ($2615cm^{-1}$), C-C stretch ($1471cm^{-1}$), C-N stretch ($1319.07cm^{-1}$), C=O ($1710.55cm^{-1}$). The features of peaks were not changed significantly even after drugs combination in the form of a mixture exhibiting ingredient compatibility. UV scan of the drugs has reviled that 226nm and 315nm were the λmax for SS and MCH respectively. Satisfactory linearity of both drugs at their respective λmax was observed, indicating suitability for further analysis including drug contents and drug release studies.

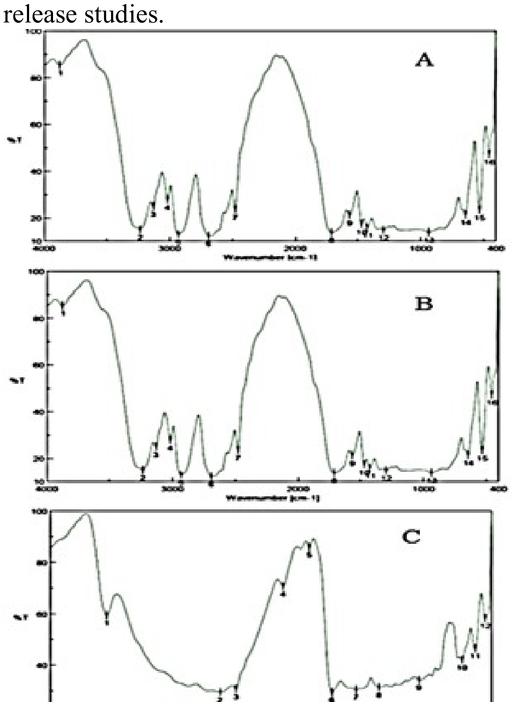

Fig. 1: FTIR spectra of SS (A), MCH (B), and Mixture of both drugs (C)

Characterization of formulations

Visual inspection

All the films of both polymers were colorless. Results showed that the lowest concentration of HPMC E5 exhibited crystallization in the strips, which caused poor uniformity, powdery surface touch and lesser transparency. By increasing the HPMC E5 concentration, uniformity and transparency were increased, thus formulations 1Ec, 2Ec and 3Ec were found to be better as compared to 1Eb, 2Eb and 3Eb respectively and these were better as compared to 1Ea, 2Ea, and 3Ea respectively. A slight increase in uniformity was observed on increasing glycerol from 20-30% while keeping the concentration of HPMC E5 constant thus the uniformity of 2Ec was found to be slightly more as compared to 1Ec.

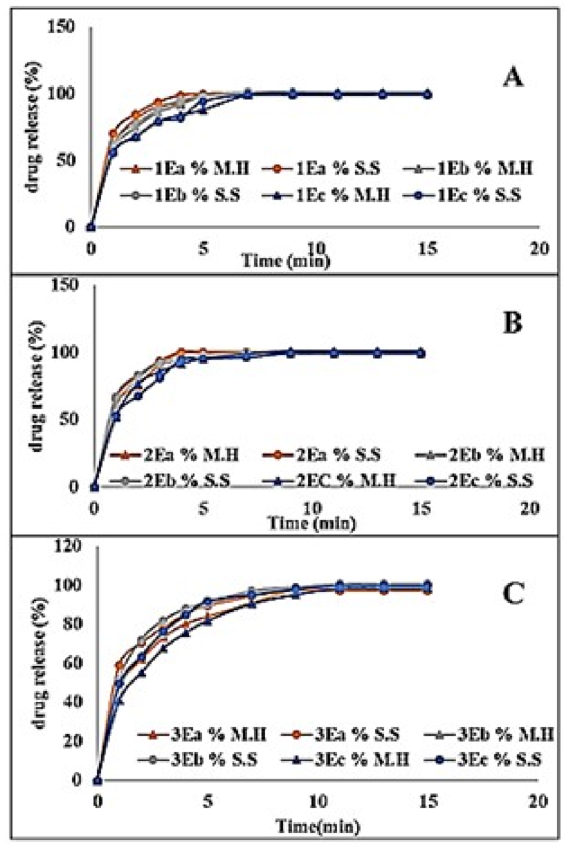

Fig. 2: Graphical presentation of dissolution studies on formulations containing (A) containing glycerol 20%, (B) glycerol 30% and (C) glycerol 40%.

Light Microscopy

In microscopic evaluation results showed that formulations having the least amounts of polymers exhibited drug crystals as compared to films having higher concentrations of polymers. Thus, at each concentration of plasticizer, films with 150mg polymer concentration load the highest dissolved drugs. Among HPMC E5 preparations 2Ec exhibited the highest uniformity.

Physicochemical characterization

All formulations were evaluated for physicochemical characterization and results are tabulated in tables 3 and 4. Findings represented that the mean weight of the HPMC

Table 1: Formulation of IRBFs

Constituents	1E			2E			3E		
	1Ea	1Eb	1Ec	2Ea	2Eb	2Ec	3Ea	3Eb	3Ec
Sumatriptan Succinate (ml)	1	1	1	1	1	1	1	1	1
Metochlopramide HCl (ml)	1	1	1	1	1	1	1	1	1
HPMC E5 solution(ml)	1	1.25	1.5	1	1.25	1.5	1	1.25	1.5
PVP K30 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Glycerol solution (ml)	0.2	0.25	0.3	0.3	0.375	0.45	0.4	0.5	0.6
Menthol solution (ml)	1	1	1	1	1	1	1	1	1
Saccharine sodium (mg)	10	10	10	10	10	10	10	10	10
Distilled Water (ml)	2.3	2	1.7	2.2	1.875	1.55	2.1	1.75	1.4

Table 2: Formulation characteristics of HPMC E5 IRBFs (Mean ±S.D)

Code	Thickness (mm)	Weight uniformity (mg)	pH	F.F	% MC	T.D (sec)	D.T (sec)	%Contents/ MCH	% Contents SS
1Ea	0.064± 0.005	157.5 ±1.37	5.79 ±0.01	101.4 ±3.71	11.2± 0.09	73.8 ±1.65	14.8 ±0.20	99.9 ±0.1	99.3 ±0.4
1Eb	0.078± 0.008	174.8 ±1.60	5.74 ±0.01	170.6 ±3.04	11.5± 0.09	82.6 ±1.52	24.7 ±0.2	99.6 ±0.5	100.1 ±0.4
1Ec	0.082± 0.004	210 ±1.54	5.94 ±0.01	273.2 ±3.19	11.9± 0.11	95.3 ±2.51	28.2 ±0.3	100.6 ±0.2	98 ±1.6
2Ea	0.066± 0.008	163.8 ±1.47	5.82 ±0.01	142 ±3.16	11.6± 0.07	61.2 ±1.05	16.1 ±0.25	100.4 ±1.7	100.6 ±0.3
2Eb	0.078± 0.008	191.3 ±1.5	5.95 ±0.01	193 ±2.23	12± 0.11	69.1 ±1.15	24.2 ±0.25	99.2 ±0.05	100.2 ±0.9
2Ec	0.096± 0.008	224.0 ±0.89	6.07 ±0.02	312.2 ±1.78	12.8± 0.09	86.9 ±1.80	26.5 ±0.15	100.4 ±0.5	99.7 ±0.7
3Ea	0.074± 0.011	172.5 ±1.87	5.92 ±0.01	113 ±1.58	15± 0.09	55.4 ±1.48	12.4 ±0.20	98.03 ±0.4	96.2 ±1.1
3Eb	0.09± 0.007	209.2 ±0.98	5.84 ±0.01	134 ±2.07	15.5± 0.12	65.4 ±1.50	18.4 ±0.25	101.2 ±0.6	101.4 ±1.1
3Ec	0.098± 0.008	234.2± 1.72	6.13 ±0.01	63.4 ±2.70	15.6± 0.11	81.7 ±1.41	25.5 ±0.25	100 ±2.2	99.3 ±0.6

E5 films was in the range of 157.5±1.37 for 1Ea to 234.2 ±1.72 for 3Ec.

The findings of the FF of HPMC E5 preparations exhibited that the minimum endurance measured was 63.4 ±2.71 for 3Ec and the highest was of 2Ec 312.2±1.8. The pH values of HPMC E5 based films were within the pH range of the buccal cavity.

The HPMC E5 films exhibited a pH range from 5.74± 0.01 to 6.13±0.015 for 1Eb and 3Ec respectively. A minor pH increase was noted on glycerol and HPMC E5 addition. This may be because of the acidic nature of the drug to which adding a neutral agent causes a decrease in acidity.

The total dissolving time (T.D) and disintegration time (D.T) rely on the plasticizer and polymer concentration. The highest T.D and D.T values were measured for those preparations which have maximum polymer concentration and lowest plasticizer concentration such as 1Ec (20% glycerol and 150mg HPMC E5). The least T.D and D.T values were noted where polymer concentration was least while plasticizer concentration was highest such as 3Ea (40% glycerol and 100mg HPMC E5).

Drug contents (%)

Among all HPMC E5 preparations % contents of MCH were in the range of 98.03±0.4 in 3Ea to 101.2±0.6 in 3Eb and % contents of SS were in the range of 96.2±1.1 in 3Ea to 101.4±1.1 in 3Eb. These findings were satisfying the pharmacopeia recommendations related to drug contents as well as the HPMC E5 ability to hold suitable quantities of the drug even in the form of a combination of both selected drugs.

In-vitro drug release

In vitro dissolution study was done using magnetic stirrer apparatus (Nalluri *et al*., 2013). For film 1Ea within 5 min complete dissolution was achieved with the release of MCH (100%) and SS (99.59%). For film 1Eb complete dissolution was achieved within 7 min with the release of 100% MCH and 101.2% SS. For film 1Ec complete dissolution was achieved for MCH (100%) within 9min and SS 99.03% within 7min.

DISCUSSION

In terms of Visual inspection, all formulated films of polymers were colorless. Glycerol is a hygroscopic plasticizer and absorbs moisture present in the

Table 3: Kinetic analysis on HPMC E5 IRBF formulations' dissolution data

Kinetic Models		1Ea	1Eb	1Ec	2Ea	2Eb	2Ec	3Ea	3Eb	3Ec
Higuchi model	R^2(SS)	0.9588	0.9247	0.9352	0.9863	0.8638	0.9465	0.9746	0.9323	0.9713
	AIC(SS)	41.800	62.185	69.002	28.871	75.857	58.623	38.277	78.031	60.577
	R^2 (MCH)	0.9588	0.9334	0.9604	0.9926	0.9430	0.9412	0.9846	0.9701	0.9582
	AIC(MCH)	-22.046	60.854	56.668	25.518	51.445	59.692	35.326	69.694	73.391
Hixon-crowel	R^2(SS)	0.9912	0.9862	0.9760	0.9930	0.9770	0.9883	0.9897	0.9894	0.9710
	AIC(SS)	32.592	41.313	51.764	25.453	44.818	46.771	34.476	52.883	61.739
	R^2 (MCH)	0.9937	0.9846	0.9742	0.9893	0.9882	0.9877	0.9948	0.9858	0.9811
	AIC(MCH)	31.515	34.660	52.498	27.233	40.303	47.276	30.286	55.303	56.900
1^{st} order	R^2(SS)	0.9982	0.9961	0.9893	0.9977	0.9968	0.9950	0.9966	0.9972	0.9766
	AIC(SS)	41.538	49.406	61.713	18.957	50.168	37.784	32.711	41.829	64.075
	R^2 (MCH)	0.9983	0.9876	0.9862	0.9947	0.9986	0.9989	0.9992	0.9938	0.9881
	AIC(MCH)	22.011	30.803	46.062	22.956	24.654	27.001	17.1509	51.056	56.810
Zero order	R^2(SS)	0.8325	0.7605	0.7297	0.8963	0.7687	0.8030	0.8654	0.7893	0.8074
	AIC(SS)	52.042	74.947	107.70	40.303	63.839	72.882	50.188	94.789	92.338
	R^2 (MCH)	0.7728	0.7755	0.8283	0.9172	0.7931	0.7912	0.8907	0.8582	0.8360
	AIC(MCH)	106.079	74.158	72.002	38.970	63.210	73.5479	0.8907	0.8582	92.544
Korsmeyer -peppas model	R^2(SS)	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.9962	0.9980
	AIC(SS)	-185.229	-186.639	perfect	-187.308	perfect	-187.308	-191.467	17.394	13.518
	n(SS)	0.276	0.297	0.276	0.330	0.312	0.348	0.377	0.546	0.480
	R^2(MCH)	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.9996	0.9941
	AIC(MCH)	-187.308	perfect	perfect	-191.467	-187.308	perfect	perfect	7.2892	17.950
	n(MCH)	0.420	0.358	0.256	0.296	0.369	0.555	0.467	0.5	0.336

environment therefore glycerol at 40% disturbed the uniformity again. Moisture in the environment causes deterioration of polymer (Blasi *et al*., 2005). Increased moisture causes the hazy appearance therefore, strips shine was less in formulation 3E as compared to 1E and 2E.

Films containing HPMC E5 with glycerol (20%) were non-tacky. On increasing glycerol concentration up to 30% in formulation 2Ea moderate tack raised that reduced in 2Ec where the concentration of polymers was increased to 150mg. Similarly, 3Ea having 40% glycerol was tacky and tackiness reduced by increasing the concentration of polymer. Thus, it can be observed that constant increase in plasticizer concentration, tack characteristic reduces due to the non-tacky nature of HPMC (Kshirsagar *et al*., 2021), and at the same concentration of polymer, increase in the concentration of plasticizer increases tackiness. Because plasticizers increase the polymeric film adhesion to solids (Krongauz, 2021).

In terms of physicochemical characterization, the results demonstrated that weight is directly related to the film constituents' amount and showed minimum SD that exhibited the minimum variation among preparations (Morales and McConville, 2011). While in thickness results, films showed that thickness is directly proportional to the polymer's concentrations in the films. There was a moderate rise in the film thickness from 1Ea to 3Ec which was 0.064±0.005 to 0.098±0.008 and 1Pa to 3Pc which was 0.044±0.005 to 0.090±0.007 respectively (Prabhu *et al*., 2011). The minimum values of standard deviation of films preparation shows least alteration in thickness within the films (Sathali and Mageshkumar).

The results of FF of HPMC E5 films showed that increasing the concentration of glycerol from 20 to 30%, increased the FF due to the improved mechanical characteristics of films by plasticizers (Irfan *et al*., 2016). However, on increasing concentration of glycerol up to 40%, F.F reduces because of the anti-plasticizing characteristic of glycerol at increased concentration. The pH values of HPMC E5 based films were within the pH range of the buccal cavity as discussed above.

The film's percentage moisture content (% MC) increased because of increasing plasticizer from 1Ea to 2Ea to 3Ea, 1Eb to 2Eb to 3Eb, 1Ec to 2Ec to 3Ec. Glycerol has hydrophilic nature and an increase in glycerol concentration results in % MC of the strips (Talja *et al*., 2007) and HPMC also has a high likeliness for water absorption (Tomar *et al*., 2012).

The total dissolving time (T.D) and disintegration time (D.T) rely on the plasticizer and polymer concentration. The results displayed that a constant upsurge of plasticizer concentration increases the polymer concentration so increases T.D and D.T while at a constant concentration of polymer increasing plasticizer concentration T.D and D.T reduces, T.D and D.T values increase with increasing the concentration of polymer (Bansal *et al*., 2013) because it increases the film thickness (Prabhu *et al*., 2011) thus as the film thickness increases the more time will be required to disintegrate and dissolve while decrease in T.D and D.T with the increase in the plasticizer concentration was ascribed to decrease of the films strength with increase in the concentration of the plasticizer.

The plasticizer concentration modifies the tensile characteristics of the films. Plasticizers enhance the film's flexibility by increasing the percentage elongation, decreasing modulus of elasticity, and tensile strength (Jantrawut *et al*., 2017). It was noted that by increasing plasticizer at a particular concentration of polymer Young Modulus and tensile strength reduced and Elongation Break increased. At the same plasticizer concentration, increasing polymer concentration would be the reason for reduced Young modulus and Tensile Strength due to the inverse relation of these characteristics with the thickness of films which enhanced by increasing the concentration of polymer.

The elongation break (EB) enhances due to the concentration of plasticizer was the same with respect to the polymer but its amount was increasing with the polymer with respect to the individual film and EB is directly proportional to the concentration of plasticizer (Chaudhary *et al*., 2013). HPMC films of low viscosity grades of HPMC that dissolve quickly have reduced strength (Tomar *et al*., 2012).

In vitro dissolution study was done using magnetic stirrer apparatus (Nalluri *et al*., 2013). Findings have been advocating the effects of polymer and plasticizer in such a way that there was a gradual increase in dissolution time by increasing polymeric contents and decrease with an increase in plasticizer's concentrations and vice versa (Zaman *et al*., 2016, Zaman *et al*., 2015). There was a corresponding illustration of alike response and effect of HPMC E5 and glycerol in fig. 2. It was observed that there was a rapid release of the drugs in the initial first min of studies, which was approximately 50% and that was extended to about 70% till the completion of 2^{nd} min of the dissolution. These findings are evidence of the great influence of glycerol in enhancing the dissolution of the drug leading to instant release. The literature has also provided sufficient support to the results of current studies, which suggests that plasticizers such as glycerol can relax the chain length of the polymer allowing a greater amount of the drug to seep out from the meshwork of the polymer.

In Kinetic analysis, DD solver® was used for formulation prepared with HPMC E5 exhibited complete drug release and shows as well as significant results. Data revealed that the coefficient of correlation (R^2) of zero-order kinetics for all the IRBFs preparations had comparatively reduced values, indicating the release of both SS and MCH was not based on time. However, R^2 values of 1^{st} order kinetics for all preparations were >0.9 for both SS and MCH, representing concentration-based release (Costa and Lobo, 2001). The data plots of the Higuchi model showed high R^2 values for the majority of the formulations (>0.9) indicating the diffusion type of drug release mechanism for both drugs. Hixon-Crowell model data fitting also provided R^2 values for all the preparations > 0.9 for both SS and MCH, representing time-dependent variation in preparation surface area (Dash *et al*., 2010). On fitting the dissolution data of preparations in the Korsmeyer-Peppas model, R^2 values (1.000) were highest as compared to all other models excluding 3Eb and 3Ec and minimum corresponding values of AIC values. The high R^2 values corroborated the diffusion mechanism of drug release (Costa and Lobo, 2001). Values of 'n' for all the preparations were <0.5 excluding 3Eb SS and 2Ec MCH, hence, exhibiting Fickian diffusion. The smallest AIC values were obtained for the Korsmeyer-Peppas model showing the best fit of data in this model (Costa and Lobo, 2001). Results of all kinetic models were tabulated in table 3.

CONCLUSION

The present study was conducted to prepare the IRBFs of Metoclopramide HCl and Sumatriptan Succinate for migraine and nausea associated with migraine to improve patient compliance and to improve these drugs onset of action leading to improve bioavailability. The objective was accomplished as IRBFs, capable of disintegrating in less than 15 seconds, and dissolving in a minute (3Ea), and releasing about 100% of the drugs in about 5 mins was formulated. This was considerable that by suitable quantities of both polymer and plasticizer IRBFs should be prepared without the use of any additional excipient (super disintegrants agent). It would also be of great importance in reducing the cost of the formulation.

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REFERENCES

Ahmad A, Butt MH, Misbah S, Saleem RT, Jamshaid M and Alvi MN (2020). Development and evaluation of orodispersible films by solvent casting method using eletriptan hydrobromide as a model drug. *Lat. Am. J. Pharm.,* **39**(10): 1951-1956.

Bajdik J, Marciello M, Caramella C, Domjan A, Süvegh K, Marek T and Pintye-Hodi K (2009). Evaluation of surface and microstructure of differently plasticized chitosan films. *J.Pharm.Biomed. Anal.,* **49**(3): 655-659.

Bansal S, Bansal M and Garg G (2013). Formulation and evaluation of fast dissolving film of an antihypertensive drug. *Int. J. Pharm. Chem. Sci.,* **3**(4): 1097-08.

Bhupinder B and Sarita J (2012). Formulation and evaluation of fast dissolving sublingual films of rizatriptan benzoate. *Int. J. Drug Dev. Res.,* **4**(1): 133-43.

Blasi P, D'souza SS, Selmin F and Deluca PP (2005). Plasticizing effect of water on poly (lactide-co-glycolide). *J. Control Release,* **108**(1): 1-9.

Brennan K and Pietrobon D (2018). A systems neuroscience approach to migraine. *Neuron,* **97**(5): 1004-21.

Chaudhary H, Gauri S, Rathee P and Kumar V (2013). Development and optimization of fast dissolving orodispersible films of granisetron HCl using box–behnken statistical design. *Bull. Fac. Pharm. Cairo Univ.,* **51**(2): 193-201.

Costa P and Lobo JMS (2001). Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci,* **13**(2): 123-133.

Dash S, Murthy PN, Nath L and Chowdhury P (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol. Pharm,* **67**(3): 217-23.

El-Setouhy DA and El-Malak NSA (2010). Formulation of a novel tianeptine sodium orodispersible film. *Aaps Pharmscitech,* **11**(3): 1018-1025.

Intl A (2001). Standard test method for tensile properties of thin plastic sheeting. D 882-01. Annual Book of Astm Standards. Philadelphia, PA.: Astm Intl. pp.162-70.

Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F and Khan A (2016). Orally disintegrating films: A modern expansion. *In*: Drug delivery system. *Saudi Pharm. J,* **24**(5): 537-546.

Jantrawut P, Chaiwarit T, Jantanasakulwong K, Brachais CH and Chambin O (2017). Effect of plasticizer type on tensile property and *in vitro* indomethacin release of thin films based on low-methoxyl pectin. *Polymers,* **9**(7): 1-14.

Jhee SS, Shiovitz T, Crawford AW and Cutler NR (2001). Pharmacokinetics and pharmacodynamics of the triptan antimigraine agents. *Clin. Pharmacokinet.,* **40**(3): 189-205.

Ketul P, Patel K, Patel M and Patel N (2013). Fast dissolving films: A novel approach to oral drug delivery. *Int. J. Pharm. Teach. Pract.,* **4(2)**: 655-661.

Koland M, Sandeep V and Charyulu N (2010). Fast dissolving sublingual films of ondansetron hydrochloride: effect of additives on in vitro drug release and mucosal permeation. *J. Young Pharm,* **2**(3): 216-222.

Krongauz V (2021). Kinetics and mechanism of plasticized poly (vinyl chloride) films autohesion. interface effect. *J. Therm. Anal. Calorim.*, pp.1-19.

Kshirsagar T, Jaiswal N, Chavan G, Zambre K, Ramkrushna S and Dinesh D (2021). Formulation and evaluation of fast dissolving oral film. *World J. Pharm. Res.,* **10**(9): 503-561

Kulkarni N, Kumar L and Sorg A (2003). Fast dissolving orally consumable films containing an antitussive and a mucosa coating agent. Google Patents. 1-13

Leung SHS, Leone RS, Kumar LD, Kulkarni N and Sorg AF (2005). Fast dissolving orally consumable films. Google Patents. 1-15

Mashru R, Sutariya V, Sankalia M and Parikh P (2005). Development and evaluation of fast-dissolving film of salbutamol sulphate. *Drug Dev Ind Pharm.* **31**(1): 25-34.

Morales JO and Mcconville JT (2011). Manufacture and characterization of mucoadhesive buccal films. *Eur J Pharm Biopharm,* **77**(2): 187-199.

Nalluri BN, Sravani B, Anusha VS, Sribramhini R and Maheswari K (2013). Development and evaluation of mouth dissolving films of sumatriptan succinate for better therapeutic efficacy. *J. App. Pharm. Sci.*, 3(8): 161-166

Prabhu P, Malli R, Koland M, Vijaynarayana K, D'souza U, Harish NM, Shastry CS and Charyulu RN (2011). Formulation and evaluation of fast dissolving films of levocitirizine di hydrochloride. *Int. J. Pharm. Investig.,* **1**(2): 99-104.

Sanya E, Brown C, Wilmowsky C, Neundorfer B and Hilz M (2005). Impairment of parasympathetic baroreflex responses in migraine patients. *Acta Neurol. Scand.,* **111**(2): 102-107.

Sathali AAH and Mageshkumar L (2013). Studies on the development of transdermal patches of nisoldipine. *J Curr Chem Pharm Sci*, *3*, 146-60

Shakhatreh M, Jehangir A, Malik Z and Parkman HP (2019). Metoclopramide for the treatment of diabetic gastroparesis. *Expert Rev Gastroenterol Hepatol,* **13**(8): 711-721.

Smith R (2005). Biodegradable polymers for industrial applications, CRC Press. pp.1-517

Talja RA, Helen H, Roos YH and Jouppila K (2007). Effect of various polyols and polyol contents on physical and mechanical properties of potato starch-based films. *Carbohydr. Polym.,* **67**(3): 288-295.

Tomar A, Sharma K, Chauhan NS, Mittal A and Bajaj U (2012). Formulation and evaluation of fast dissolving oral film of dicyclomine as potential route of buccal delivery. *Int. J. Drug Dev. Res.*, 4(2): 408-417.

Wood AJ, Goadsby PJ, Lipton RB and Ferrari MD (2002). Migraine current understanding and treatment. *N. Engl. J Med,* **346**(4): 257-270.

Zaman M and Hanif M (2018). *In vitro* and *ex vivo* assessment of hydrophilic polymer-and plasticizer-based thin buccal films designed by using central composite rotatable design for the delivery of meloxicam. *Adv. Polym. Technol.,* **37**(6): 1823-1836.

Zaman M, Hanif M and Qaiser AA (2016). Effect of polymer and plasticizer on thin polymeric buccal films of meloxicam designed by using central composite rotatable design. *Acta Pol. Pharm.,* **73**(5): 1351-1360.

Zaman M, Rasool S, Ali MY, Qureshi J, Adnan S, Hanif M, Sarfraz RM, Ijaz H and Mahmood A (2015). Fabrication and analysis of hydroxypropylmethyl cellulose and pectin-based controlled release matrix tablets loaded with loxoprofen sodium. *Adv. Polym. Technol.,* **34(3)**: 1-7