Fabrication of polyvinyl alcohol based fast dissolving oral strips of sumatriptan succinate and metoclopramide HCL

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Abstract

Migraine is a throbbing condition, usually associated with nausea and vomiting and requires concurrent administration of anti-migraine along with anti-emetic therapy. The current study was undertaken with an aim to fabricate fast dissolving oral strips (FDOs) containing Sumatriptan succinate (anti-migraine) and Metoclopramide HCl (anti-emetic) in combination without involving any superdisintegrant. Hydrophilic polymer polyvinyl alcohol (PVA) was used alone with three concentrations of 100, 125, and 150 mg using variable concentrations of glycerol. The solvent casting technique was employed to formulate FDOs and were evaluated for surface morphology, mechanical properties, surface pH, % moisture content, disintegration time (DT), total dissolving time (TDT), drug contents, and dissolution profile. PVA (150 mg) with 5% glycerol concentration gave best formulation results. FDOs have exhibited good tensile strength with smooth and uniform surface morphology. DT was ranged from 7.7 to 28 s; while TDT was from 26.4 to 77.6 s. Both polymer and plasticizer concentrations were found to be influencing the characteristics of the strips. Dissolution studies were carried out in distilled water for 15 min and all the formulations have shown released more than 50% drug within first 2 min thereby highlighting the usefulness of FDOs for the delivery of both drugs in combination significantly. Optimized combination of ingredients was found to be suitable for the formulation of FDOs for simultaneous delivery of Metoclopramide HCl and Sumatriptan succinate.

Keywords

Polyvinyl alcohol, oral strips, mechanical strength, dissolution studies

Introduction

Migraine is a disorder of recurrent headache involving trigeminovascular system and the cerebral cortex.\(^1\)\(^-\)\(^3\) Duration of headache attacks may exceed from 4 h to as long as 72 h. It is characterized by some associated symptoms like stomach revulsions, photalgia.\(^4\) Serotonin with its receptors 5-HT\(_{1B}\) and 5-HT\(_{1D}\) are strongly believed to play its role in the pathophysiology of migraine.\(^5\) Surprisingly, autonomic nervous system also plays an important role in migraine.\(^6\) Decrease level of norepinephrine activates sympathetic system and parasympathetic baro-reflex response linked with migraine.\(^7\) Migraine drastically affects the daily life due to intolerable pain, nausea and vomiting. Treatment options for migraine are divided into two, prophylactically NSAID, \(\beta\)-blockers, serotonin antagonists, valproate, and selective serotonin reuptake inhibitors (SSRIs), etc. are recommended, while for treatment therapy ergot derivatives and triptans are preferably used.\(^8\) Ergot derivatives and triptans are used due to their significant vaso-constrictive potentials.\(^4\) Triptans are 5-HT\(_{1B}\) and 5-HT\(_{1D}\) agonists. Vasoconstriction of extra-cranial blood vessels and inhibition of neuropeptides release make sumatriptan as an effective treatment option for migraine.\(^5\) Metoclopramide is a prokinetic agent used to treat nausea and vomiting, GIT motility disorders, and gastro-esophageal reflux

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There are different routes available for drug administration, but oral route is the most preferable. Surface area of the oral cavity is sufficient for rapid disintegration, dissolution, and absorption of fast dissolving films. Highly vascularized mucosal lining makes it an appropriate route for the administration of drugs that provides a quick response. Conventional dosage forms of sumatriptan and metoclopramide like tablets, capsules, and injections have also been used to control pain threshold and other symptoms. Insufficient dose and frequent dosing result in patient non-compliance. Therefore, fabrication of FDOS is an ideal candidate to fulfill all basic requirements. The film is preferable over fast dissolving tablets due to its delicacy; flexibility while tablets are brittle, fragile and need to be disintegrated before their dissolution.

The purpose of the study was to target the migraine and its associated symptoms of nausea and vomiting by formulating FDOSs having the potential to deliver both drugs in combination through buccal route and to bypass stomach that cause therapy failure.

Materials and methods

Candidate drugs were Sumatriptan succinate (generously gifted by ATCO laboratories Pvt. Ltd, Karachi, Pakistan) and Metoclopramide HCl (gifted by Unexo laboratories, Lahore, Pvt. Ltd.) used as anti-migraine and anti-emetic, respectively. PVA (film former was purchased from Merck, Darmstadt, Germany), Glycerol (plasticizer was obtained from Merck, Darmstadt, Germany), Ethanol (permeation enhancer), PVP K30 (channeling agent was purchased from Sigma-Aldrich GmbhChemie, Germany), Saccharin Sodium (sweetener), and Menthol (flavoring agent) were purchased from Pulcra Chemicals Shanghai China. Distilled water was freshly prepared in the research laboratory of the faculty of Pharmacy, The University of Lahore.

Preparation of fast dissolving oral strips

Stock solutions of each ingredient were prepared for the formation of strips, except for saccharine sodium. Concentrations of these solutions were 100 mg PVA/mL of water, 100 mg glycerol/mL of water, 20 mg PVP K30/mL of water, 25 mg SS/mL of water, 5 mg MH/mL of water and 10 mg menthol/mL of ethanol. Plasticizer-polymer ratio has an integral role in film formulation, so to obtain suitable formulation, three different concentrations of plasticizer including 5%, 7.5%, and 10% were used. Similarly, for particular glycerol concentration, three concentrations of polymer, including 100, 125, and 150 mg were used. Total nine formulations were developed for co-delivery of both as per compositions provided in Table 1. Oral strips were prepared by mixing the respective solutions of each ingredient and added sodium saccharin accordingly. All the solutions were mixed in a beaker on hot plate magnetic stirrer then homogenous mixture was poured into pre-dried petri dishes. Casted films were then hot air dried at the 40°C for 24 h having inverted funnels on
them. After drying, they were peeled off cautiously with the help of a sharp knife, packed in aluminum foil separately and stored in the desiccator for further evaluation (Figure 1).

- Constant quantities of Sumatriptan Succinate (SS = 1 mL), Metoclopramide HCl (MH = 1 mL), PVP K30 solution (0.5 mL), menthol solution (1 mL), and Saccharine sodium 10 mg were used

**Light microscopy**

Light microscopy of films was done to study the surface morphology of the films at micro level. Optika microscope 4083B3, Italy was used for this purpose. A small portion of each strip was cut and placed over the glass slide for observation at 40× power lens, under optical microscope.

**Fourier transform infrared analysis**

Fourier transform infrared (FTIR) spectroscopy was performed in order to check the compatibility of formulation ingredients. IR spectra of neat ingredients and optimized formulation were recorded. Samples were scanned over the wave number range of 4000 to 400 cm⁻¹ at ambient temperature.

**Thickness**

The thickness test was carried out by using the digital vernier caliper. Zero error was checked and then single strip selected from each prepared batch was subjected to thickness measurement at three different places by placing strips between jaws of a vernier caliper. Readings were measured and recorded as a mean and standard deviation.¹¹

**Tack test**

Property of adhesion to a surface is called tack.¹² For evaluating tack, a piece of paper was pressed between two strips. Results were recorded as tack-free, slightly tacky, tacky, and very tacky according to the adhesion of the strips to the paper.¹³

### Table 1. Composition of FDOSSs.

| Ingredients       | 1P | 2P | 3P |
|-------------------|----|----|----|
|                   | Pa | Pb | Pc |
| PVA solution      | 1  | 1.25 | 1.5 |
| Glycerol solution | 0.5 | 0.625 | 0.75 |
| Water (mL)        | 2  | 1.625 | 1.25 |

1. Science Progress
Tensile testing

Tensile testing is the primary test for the evaluation of mechanical strength of the strips.\textsuperscript{14} Tensile testing was performed on TIRA test 2810 E6 Universal Testing Machine, Germany, equipped with 10 kN load cell, using TIRA test software. Strips of 10 mm width and 80 mm length were cut using a specimen cutter to prevent imperfections along the length and edges. About 50 mm initial grip separation was used and test was performed using 50 mm per minute crosshead speed. For strong gripping a thin polystyrene thermoform sheet was placed on both sides of the film strip, to avoid slippage.\textsuperscript{15}

Folding fortitude

It is usually called the Folding Endurance and is the resistance of a strip to break upon repeated foldings at a single point. It is stated as the number of times, a strip can be folded at the same point until a fracture occurred at that point. Strip was held in two hands by thumb and index finger of each hand and then it was folded at the same point repeatedly. Number of times taken by the strip to break were reported as folding fortitude (FF).\textsuperscript{16}

Weight uniformity

Weight uniformity is very important in the dose uniformity of formulations. The usual dose is determined per calculated surface area in the case of strips. For evaluation of the weight, six strips of each formulation were weighed individually and accurately on the electronic weighing balance, previously set to zero. Calculated mean weight and standard deviation of each formulation.\textsuperscript{17}
**PH determination**

FDOSs are made to dissolve in the oral cavity, so their pH should lie in the range of the buccal cavity (5.5–7.4). One strip was selected from each batch, for pH measurement it was first dissolved in 2 mL of distilled water. pH was measured by 25CW microprocessor benchtop pH/mV meter, BANTE instruments, China. The electrode of the pH meter was brought to the contact with strip solution and waited for 10 min to stabilize the pH reading then pH was noted.

**Percent moisture content**

Percent moisture contents (%MC) were determined by drying the strips till constant weight. Hot air oven was used for drying the films. Two films from each batch were taken and their weight was noted, then these were kept in hot air oven at 50°C for 24 h (so that constant weight can be achieved). Percent moisture contents or percent moisture loss was calculated from the equation (3.5).

\[
\% \text{Moisture Contents} = \frac{W_o - W_d}{W_o} \times 100
\]

Where; \(W_o\) is initial weight and \(W_d\) is dried weight of the strip.

**In-vitro disintegration time and total dissolution time**

FDOSs show rapid disintegration as less as not more than one minute. Distilled water (10 mL) was poured in a petri dish that was previously heated to 37°C. About 1 \( \times \) 1 cm\(^2\) area was cut from a strip. This strip was then carefully placed on the surface of water in floating position without any sinking and sticking of strip in water and with walls, respectively. The stopwatch was turned on while placing the strip over water. Petri dish was slightly shaked and time consumed for complete disintegration was noted. Time was counted for three cut portions of a strip from each batch.

**Data analysis and numerical Optimization**

Disintegration time (DT) and total dissolution time (TDT) were the studied responses. A polynomial equation with interaction and quadratic factors was developed by Multiple Linear Regression Analysis (MLRA) approach to study the selected responses. The mathematical expression of the MLRA model is described in equation:

\[
Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_1^2X_1^2 + \beta_2^2X_2^2
\]

Where, \(\beta_0\) was the intercept, demonstrating the mathematical mean of all numerical outcomes of 13 trials, \(\beta_1\) and \(\beta_2\) were the coefficients, which were calculated from the observed experimental values of \(Y\), and \(X_1\) and \(X_2\) were coded levels of
the independent variable. The terms $X_1X_2$ and $X_i^2$ ($i = 1$ to $2$) symbolize the interaction and quadratic terms of the studied model, respectively. Analysis of variance (ANOVA) was used to validate the experimental outcomes, which were described in the form of polynomial equations. Various combinations were tried to find out optimized formulation for the delivery of MLX in the form of rapidly dissolving buccal films. The 3-D response surface methodological graphs (RSM) and 2-D contour plots were created using the output files generated by the software to describe the effects of hydrophilic polymer and plasticizer on studied parameters.\textsuperscript{26,27}

Two responses, including DT and TDT were also analyzed statistically through design expert ver. 7.0 by the application of ANOVA.

**Drug contents**

Drug contents in strips were estimated by the standard assay method. For content uniformity individual film was dissolved in 250 mL media and 2 mL from this solution was diluted to 10 mL (S1) and from S1 2 mL was diluted further to 10 mL (S2). Absorbance of S1 was taken at 315 nm for MH and that of S2 was taken at 226 nm for SS then % drug contents were calculated by comparing them with the MH standard dilution and SS standard dilution, respectively.

**In-vitro drug release**

In vitro drug release was determined by using the magnetic stirrer method.\textsuperscript{28} Distilled water was used as dissolution media in this method. 250 mL beaker was placed on a preheated hot plate magnetic stirrer, set at 37°C. Dissolution media (250 mL) was heated to 37°C in a separate beaker. Then oral strip containing one dose was attached to the inner moistened wall of the beaker. Dissolution media maintained at 37°C was immediately poured into the beaker, RPM was set to 500 and stopwatch was turned on, all three steps at the same time. As the quantity of the dissolution media was reduced to half so, the quantity of the aliquots was also reduced to half. About 2 mL was drawn at every time point and was diluted to 10 mL for analyzing MH and 2 mL from this 10 mL was taken and diluted to 10 mL for SS.

**Kinetic analysis**

Kinetic models were applied to release model in order to find out the best fit model and mechanism of release. Release data of all the formulations was evaluated for Highuchi, zero order, first order, Hixon Crowell, etc. by using DD solver, that is, a Microsoft Excel based adds in program.\textsuperscript{29}
Results and discussions

Fourier transform infrared analysis

FTIR spectra of polyvinyl alcohol, sumatriptan succinate, metoclopramide, and optimized formulation were recorded and presented in Figure 2. IR spectrum of pure PVA has revealed a number of peaks at different wave numbers. Initially, at 3271.33 cm\(^{-1}\) a broad band was observed due to O-H stretching vibrations of hydroxyl group followed by a strong peak at 1424.15 cm\(^{-1}\) due to bending vibrations of secondary O-H groups. Sharp and intense peaks at 2917.22 and 1322.17 cm\(^{-1}\) were due to stretching vibrations of C-H groups from aliphatic backbone. IR spectrum of sumatriptan succinate has exhibited evident peaks at 3371.21, 1299.17, 1237.15, 1082.33, and 637.12 cm\(^{-1}\) due to stretching vibrations of N-H bond, C-N bond, S=O functional group, and C-S bond, respectively. IR spectrum of metoclopramide exhibited prominent and sharp peaks at 3389, 3305.11, 3185.88 cm\(^{-1}\) due to stretching vibrations of N\(^{+}\)-H bond, 1538 cm\(^{-1}\) due to aromatic vibrations of C=C, 1595.12 cm\(^{-1}\) due to bending vibrations of N\(^{+}\)-H group, 1262.11 cm\(^{-1}\) due to C–O bond and at 1632.31 cm\(^{-1}\) due to bending vibrations of carbonyl (C=O) group. Optimized formulation spectrum was slightly different from the IR spectrum of individual formulation ingredients. In the IR spectrum of formulation, all the peaks present at 3271.33 and 2917.22 cm\(^{-1}\) due to O-H stretching vibrations of hydroxyl groups and C-H stretching vibrations of aliphatic backbone in PVA were completely absent. Few peaks of drugs were also not present in formulation spectrum. Moreover, intensity of few peaks at 1299.17, 1237.15, 1082.33 cm\(^{-1}\) due to stretching vibrations of the N-H group of sumatriptan succinate and C=C (1538 cm\(^{-1}\)), N\(^{+}\)-H group (1595.12 cm\(^{-1}\)), C-O
(1262.11 cm$^{-1}$), C=O (1632.31 cm$^{-1}$) was markedly reduced in formulation IR spectrum that the confirmed compatibility of ingredients, complexation and existence of both drugs within prepared oral strips.

**Characterization of formulations**

*Visual inspection.* Prepared formulations were optically observed for their color, transparency, shine, surface touch, uniformity, and tackiness (Table 2).

Strips containing 150 mg PVA (1Pc, 2Pc, and 3Pc) were more transparent and uniform as compared to other formulations. At constant polymer concentration, tackiness was increased with increase in plasticizer. Because plasticizers enhance the adhesion of polymeric films to solids.$^{30}$ Similar results were obtained from current studies with PVA films. Moreover, plasticizer also promotes crystallization of PVA molecules and migrate to the surface of films$^{31}$ so it should be added in appropriate and precise quantities while formulating PVA films.

*Light microscopy.* Light microscopy results explained that formulations having least quantities of polymers showed the distribution of drugs as crystals than films having more polymers. So, at each plasticizer concentration, films having 150 mg polymer load maximum dissolved drugs. Among all the PVA based formulations, 1Pc showed highest uniformity (Figure 3).

**Physicochemical characterization.** Results have indicated that, average weight of the strips was ranged from 134.5 ± 1.04 mg for 1Pa to 192.7 ± 1.75 mg for 3Pc. Results have suggested that weight is directly proportional to the quantity of ingredients in a film and gave least SD that present least variability among formulations.$^{32}$ Thickness of strips was ranged from 0.044 ± 0.005 mm to 0.09 ± 0.007 mm (Table 3). Results have indicated that the thickness of the strips is directly proportional to the concentrations of polymeric contents of the films.$^{16}$ The least values of SD for all the formulations indicates the minimum variation in thickness within the strip. Results of folding endurance of PVA films have exhibited excellent, good mechanical strength. All films showed no fracture. This high folding endurance of

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**Table 2. Results for optical surface morphology evaluation of PVA strips.**

| Code | Color | Transparency | Shine | Surface touch | Uniformity | Tack test |
|------|-------|--------------|-------|---------------|------------|-----------|
| 1Pa  | Colorless | Good         | Best  | Smooth but slightly powdery | Average    | Slightly tacky |
| 1Pb  | Colorless | Best         | Best  | Smooth        | Best       | Slightly tacky |
| 1Pc  | Colorless | Best         | Best  | Smooth        | Excellent  | Tack-free  |
| 2Pa  | Colorless | Good         | Good  | Smooth        | Average    | Tacky      |
| 2Pb  | Colorless | Good         | Best  | Smooth        | Good       | Slightly tacky |
| 2Pc  | Colorless | Best         | Best  | Smooth        | Excellent  | Slightly tacky |
| 3Pa  | Colorless | Good         | Good  | Smooth        | Good       | Very tacky |
| 3Pb  | Colorless | Good         | Good  | Smooth        | Good       | Tacky      |
| 3Pc  | Colorless | Good         | Good  | Smooth        | Best       | Slightly tacky |
PVA films was due to high mechanical strength and flexibility of PVA. The values of pH for PVA were within the acceptance range of buccal pH. Films showed pH range 5.61 ± 0.015 for 1Pb formulation and 6.02 ± 0.015 for 3Pc. A slight increase in the pH was observed with the addition of plasticizer (glycerol) and polymer. This may be due to the fact that drugs were having an acidic nature and the addition of neutral agents may lower down the acidity. Percentage moisture contents (% MC) 1Pa to 2Pa to 3Pa, 1Pb to 2Pb to 3Pb, 1Pc to 2Pc to 3Pc in Table 3, respectively. PVA films have the concentration of glycerol (5%–10%). Glycerol is a hydrophilic plasticizer and increase in concentration of glycerol causes increase in % MC of the strips. Disintegration time (DT) as well as total dissolving time (TD) depends on the polymer and plasticizer concentration. Maximum DT and TD values were observed in those formulations which have the highest concentration of polymer and lowest concentration of plasticizer as in 1Pc (150 mg PVA and 5% glycerol) with DT 28.2 ± 0.3 s and 27.6 ± 0.2081 s and TD 95.3 ± 2.5166 s and 77.8 ± 1.6802 s, respectively. Minimum DT and TD values were observed where the polymer was at minimum concentration while plasticizer was maximum as in 3Pa (100 mg PVA and 10% glycerol), which have DT 7.7 ± 0.2081 s and TD 26.4 ± 0.7937 s, respectively (Table 3). Results showed that with increase in concentration of polymer when plasticizer became constant DT and TD increases, but when polymer became constant and plasticizer ratio changes DT and TD decreases, DT

**Figure 3.** Optical microscopic images of PVA based FDOSs describing uniform distribution of drugs and polymers with smooth surface.
and TD values increases with increases polymer concentration because it increases the thickness of film so as thickness increases films will take more time to dissolve and disintegrate while decrease in DT and TD with increased plasticizer was an attribute of depression of strength of the films with increase in plasticizer.

Data analysis and numerical Optimization

\[
DT = 11.79 - 34.16X_1 + 19.16X_2 - 34.47X_1X_2 + 38.40X_1^2 + 7.70X_2^2
\]

\[
TDT = 61.01 - 112.72X_1 + 42.96X_2 - 117.33X_1X_2 + 115.74X_1^2 + 39.90X_2^2
\]

Results of ANOVA for the response surface quadratic model have suggested that the applied model was significant. Values of \( F, P \), and \( R^2 \) for both responses were significant (Table 4). Furthermore, polynomial equations generated through the application of ANOVA have indicated that responses are constructive as the values of the mean are positive (11.79 and 61.01 for DT and TDT, respectively). However, the negative value of \( X_1 \), which was the first variable (PVA) were advocating the comparatively resistive nature of the polymer against the disintegration as well as total dissolving times of the prepared films. On the other hand, glycerol, being a good solubilizer and plasticizer has left its impact by providing assistance in breaking and solubilizing the films. Illustration in contour as well as 3D graphs has been strengthening the findings of the studies that polymer is increasing and plasticizer has been decreasing the both DT and TDT significantly. It is the common observation in the literature that, usually, increase in the polymeric contents of the polymer is the reason behind the possible delay of solubilization of the films. While plasticizers like glycerol and PEG 400 etc. can decrease the dissolution time of strips. This might be ascribed by the fact that plasticizer decreases the confrontation of the polymer based film against the solubility, as it seeped out from the films, as they exposed to the dissolution medium. Loss of plasticizer from the film improves the penetration of the aqueous contents and henceforth quicker dissolution of the films.

Table 3. Characteristics of PVA formulations.

| Code | Weight uniformity (mg) | Thickness (mm) | FF | pH | \% MC | DT (s) | TD (s) |
|------|------------------------|----------------|----|----|-------|--------|--------|
| 1Pa  | 134.5 ± 1.04 0.044 ± 0.005 >400 5.74 ± 0.01 6.4 ± 0.0919 10.6 ± 0.2 37.8 ± 1.2 |
| 1Pb  | 162.3 ± 1.75 0.056 ± 0.005 >400 5.61 ± 0.01 7.6 ± 0.09805 15.9 ± 0.2 47.1 ± 1.6 |
| 1Pc  | 185.5 ± 1.76 0.074 ± 0.005 >400 5.76 ± 0.01 8.3 ± 0.0919 27.6 ± 0.2 77.8 ± 1.6 |
| 2Pa  | 137 ± 1.41 0.046 ± 0.005 >400 5.53 ± 0.01 7.2 ± 0.09956 9.3 ± 0.2 32.9 ± 1.4 |
| 2Pb  | 164.3 ± 1.51 0.06 ± 0.007 >400 5.77 ± 0.01 9.2 ± 0.0994 14.3 ± 0.1 41.5 ± 0.9 |
| 2Pc  | 188.5 ± 1.87 0.088 ± 0.008 >400 5.79 ± 0.01 9.8 ± 0.07845 19.3 ± 0.2 50.4 ± 1.6 |
| 3Pa  | 141.7 ± 1.36 0.058 ± 0.004 >400 5.94 ± 0.01 7.4 ± 0.1126 7.7 ± 0.2 26.4 ± 0.7 |
| 3Pb  | 167 ± 1.26 0.072 ± 0.008 >400 6.01 ± 0.01 8.6 ± 0.0919 11.6 ± 0.2 35.7 ± 0.8 |
| 3Pc  | 192.7 ± 1.75 0.09 ± 0.007 >400 6.02 ± 0.01 9.5 ± 0.09956 15.5 ± 0.2 42.6 ± 1.2 |
and lower dissolving time. On the other hand PVA has the ability to form a swollen matrix that would be the cause of dissolution and less loss of the constituents of prepared films\(^\text{38}\) (Figure 4).

Considering the instant disintegration and rapid dissolution as factors, and their minimum values as desired target, the optimized values of the polymer and plasticizer were found to be 1.50 and 0.97, respectively. The formulation prepared by optimized values, the formulation has disintegrated and dissolved in approximately 7 and 25 s, respectively.

**Tensile testing**

Tensile strength depends on the concentration of plasticizer, as it modulates the tensile properties of the films. Flexibility of the films can be increased by increasing the percentage elongation values and decreasing the tensile strength and modulus of elasticity.\(^\text{37,39}\) As described in Table 5 that tensile strength and Young Modulus were decreased and elongation break increased by increase in plasticizer at specific polymer concentration. At a constant concentration of the plasticizer, an increase

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**Table 4.** Statistical output of studied responses including DT and TDT.

| Response | Model     | df | F    | p value | \(R^2\)  | Significant |
|----------|-----------|----|------|---------|-----------|-------------|
| DT       | Quadratic | 5  | 40.02| 0.0060  | 0.9852    | Yes         |
| TDT      | Quadratic | 5  | 15.78| 0.0230  | 0.9634    | Yes         |

**Figure 4.** Contour and 3D graphs describing the effect of polymer and plasticizer on DT and TDT of the films.
in the concentration of polymer would be the cause of the decrease in Tensile Strength and Young modulus because these characteristics are inversely related to the thickness which increased by increasing the polymer concentration. But Elongation break (EB) increases because plasticizer concentration was constant in regard to polymer but its amount was increased with the polymer in regard to the individual film and EB is directly related to plasticizer concentrations.\textsuperscript{13}

**Table 5.** Results of tensile testing of PVA formulations.

| Code | Tensile strength (N/mm\(^2\)) | Strain | Elongation at break (%) | Young’s modulus (N/mm\(^2\)) |
|------|-------------------------------|--------|-------------------------|-------------------------------|
| 1Pa  | 15.2                          | 1.6768 | 167.62                  | 8.229962                      |
| 1Pb  | 13.83                         | 2.3038 | 230.3                   | 6.000955                      |
| 1Pc  | 13.32                         | 2.6716 | 265.09                  | 4.985776                      |
| 2Pa  | 11.16                         | 2.4518 | 245.1                   | 4.551758                      |
| 2Pb  | 13.25                         | 3.0032 | 300.13                  | 4.411961                      |
| 2Pc  | 12.92                         | 4.285  | 428                     | 3.618825                      |
| 3Pa  | 12.38                         | 3.2764 | 327.54                  | 3.779555                      |
| 3Pb  | 14.03                         | 3.9534 | 395.2                   | 3.541256                      |
| 3Pc  | 20.31                         | 4.0224 | 402.14                  | 5.048396                      |

**Table 6.** Drug contents of PVA formulations.

| Code | % Contents MH | % Contents SS |
|------|---------------|---------------|
| 1Pa  | 100.4 ± 1.7   | 99.15 ± 0.6   |
| 1Pb  | 101.6 ± 1.1   | 102.3 ± 0.1   |
| 1Pc  | 100.4 ± 0.5   | 99.1 ± 1.6    |
| 2Pa  | 99.6 ± 1.7    | 100.9 ± 1.6   |
| 2Pb  | 99.9 ± 1.1    | 100.8 ± 1.4   |
| 2Pc  | 99.6 ± 0.6    | 100.4 ± 2.3   |
| 3Pa  | 99.4 ± 0.3    | 100 ± 1.3     |
| 3Pb  | 99.2 ± 0.007  | 100.6 ± 1.4   |
| 3Pc  | 99.60 ± 0.5   | 100.7 ± 1.2   |

**Drug contents (%)**

PVA based formulations have shown the ability to hold the satisfactory amount of the drugs as % contents of MH ranged from 99.2 ± 0.007 in 3Pb to 101.6 ± 1.1 in 1Pb and % contents of SS ranged from 99.1 ± 1.6 in 1Pc to 102.3 ± 0.1 in 1Pb (Table 6). All results lie within the acceptance criteria of USP27 (85%–115%).\textsuperscript{13}

**In-vitro drug release**

Different concentrations of 2 to 20 μg/mL were prepared to construct a calibration curve by using a UV spectrophotometer. Absorbance of SS for each concentration
in the presence of MH at 226 nm and observance of MH for each concentration in the presence of SS at 315 nm were measured. The curve of SS showed linearity over the range of 2 to 18 μg with a coefficient of correlation and linear regression values of 0.9993 and $y = 0.1481x + 0.0109$ while the curve of MH was shown linearity over the range of 2 to 20 μg with a coefficient of correlation and linear regression values of 0.9992 and $y = 0.031x - 0.0083$ (Figure 5).

**Dissolution results**

In vitro dissolution test was performed on a magnetic stirrer apparatus containing 250 mL distilled water in a 250 mL beaker with 1.5 inch magnet bar on magnetic stirrer at 500 rpm. PVA based formulations (Table 6) have shown complete dissolution of 1Pa, 1Pb, and 1Pc in 9 min (101.6% MH and 98.69% SS), 13 min (100.8% MH and 102.5% SS) and 15 min (100% MH and 100.2% SS), respectively (Figure 4(a)). The complete dissolution, 2Pa gave 98.46% release of MH in 7 min and 102.1% release of SS in 9 min. 2Pb gave 99.22% release of MH and 101.8% release of SS in 11 min and 2Pc gave 100% release of MH and 102.1% release of SS in 13 min (Figure 4(b)). Results showed complete dissolution of 3Pa in 9 min releasing 99.61% MH and 101% SS and 3Pb in 11 min releasing 99.23% MH and 102.3% SS. 3Pc released 99.19% MH in 13 min and 100.7% SS in 11 min (Figure 6).

**Kinetic analysis**

DD solver was employed on all formulations which showed complete release and significant results. For this all kinetic model like Zero order, first order, Higuchi, Korsmeyer–Peppas and Hixon-Croswell models were applied on the release profile of such formulations. Results Table 7 demonstrated that the coefficient of correlation ($R^2$) in zero order for all the formulations of PVA had lower values. These values were lower than all other models, for both MH and SS release data. So the drug release was not time dependent. But $R^2$ values of first order kinetics for all formulations were higher than 0.9 for both MH and SS, indicating concentration dependent release.
The data plots of Higuchi model represented high $R^2$ values more than 0.9 except for SS in 1Pa. So it can be concluded that the diffusion mechanism of drug release was nearly followed. Hixon-Crowell model data fitting also gave values of regression, correlation co-efficient $R^2$ for all the formulations, higher than 0.9 for both MH and SS, indicating a time dependent change in surface area of the formulations. On fitting the beaker stirring dissolution data of formulations in Korsemeyer-Peppas model, values of $R^2$ were higher than all other models ranging from 0.9983 to 1.000 for MH and 0.9960 to 1.000 for SS. These extremely high $R^2$ values confirmed the diffusion mechanism of drug release. $n$ values for all the formulations were less than 0.5 thus representing Fickian diffusion.

AIC values of Korsmeyer-peppas model were smaller and even perfect representing the best fit of data in this model.

**Thermal analysis**

DSC thermograms of individual ingredients as well as optimized formulation were recorded to confirm their stability as shown in Figure 5(a). Metoclopramide hydrochloride thermogram has indicated initial endothermic peak due to the loss of moisture. DSC thermograms of Metoclopramide hydrochloride (A), HMPC E5 (B), Sumatriptin succinate (C) and PVA(D) have shown prominent endothermic peaks at their melting points, that is, 171°C, 165°C, 171–180°C, and 200°C, respectively. DSC thermogram of optimized formulation () was also recorded to check the stability of developed delivery system for combinational therapy, initially there was a short endothermic peak near 80°C due to the loss of moisture that was followed by a broad endothermic peak 225°C–375°C. These studies have proved that stability of the developed was markedly increased at higher temperature values (Figure 7(a)).

Thermal gravimetric analysis (TGA) studies were carried out to assess the stability of neat ingredients and fabricated patches over an increasing temperature range. TGA thermogram of Metoclopramide hydrochloride reflected initial mass loss of 25.21% at 110°C. Further loss of mass loss of 20% occurred at 200°C and
Table 7. Kinetic modeling of dissolution data of PVA formulations.

| Kinetic models          | 1Pa   | 1Pb   | 1Pc   | 2Pa   | 2Pb   | 2Pc   | 3Pa   | 3Pb   | 3Pc   |
|-------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Zero order              |       |       |       |       |       |       |       |       |       |
| $R^2$ (MH)              | 0.7077| 0.8236| 0.8629| 0.8164| 0.8281| 0.8342| 0.7863| 0.8599| 0.8270|
| AIC (MH)                | 98.018| 92.867| 101.012| 62.175| 81.925| 92.096| 73.644| 80.274| 103.47|
| $R^2$ (SS)              | 0.6531| 0.7671| 0.7827| 0.7652| 0.7802| 0.7806| 0.7450| 0.8126| 0.7728|
| AIC (SS)                | 99.050| 95.896| 105.475| 63.904| 84.453| 95.012| 75.288| 83.355| 106.07|
| First order             |       |       |       |       |       |       |       |       |       |
| $R^2$ (MH)              | 0.9864| 0.9834| 0.9819| 0.9946| 0.9904| 0.9872| 0.9926| 0.9814| 0.9902|
| AIC (MH)                | 46.325| 61.312| 69.093| 33.960| 50.277| 65.514| 41.448| 55.274| 61.785|
| $R^2$ (SS)              | 0.9869| 0.9872| 0.9801| 0.9938| 0.9907| 0.9872| 0.9976| 0.9823| 0.9844|
| AIC (SS)                | 46.824| 57.549| 69.817| 54.385| 49.343| 64.204| 32.241| 54.219| 66.397|
| Hixon-Crowell           |       |       |       |       |       |       |       |       |       |
| $R^2$ (MH)              | 0.9605| 0.9720| 0.9738| 0.9857| 0.9812| 0.9767| 0.9781| 0.9702| 0.9821|
| AIC (MH)                | 55.790| 68.895| 75.948| 41.848| 58.148| 67.558| 51.444| 61.087| 64.667|
| $R^2$ (SS)              | 0.9458| 0.9612| 0.9572| 0.9565| 0.9720| 0.9666| 0.9712| 0.9684| 0.9666|
| AIC (SS)                | 58.158| 72.182| 81.194| 56.885| 61.084| 70.676| 53.807| 61.565| 70.329|
| Higuchi model           |       |       |       |       |       |       |       |       |       |
| $R^2$ (MH)              | 0.9264| 0.9527| 0.9696| 0.9551| 0.9586| 0.9588| 0.9390| 0.9726| 0.9649|
| AIC (MH)                | 61.728| 74.715| 78.675| 49.544| 64.638| 73.111| 60.039| 61.143| 71.745|
| $R^2$ (SS)              | 0.8960| 0.9203| 0.9249| 0.9038| 0.9324| 0.9284| 0.9152| 0.9492| 0.9339|
| AIC (SS)                | 64.234| 80.271| 88.226| 64.053| 69.566| 78.876| 62.993| 67.278| 77.937|
| Korsmeyer-Peppas model  |       |       |       |       |       |       |       |       |       |
| $R^2$ (MH)              | 1.000 | 1.000 | 0.9995| 1.000 | 0.9989| 0.9999| 1.000 | 0.9983| 0.9996|
| $n$ (MH)                | 0.191 | 0.259 | 0.258 | 0.266 | 0.364 | 0.334 | 0.257 | 0.324 | 0.246 |
| AIC (MH)                | Perfect| Perfect| 7.3952| 11.596 | −0.7848| Perfect| 12.965| 7.225 |
| $R^2$ (SS)              | 1.000 | 1.000 | 0.9983| 1.000 | 0.9999| 1.000 | 1.000 | 0.9984| 0.9960|
| $n$ (SS)                | 0.098 | 0.228 | 0.235 | 0.256 | 0.318 | 0.302 | 0.329 | 0.298 | 0.274 |
| AIC (SS)                | −187.308| −191.467| 13.453| Perfect| 0.4294 | −1.157| Perfect| 13.9217| 17.0740|
55% mass remained intact. Likewise, TGA thermogram of PVA has revealed 73.23% mass loss of PVA near 220°C and 25% mass loss retained intact over the entire temperature range. Sumatriptan succinate remained intact, that is, 52% at 231°C. HPMC E5 thermogram has shown a mass loss of 43% at 237°C. However, TGA thermogram of developed matrix patches have shown that 35% mass remained intact at higher temperature 310.15°C. Thermal studies have proved the stability of polymeric patches was improved at higher temperature values (Figure 7(b)).

**Conclusion**

Co-administration of anti-migraine and anti-emetic drugs was successfully achieved by formulating fast dissolving oral strips. Developed formulations were uniform, stable, economical, and have potentiated dissolution assisted bioavailability without involving superdisintegrants and surfactant in composition. Frequency of dosing was decreased and patient compliance was remarkably increased. Moreover, FDOS’s can serve as an ideal delivery system for drugs having poor oral bioavailability, short half-life and those are degraded within the stomach. Aims and objectives of the studies have been achieved by formulating fast dissolving buccal films
co-loaded with the combination of anti-migraine and anti-emetic drugs. Rapid disintegration and dissolution have been achieved, followed by the instant release of both drugs. It would be a wrathful addition to improve the patient compliance not only by reducing the cost, (as neither superdisintegrant nor any surfactant has been added in the formulation) but also enhancing the bioavailability due the rapid dissolution followed by absorption through buccal cavity and hence avoiding the hepatic metabolism.

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