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Research Article

DESIGN AND EVALUATION OF FAST DISSOLVING FILM OF DOMPERIDONE

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ABSTRACT:

The objective of present research work was formulation and development fast dissolving film of domperidone. Domperidone is a specific blocker of dopamine receptors Solvent casting method was used for preparation of fast dissolving film. Various film forming polymers were evaluated for selection of suitable polymer. Different polymers like maltodextrin, polyvinyl alcohol and different grades of hydroxypropyl methylcellulose like HPMC E5 LV, HPMC E15 LV and HPMC E3 LV were used in study for selection of polymers. Amongst them HPMC E3 LV, HPMC E5 LV was selected as film forming polymer and propylene glycol was used as plasticizer. For solubility enhancement inclusion complex from β-cyclodextine was prepared by kneading method. Films were evaluated for physical and mechanical properties, drug content, disintegration time, *in vitro* dissolution and stability study. Prepared films showed satisfactory physical and mechanical properties. Drug-excepients interaction study (IR spectroscopy), Differential scanning calorimetry (DSC), Drug content, disintegration time and *in vitro* dissolution were also acceptable. 3^2 factorial design were used for optimization of film formulation. Batch F4 was found to be optimized film formulation which has 35.33 second disintegration time, tensile strength 2.180 N/cm^2, drug release 75.26% after 15 min. Acelerated stability studies on the promising formulations indicated that there were no significant changes in drug content, *in vitro* disintegration time, tensile strength, *in vitro* dissolution and surface pH.

Keywords: Domperidone, Fast dissolving film, β-cyclodextine, Solvent casting method, 3^2 Factorial design.

INTRODUCTION

Among the various routes, Oral route is most preferred for drug administration. Most of the drugs are being taken in the form of tablets and capsules by all patients, including adult, pediatric and geriatric patients. As a site for drug delivery, oral cavity offers advantages over the conventional gastrointestinal route and the parenteral and other mucosal routes of drug administration. It provides direct entry into the systemic circulation thereby avoiding the hepatic first pass effect, ease of administration. Intraoral drug delivery has become an important route of drug administration. Various intraoral dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, fast-dissolving drug delivery systems (FDDDS). FDDDS is the most convenient mode of administering drugs to overcome problems related to swallowing difficulties. These delivery systems dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. Dissolution within oral cavity also permits intra-oral absorption, thus bypassing first-pass effects.[1]

A fast-dissolving film drug delivery system in this a film containing active ingredient that dissolves or disintegrates in the saliva remarkably fast, within a few seconds without the need for water or chewing. Some drugs are absorbed well from the mouth, pharynx and esophagus. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients[2]

Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure. The antiemetic properties of domperidone are related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which - among others - regulates nausea and vomiting.

The objectives of the present work were preparation of fast dissolving films of domperidone using water soluble polymers having acceptable mechanical properties and faster dissolution, to achieve faster onset of action, to increase the bioavailability of Domperidone, to improve compliances & ease of dosing for the patients and bypass the first pass metabolism.

MATERIALS AND METHODS

Domperidone was obtained as gift sample from Esquire Drug House (Surendranagar, India). Hydroxypropylmethylcellulose (HPMC E3, HPMC E5, HPMC E15) were procured from Colorcon Pvt. Ltd, Mumbai. Polyvinyl Alcohol (PVA), β-cyclodextrine (β-CD), Xanthan gum were procured from SD Fine Chem Ltd, Mumbai, India. Glycerol IP was obtained from RFCL Ltd, New Delhi. All other reagents used were of analytical grade. The inclusion complexes were prepared by kneading method and films were prepared by solvent casting method.

Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors. An excess amount of Domperidone (10 mg) was added to 10 ml of distilled water containing rising amounts of β-CD solutions at various concentrations (0.001-0.01 M) in 10 ml volumetric flask. The contents were stirred at 37°C for 72 h on a rotary flask shaker. After equilibrium, the samples were filtered through whatman filter paper and absorbances were recorded at 283 nm using UV visible spectrophotometer, if necessary, after suitable dilution. The apparent stability constant was calculated from the initial straight portion of the phase solubility diagram using the following equation:

$$K\,1{:}\,1 = \frac{\text{Slope}}{S(1 - \text{Slope})} \times m - 1$$

Where, S = solubility of drug without cyclodextrine; M = molar concentration; K = apparent stability constant; Slope is calculated from regression equation.

Preparation of inclusion complexes

Domperidone inclusion complexes were prepared with β-CD in different ratio (1:0.5, 1:1, 1:1.5 and 1:2) by kneading method. Domperidone and β-CD were weighed and transferred to mortar and kneaded for 45 min using alcohol-water mixture in ratio 1:1, sufficient solvent was added to maintain paste like consistency. The resulting paste was then dried in the oven at 50° for 24 h. The dried complexes were ground in a mortar for 2 min and passed through sieve No.100. The prepared complexes were stored in glass vials and used for further studies.

Dose calculation for Domperidone

The dose to be incorporated in a patch was calculated in film was calculated using the following mathematical equation:

$$\text{Drug input} = C_{ss} \times K_e \times V_d$$

Where, C_{ss} is concentration at steady state (20.7 µg L^{-1}), K_e is elimination rate constant (0.7545 h^{-1}). V_d is volume of distribution (440 L).[3]

The dose of Domperidone is 7 mg/4 cm^2. Amount of drug present in 70.84 cm^2 of petridish was 123.97 mg for all formulations.[3,4]

Preparation of fast dissolving films

Fast-dissolving film of domperidone was prepared by the solvent-casting method. From the preliminary physical observation of the films prepared the best compositions were selected for the incorporation of domperidone. Aqueous solution was prepared by dissolving the polymer in 15 ml distilled water and was allowed to stirr for 4 h and kept for 1 h to remove all the air bubbles entrapped. The drug and plasticizer were dissolved in smaller amounts of ethanol. This mixture was then added to the aqueous viscous solution and stirred for 1 h. The entrapped air was removed by vacuum. Then the mixture solution was casted as a film onto a plastic petridish and dried in the oven at 50°C for 24 h. The film was carefully removed from the petridish, checked for any imperfections, and cut into the 2 cm×2 cm in size, in which 7 mg domperidone was present. The films were stored in a glass container maintained at a temperature of 30°±1°C and relative humidity 60±5% until further analysis.[5,6,7]

Experimental design

A 3^2 full factorial design was employed to study the effect of independent variables such as HPMC E3 (X_1) and HPMC E5 (X_2) on the dependent variables like Tensile strength (N/cm^2), Disintegration time (sec) and percentage of drug dissolved (%). In this design, two factors were evaluated, each at three levels and experimental batches were performed at all nine possible combinations. The data were subjected to contour and 3-D response surface plot in Design-Expert® 8.0.7.1 (a software developed by Stat-Ease) to determine the effect of polymers on the release of drug and the dependent variables. The values of variables in 3^2 factorial designs are indicated in Table 1. A statistical model incorporating interactive and polynomial terms was used to calculate the responses as follows:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1X_2 + b_{11} X_1X_1 + b_{22} X_2X_2$$

Where, *Y* is the dependent, b_0 is the arithmetic mean response of the all trials, and b_i (b_1, b_2, b_{12}, b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_1X_2, X_{11} and X_{22}) which represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1 X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate the nonlinearity. The composition of the factorial design batches F1 to F9 are shown in Table 1 and Table 2. Each formulation was contained 1%W/V of PVA, 0.35%W/V of mannitol, 0.15%W/V of xanthan gum, 1.3 ml of PG and 0.3 ml of glycerol.[8]

Thickness Measurement

The thickness of the Fast dissolving film (2×2 cm^2) was determined by using a screw gauge. The thickness of each film at three different places determined and standard deviation was also calculated.[9,10]

Drug content uniformity

Fast dissolving film of size 4 cm^2 was cut into small pieces and transferred into a graduated glass stoppered flask containing about 10 ml of 6.8 pH phosphate buffers. The flask was charge on rotary flask shaker for 24 hrs. The solution was filter and the amount of drug present is determined by UV spectrophotometric method.[11,12]

Weight variation

Three individual batches of fast dissolving film of size (2×2 cm^2) was weighed on an electronic balance and the average weight and standard deviation was calculated.[13]

Surface pH

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect *in vivo*. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported.[14]

Tensile strength

Mechanical properties of the polymeric fast dissolving film were conveniently determined by measuring their tensile strength. The tensile strength of the fast dissolving film was determined using handmade tensile strength instrument. Average reading of three fast dissolving films was taken as the tensile strength. The fast dissolving film was fixed to the assembly, the weights required to break the film was noted.[15-18] Tensile strength was calculated using the following formula,

$$\text{T. S.} = \text{break force} / L$$

Where, L = elongated length of the film.

Percentage elongation

Percent elongation was mainly based on tensile strength of films. The nature of polymers affects tensile strength and % elongation. Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement using the following formula.[9,19]

$$\text{Percentage Elongation} = \frac{(L_F - L_O)}{L_O} X\ 100$$

Where, L_F = final length, L_O= initial length.

Folding endurance

Folding endurance measures the ability of patch to withstand rupture, higher the folding endurance lower was chances of film to rupture easily and vice versa. This parameter was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking give the value of folding endurance.[20,21,22]

% Moisture content

This test was also carried to evaluate the integrity of films at dry condition. Film of 4 cm^2 area was cut out and weighed

accurately and kept in a desiccator containing fused anhydrous calcium chloride. After 24 h the film was removed and weighed. Percentage moisture content of film was determined as follows.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (5)$$

***In vitro* Disintegration Time**

The disintegration time is the time when a film breaks or disintegrates. The test was performed using the same method as mentioned by setouhy et al. with slight modification. The film size required for dose delivery (2×2 cm) was placed on glass petri dish containing 10 ml of 6.8 phosphate buffer. The time required for breaking of film was noted as *in vitro* disintegration time.[7,11]

***In vitro* Dissolution Time**

Cumulative drug release and cumulative % drug retained were calculated on the basis of drug content of domperidone present in the respective film. The *in vitro* dissolution test was performed using the USP basket type apparatus. The dissolution studies were carried out at 37±0.5°C; with stirring speed of 100 rpm in 400 ml phosphate buffer pH 6.8 with 20% v/v propylene glycol. The film size required for dose delivery (2×2 cm) was used. Five milliliters aliquots of dissolution media were collected at predetermined time intervals of 2, 4, 6, 8, and 10 min and replaced with equal volumes of distilled water. The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved domperidone was determined at appropriate wavelength using the UV-Visible spectrophotometer.[11,23,24]

***In vitro* permeation studies**

In vitro permeation studies through cellophane membrane was carried out using the Franz diffusion cell of internal diameter of 2.5 cm. The cellophane membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with 15 ml of phosphate buffer of pH 7.4 with 20% v/v PEG which was maintained at 37± 0.2°C and hydrodynamics were maintained using magnetic stirrer. One film of dimension 2 cm × 2 cm was previously moistened with a few drops of pH 6.8 phosphate buffer and placed in donor compartment. The donor compartment was filled with 1 ml of pH 6.8 phosphate buffer. 1 ml samples from receptor compartment were withdrawn at suitable time interval which was then replaced with 1 ml of pH 7.4 phosphate buffer. The percentage of domperidone permeated was determined by measuring the absorbance in UV spectrophotometer at λmax of 283 nm.[14,17,18]

Viscosity measurement

Viscosity of the samples was determined using a Brookfield digital viscometer (Model no: Brookfield LV.DV-III ULTRA Programmable Rheometer) with spindle S62.The sample temperature was controlled at 25±1ºC before the each measurements. The optimized formulation viscocity by dissolving film in 3 ml 6.8 phosphate buffer.[16]

Stability studies

The optimized formulation was subjected to stability studies as per International Conference on Harmonization (ICH guidelines) the sample was packed in an aluminum foil. Then stored stability chamber controlled at accelerated testing condition at 40^{0}C / 75 % RH for 3 months and evaluated for their physical appearance, drug content, *in vitro* disintegration time, drug release at 1 month intervals of time and results were reported.[25,26]

Pharmacokinetic study of prepared fast dissolving films

Data obtained from dissolution studies were fitted to various kinetic equations. The kinetic models used were zero order (% unreleased drug vs time), first order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time) and Korsmeyer (log cumulative percentage of drug released vs log time) equation.

RESULTS AND DISCUSSIONS

Compatibility studies were performed using FTIR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic absorption peaks of Domperidone were obtained at different wave numbers in different samples.

The peaks obtained in the spectra of each physical mixture correlates with the peaks of drug spectrum. The FT-IR of pure drug was characterized by N-H stretching at 3126 cm^{-1} and C=O stretching at 1717 cm^{-1}, indicating the presence of –CONH group, asymmetric C-H stretching at 2817 cm^{-1}, C=C at 1623 cm^{-1} and N=C stretching at 1489 cm^{-1}.(Fig. 1) The FTIR spectra of fast dissolving film formulation was described by N-H stretching at 3127.26cm^{-1}, Asymmetric C-H stretching at 2936.66 cm^{-1}, N=C stretching at 1488.87 cm^{-1} (Fig. 2). All these peaks clearly indicate that they are closely similar to the peaks of pure drug. This indicates that the drug is compatible with the formulation components.

The DSC thermogram of domperidone exhibited an endothermic peak at 245.54^{0}C corresponding to its melting point. The DSC thermograms of domperidone with other excepitents does not show profound shift in peaks (245.54^{0}C) which indicates compatibility. The DSC thermogram of the individual drug and final formulation show in Fig. 3 and Fig. 4.

In order to study the possibility of any drug polymer interaction, UV spectrum of the various drug loaded inclusion complexes were carried out in phosphate buffer pH 6.8 and 20% PG. The spectrum indicated that there was no interference or shifting of λ_{max} of domperidone which reflects no drug polymer interaction. Drug content of all inclusion complexes were in the range of 95.14% - 97.54%. This indicates the proper loading of drug in inclusion complexes and effectiveness of kneading method.[27] The drug content of inclusion complexes are as shown in (Table 3).

It was evident at a glance that all system with CDs exhibited better dissolution properties than pure drug alone. Statistically significant differences in term of dissolution were found in all the domperidone- β-CD inclusions. The increased dissolution rate (physical mixture) is attributable both to improvement in drug wettability and to formation of readily soluble complexes in dissolution medium. Further improvement obtained with kneading could be explained by the more intimate contact between drug and carrier and the decrease of drug crystallinity, as well as a phenomenon of at least partial drug inclusion complexation. The best performance of these product seemed to confirm that drug inclusion complexation occurred substantially only in such systems, thus allowing to obtain the highest dissolution improvement.[27,28] Dissolution data of inclusion complexes also indicated that there was an increase in dissolution (54-98% w/v) as compared to pure drug (42% w/v), and maximum increase was observed in case of inclusion complexes I_2 containing 1:1 drug to β-CD ratio (Fig. 5). So, 1:1 drug to β-CD ratio was selected for further studies.

Preliminary Studies

Preliminary studies were carried out to select a suitable polymer system and to decide on a good polymer plasticizer system, capable of producing films of desirable mechanical property and disintegration time. The film casting solution was prepared as per solvent casting method.

The films prepared from different combination of polymer like, HPMC E3, HPMC E5 and PVA in different concentration (B_1 to B_{12}) were shown good physical property characteristic and inclusion complex loading capacity. From all the films, films having HPMC E3 (3%) and HPMC E5 (4%) (B_{10}) were shown most desired properties and lower disintegration time (31.67±3.06 sec) than other films (Table 4). As a result an attempt was made to prepare films using combination of HPMC E3 (3%) and HPMC E5 (4%) for the further studies.

Experimental Design

3^2 Factorial design has often been applied to optimize the formulation variables with basic requirement of understanding interaction of independent variables. Preliminary investigations of the process parameters revealed that factors like concentration of HPMC E3 (X1) and concentration of HPMC E5 (X2) showed significant influence on disintegration time (R_1), amount of drug dissolve in 30 min (CPR Q_{30}; R_2) and tensile strength (R_3) of drug loaded fast dissolving film. Hence, they were utilized for further systematic studies. For all 9 batches, both the selected dependent variables (X1 and X2) showed a wide variation in disintegration time, amount of drug release in 30 min and tensile strength. The data clearly indicated strong influence of X1 and X2 on selected responses (R1, R2 and R3). The polynomial equations can be used to draw conclusions after considering magnitude of coefficients and mathematical sign it conveys either positive or negative (Table 5). Results for experimental design batches and its ANOVA were shown in table 10 and figure 6, 7 & 8.

Effect of design factors on Disintegration time

The ANOVA results, contour plot and 3D surface plot for the disintegration time (Figure 6) showed the strong effect of the two factors (concentration of HPMC E3 and concentration of HPMC E5. Polynomial equation of the disintegration time was indicated that the both polymer concentration have positive effect on the disintegration time. *In vitro* disintegration time of the films was found to increase with increase in the amount of the polymer. It was observed that in vitro disintegration time varies from 27 to 79 sec for all the formulations. *In vitro* disintegration time of FDF containing HPMC E-3 and HPMC E-5 as polymer was affected by the thickness of the film. *In vitro* disintegration time of the formulation F9 was maximum than other formulations. Maximum concentration of polymers in F9 may be the reason for maximum disintegration.

Effect of design factors on CPR Q_{30}

The ANOVA results, contour plot and 3d surface plot for the amount of drug released in 30 min (CPR Q_{30}; Figure 7) showed the strong effect of the two factors concentration of HPMC E3 and concentration of HPMC E5. Polynomial equation of the CPR Q_{30} was indicated that the both polymer concentration have positive effect on the CPR Q_{30}. CPR Q_{30} of the films were found to decrease with increase in the amount of the polymer. It was observed that CPR Q_{30} varies from 78.42 to 95.90 for all the formulations. CPR Q_{30} of the formulation F4 was maximum than other formulations. Minimum CPR Q_{30} was observed in F9. Maximum concentration of polymers in F9 may be the reason for Minimum CPR Q_{30}.

Effect of design factors on Tensile strength

The ANOVA results, contour plot and 3D surface plot for the tensile strength (Figure 8) showed the strong effect of the two factors (concentration of HPMC E3 and concentration of HPMC E5. Polynomial equation of the tensile strength was indicated that the both polymer concentration have positive effect on tensile strength. Tensile strength of the films was found to increase with increase in the amount of the polymer. It was observed that tensile strength varies from 1.231±0.145 to 3.093±0.177 for all the formulations. Tensile strength of the formulation F9 was maximum than other formulations. Maximum concentration of polymers in F9 may be the reason for maximum disintegration. Tensile strength of optimized formulation F4 was found 2.180±0.065.

Evaluation parameter of film formulations

Thickness

The thicknesses of formulated films were found to be in range of 0.33±0.03 to0.41±0.06 mm. The mean values are tabulated in Table 6. The values indicating that as the concentration of polymer increases thickness was gradually increased. The values are almost uniform in all formulations. Obtained results has shown that increase in film thickness decreases tensile strength while increases % elongation.[29]

Weight variation test

The percentage weight variation for all the formulation is tabulated in Table 6. All the films passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5%. It was found to be in range of 121.66±3.51to151.34±6.42 mg. The weight of all the films was found to be uniform.

Drug content

The drug content and content uniformity test was performed to ensure uniform and accurate distribution of drug. The content uniformity was performed for all the nine formulations and results are tabulated in Table 6. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The results indicated that in all the formulations the drug content was uniform. The cumulative percentage drug released by each film to the *in vitro* release studies was based on the mean content of the drug present in the respective film. The ranges of drug content in all the formulations were 89.375±0.962 to 104.279±0.962.

Surface pH

The surface pH of the films was ranging from 6.65±0.015to 6.94±0.080 as shown in table 6. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity. The standard deviation values calculated for all the films are very low which conclude that the surface pH of all the films was uniform and within the range.

% Elongation

Percent elongation is mainly based on tensile strength of films. The nature of polymers affects tensile strength and % elongation. The percentage elongation of all the batches ranges from 5-23% and percentage elongation of all films was given in Table 7. It increased upon increasing the amount of polymer as shown by the formulations. Formulation F9 had highest percentage elongation.

Folding endurance

Folding endurance measures the ability of patch to withstand rupture, higher the folding endurance lower will be chances

of film to rupture easily. The folding endurance of the films was determined by repeatedly folding a small strip of the films at the same place till it broke and the average folding endurance of all films was given in Table 7. Folding endurance of all the batches ranges from 38.67±1.53 to 54.33±2.08.

Increase in concentration of polymer increases folding endurance of films but after specific concentration increase in concentration of polymer decreases folding endurance. This was due to film thickness. More the thickness of lower will be folding endurance. F5 formulation showed high folding endurance 54.33±2.08.

Moisture content

Moisture loss is defined as the quantity of moisture transmitted through unit area of film in unit time. The moisture content study gives an idea about films stability nature and ability of films to withstand its physicochemical properties under normal conditions. It also gives idea about hydrophilicity of film formulations.[29] The obtained results are tabulated in Table 7. The obtained values are almost uniform and ranges from 1.37 ± 0.48% to 3.13 ± 0.53%. F9 formulation showed high % moisture content while F1 and F2 formulations showed low % moisture content. Higher concentration of polymers in F9 may be the reason for higher percentage of moisture content.

In vitro dissolution study

In vitro release studies of Domperidone patches were carried out in phosphate buffer (pH 6.8). Cumulative drug release was calculated on the basis of drug content of Domperidone present in the respective film. The results obtained in the *in vitro* drug release for the formulations F1 to F9 is tabulated in Table 8. Rapid drug dissolution was observed in F1, F4, which release 92.43, 95.90 %, respectively, at end of 30 min. F4 formulation shows highest percent of drug release (95.90%) than other formulations and drug release 75.26% after 15 min.

Slow drug dissolution was observed in F6, F9 with release 81.34%, 78.42 respectively at end of 30 min, the concentration of the polymer increased, and the drug release was found to be decreased. This might be due to the increase concentration of polymer, results in formation of strongmatrix layer caused by more intimate contact between the particles of HPMC results in decreased in mobility of drug particles in swollen matrices, which leads to decrease in drug release.[30,31] From all the evaluation parameters, it has been seen that F4 formulation fulfill all the characteristics of fast dissolving films, so F4 formulation was selected as best formulation.

In-vitro drug permeation

From *in-vitro* drug permeation study, it was found that the formulation F4 showed better drug permeation of 66.47% in 30 min and 80.38% in 45 min. The percentage amount of drug permeated was plotted against time to obtain permeation profile as shown in Figure 10. It was observed that domperidone was easily permeated across membrane due to BCS class II drug and shown the flux 65.15 µg/h/cm^2. So, the result of *in- vitro* study showed that the domperidone from fast dissolving film formulation was easily solubilized and absorbed from pregastric route, mouth, pharynx and esophagus.[2,20,32]

Viscosity

The viscosity of the optimized formulation F4 and marketed syrup formulation was measured using Brookfield digital viscometer. Viscosity of optimized F4 formulation was measured using spindle No: 62 at 65 rpm having torque 99.4 at 36.8^{0}c temperature viscosity of film solution was found to be 1056 cps. Viscosity of marketed formulation was measured using spindle No: 62 at 55 rpm having torque 98.9 at 36.6^{0}c temperature viscosity of marketed formulation was found to be 522 cps. Viscosity of F4 formulation was sufficient to absorb from pregastric route.[33,34] Increasing the concentration of a dissolved or dispersed substance generally gives rise to increasing viscosity, and also as molecular weight of a solute increases viscosity increases.

Stability Studies

The optimized formulations F4 was evaluated for stability studies which were stored at 40^{0}C at 75% RH tested for 3 month and were analyzed for their tensile strength, surface pH, *In vitro* disintegration time, drug content, *in vitro* drug release 1 month interval. *In vitro* drug release show in Figure 11. The residual drug contents of formulations were found to be within the permissible limits and the results were shown in the Table 9. There was no significance difference seen in the observable parameter.

Pharmacokinetic study of prepared fast dissolving films

Data obtained from dissolution studies were fitted to various kinetic equations. The kinetic models used were zero order (% unreleased drug vs time), first order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time) and Korsmeyer (log cumulative percentage of drug released vs log time) equation.

The data of average values were processed as per Hixon–Crowell cube root law and are given in the Table 12 and the Figure 14. The data of average values were processed as per Higuchi's equation and are represented in the Figures 15. The data of average values were processed as per Korsmeyer-Peppas model and are represented in the Figures 16. The linearity of data for all the models was identified from the Figures. The equations were generated through statistical procedures and reported in the Table 11 and 12.

The release data of Domperidone from all the patches were given in Figure 9. A perusal to Figure 9 indicated that the drug release was highest in F4. Data of the *in vitro* release were fit into different equations and kinetic models to explain the release kinetics of domperidone from these films. The release kinetics of domperidone followed first order from all the films F1 to F9. The better fit (highest R^2 values) was observed in case of Higuchi's model than Hixon–Crowel model in all the films. Hence mechanism of drug release from the domperidone patches F1 to F9 followed are diffusion controlled. Application of Hixon – Crowell cube root law, the equation $(M_0^{1/3} - M^{1/3}) = kt$, provides information about the release mechanism, namely dissolution rate limited. Application of Higuchi's equation ($M = K\ t^{1/2}$) provides information about the release mechanism, namely diffusion rate limited. Korsmeyer-Peppasmodel indicates that release mechanism is not well known or more than one type of release phenomena could be involved. The 'n' value could be used to characterize different release mechanisms.

According to Korsmeyer-Peppas model a value of slope between 0.5 and 1indicates an anomalous behavior (Non-Fickian). So, it indicates that release mechanism from the films F1 to F8 follows non-Fickian diffusion (anomalous behaviour). However, film F9 follows case II transport.

CONCLUSION

Inclusion complex of Domperidone with β-CD showed improve dissolution behavior pure drug which was prepared by kneading method. Among all complexes prepared with β-CD (1:1) molar ratio was optimized. The fast dissolving film

of Domperidone was prepared by the solvent casting method showed acceptable mechanical properties and satisfactory drug release. The multiple regression analysis of the results led to the equations that describe adequately the influence of the selected variables concentration of HPMC E-3 LV and HPMC E-5 LV on the responses under study. Batch F4 was found to be optimized batch which contain 2% w/v of HPMC E-3 LV, 4% of HPMC E-5 LV and 1% w/v PVA. It was observed from the results that, F4 formulations which have 35.33 seconds disintegration time and showed maximum dissolution rate compare to other formulations about 95.90% of drug release in 30 min *In vitro* permeation 80.38% in 45 min. *In vitro* release and *In vitro* permeation evaluation of film confirmed their as an innovative dosage from to improve delivery of Domperidone.

Table 1: AMOUNT OF VARIABLES IN A 3^2 FACTORIAL DESIGN

Coded values	Actual values	
	X_1:HPMC E3	X_2:HPMC E5
-1	2%	3.00%
0	3%	4.00%
1	4%	5.00%

Table 2: 3^2 FACTORIAL DESIGN

Formulations	X1	X2
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

Table 3: OPTIMIZATION OF β-CYCLODEXTRIN

Formulation	Drug + β-CD	Drug content (%)*	CPR at 90 min
I_1	1:0.5	95.30±1.47	81%
I_2	1:1	97.54±0.83	98%
I_3	1:1.5	96.41±1.21	54%
I_4	1:2	95.14±1.27	65%
Drug	-	-	42%

*All results are shown in mean± S.D. (n=3)

Table 4: Characteristics of Domperidone inclusion complex loaded film prepared using different polymer

Batch[a]	Polymer	Concentration (%w/v)	Remark	Disintegration time[b] (sec)
B_1	HPMC E3	3	Poor	--
B_2	HPMC E3	4	Poor	--
B_3	HPMC E3	5	Poor	--
B_4	HPMC E5	3	Poor	
B_5	HPMC E5	4	Poor	--
B_6	HPMC E5	5	Poor	--
B_7	HPMCE3+Maltodextrin	3+ 3	Sticky	--
B_8	HPMCE3+Maltodextrin	3+ 5	Sticky	--
B_9	HPMC E3+HPMC E5	3+ 3	Average	28.67±2.08
B_{10}	HPMC E3+ HPMC E5	3+ 4	Good	31.67±3.06
B_{11}	HPMC E3+ HPMC E5	3+ 5	Good	50.33±0.58
B_{12}	HPMC E3+ PVA	3+ 2	Average	44.34±1.52

[a]Each formulation contains 0.3 ml PG and 0.3 ml glycerin.
[b]All results are shown in mean ± S.D. (n=3)

Table 5: Design Summary

	R_1	R_2	R_3
Formulation Code	Disintegration Time* (sec)	Q_{30}	Tensile strength* (N/cm2)
F1	27.33±3.51	92.43	1.231±0.145
F2	37.33±3.06	90.64	1.584±0.172
F3	53.67±2.52	84.86	2.057±0.058
F4	35.33±2.08	95.90	2.180±0.065
F5	51.66±2.51	89.06	2.381±0.042
F6	59.33±1.53	81.34	2.875±0.058
F7	50.00±2.65	90.90	2.512±0.316
F8	64.33±3.51	83.22	2.639±0.307
F9	79.00±3.61	78.42	3.093±0.177

*All results are shown in mean± S.D. (n=3); R_1: Response 1, R_2: Response 2, R_3: Response 3.

Table 6: Characterization of fast dissolving film

Formulations	Weight variation* (mg)	Thickness* (mm)	Surface* pH	Drug content*
F1	121.66±3.51	0.33±0.03	6.65±0.015	89.375±0.962
F2	124.33±2.08	0.36±0.05	6.79±0.094	97.067±1.272
F3	140.66±7.57	0.43±0.08	6.82±0.065	93.221±1.442
F4	135.66±4.72	0.41±0.10	6.84±0.045	97.548±0.962
F5	146.33±5.13	0.47±0.08	6.70±0.032	95.625±0.481
F6	154.00±6.24	0.46±0.05	6.92±0.055	100.913±1.923
F7	143.33±5.03	0.41±0.06	6.83±0.051	102.837±2.203
F8	151.34±6.42	0.44±0.06	6.94±0.080	104.279±0.962
F9	159.33±5.03	0.51±0.08	6.72±0.037	90.817±1.733

*All results are shown in mean± S.D. (n=3)

Table 7: Characterization of fast dissolving film

Formulation code	Folding endurance*	% Elongation*	% Moisture content*	CPR (%)*
F1	41.00±2.65	5.33±1.15	1.37±0.48	99.42
F2	49.67±1.53	8.67±2.31	1.88±0.50	99.55
F3	42.33±2.52	12.67±2.31	2.37±0.37	97.73
F4	50.67±3.06	10.67±3.06	2.21±0.08	99.68
F5	54.33±2.08	16.00±2.00	2.50±0.34	98.72
F6	45.33±2.31	19.33±4.16	2.58±0.55	96.96
F7	46.33±1.15	17.33±3.06	2.56±0.43	98.07
F8	41.67±2.08	20.67±4.16	2.88±0.51	96.36
F9	38.67±1.53	22.67±5.03	3.13±0.53	97.56

*All results are shown in mean± S.D. (n=3)

Table 8: Dissolution of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00
1	6.04±1.24	9.65±12.07	7.88±2.34	8.27±01.14	11.23±2.79	6.28±1.05	4.27±1.32	4.21±2.24	0.95±1.47
2	10.50±0.92	13.16±1.45	12.89±3.04	16.40±1.26	22.05±1.44	9.32±2.88	7.71±1.65	7.60±2.20	0.95±1.47
4	22.05±2.32	29.57±1.26	21.92±2.46	28.42±2.08	28.82±1.89	19.33±2.14	14.78±2.74	17.48±1.54	7.95±0.78
6	38.64±3.12	38.53±3.08	24.60±1.34	37.24±1.42	35.70±2.01	26.15±1.26	26.73±1.26	31.67±0.98	14.75±1.65
8	47.90±1.89	43.84±1.06	34.28±1.63	51.16±1.36	47.74±1.64	32.30±3.12	32.57±3.05	39.86±2.56	28.53±2.31
10	56.91±2.47	52.34±2.48	43.19±2.87	59.01±2.41	53.42±2.25	43.68±2.75	39.27±2.58	46.46±1.89	36.06±1.23
15	68.72±1.79	63.88±1.76	61.21±1.89	75.26±2.68	65.43±3.58	58.11±1.05	54.28±1.96	58.06±2.05	49.91±2.49
20	82.56±2.42	77.15±2.43	72.79±2.08	83.49±0.89	74.53±3.11	67.68±2.47	69.04±2.78	70.61±1.74	64.37±1.81
30	92.43±1.65	90.64±1.68	84.86±3.11	95.90±2.12	89.06±2.14	81.34±1.92	90.90±1.94	83.22±2.05	78.42±0.74
45	97.11±1.46	99.49±3.14	93.94±2.26	99.62±1.75	95.73±1.29	93.35±3.16	95.86±1.25	93.52±2.70	91.35±1.88
60	99.42±2.14	99.55±1.67	97.73±2.47	99.68±1.54	98.72±1.57	96.96±2.48	98.07±0.79	96.36±1.88	97.56±2.45

Table 9: Results of accelerated stability studies

Evaluation parameters	Time period for sampling		
	Intial	After 1 month	After 3 months
pH	6.84±0.045	6.92±0.092	6.95±0.067
Disintigration time (min)	35.33±2.08	36.15±3.24	36.54±2.46
Tensile strength	2.180±0.065	2.128±0.112	2.097±0.089
Drug content (%)	97.548±0.962	96.896±1.216	96.342±1.672
CPR_{30}	95.90±2.12	94.09±0.79	91.73±3.04

All results are shown in mean± S.D. (n=3)

Table 10: Regression analysis of model

Coefficient	Disintegration time		CPR30		Tensile strength
	FM	RM	FM	RM	FM
β0	48.993	50.887	88.988	87.419	2.396
β1	13.223	13.223	-5.768	-5.768	0.350
β2	12.500	12.500	-2.565	-2.565	0.562
β11	-0.330		-0.332		0.123
β22	3.170		-2.022		-0.293
β12	0.665		-1.228		-0.061

Table 11: Comparison of order of *in vitro* release of domperidone from all the formulations

Formulation	Zero Order	First Order
F1	y = -1.664x + 76.02 R² = 0.750	y = -0.036x + 2.014 R² = 0.996
F2	y = -1.643x + 76.05 R² = 0.799	y = -0.042x + 2.066 R² = 0.960
F3	y = -1.669x + 81.68 R² = 0.840	y = -0.027x + 2.009 R² = 0.998
F4	y = -1.636x + 72.88 R² = 0.733	y = -0.046x + 2.036 R² = 0.974
F5	y = -1.560x + 74.27 R² = 0.796	y = -0.030x + 1.983 R² = 0.998
F6	y = -1.669x + 83.42 R² = 0.857	y = -0.025x + 2.012 R² = 0.998
F7	y = -1.767x + 85.14 R² = 0.851	y = -0.030x + 2.040 R² = 0.986
F8	y = -1.657x + 82.00 R² = 0.825	y = -0.024x + 1.991 R² = 0.995
F9	y = -1.726x + 87.95 R² = 0.892	y = -0.026x + 2.049 R² = 0.990

Table 12: Regression equations of *in vitro* release of Domperidone from all the formulations

Formulations	Hixon - Crowell	Higuchi	KorsmeyerPeppas
F1	y = 0.065x + 0.283 R² = 0.951	y = 15.08x + 0.156 R² = 0.923	y = 0.920x + 0.648 R² = 0.823
F2	y = 0.069x + 0.229 R² = 0.965	y = 14.68x + 1.163 R² = 0.955	y = 0.844x + 0.742 R² = 0.774
F3	y = 0.057x + 0.179 R² = 0.972	y = 14.57x - 3.694 R² = 0.960	y = 0.867x + 0.661 R² = 0.821
F4	y = 0.072x + 0.327 R² = 0.937	y = 14.96x + 3.247 R² = 0.918	y = 0.859x + 0.748 R² = 0.771
F5	y = 0.059x + 0.314 R² = 0.968	y = 13.98x + 3.933 R² = 0.958	y = 0.791x + 0.812 R² = 0.722
F6	y = 0.055x + 0.150 R² = 0.979	y = 14.49x - 5.148 R² = 0.969	y = 0.906x + 0.595 R² = 0.857
F7	y = 0.062x + 0.102 R² = 0.961	y = 15.28x - 7.939 R² = 0.955	y = 0.973x + 0.503 R² = 0.897
F8	y = 0.054x + 0.194 R² = 0.963	y = 14.58x - 4.240 R² = 0.958	y = 0.963x + 0.536 R² = 0.873
F9	y = 0.056x + 0.051 R² = 0.993	y = 14.72x - 9.509 R² = 0.973	y = 1.105x + 0.301 R² = 0.905

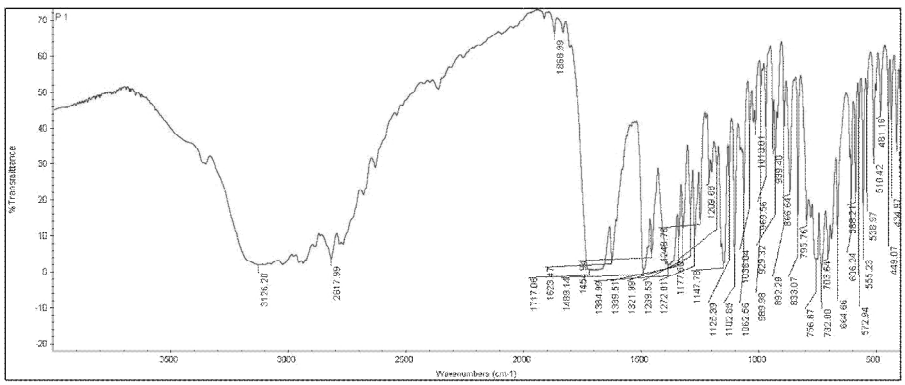

Fig. 1: FTIR of pure Domeperidone

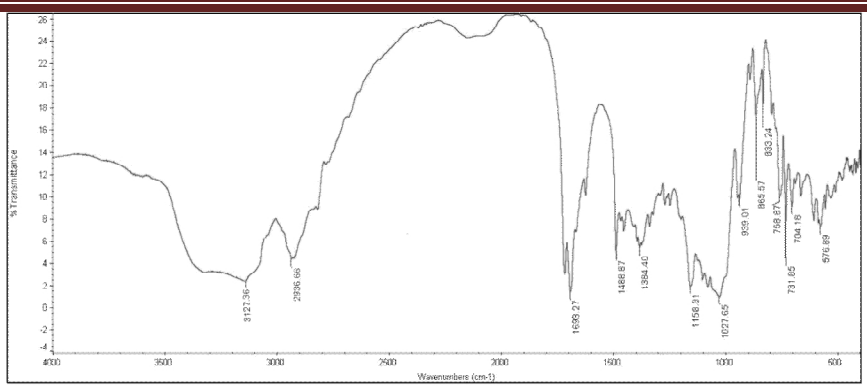

Fig. 2: FTIR of fast dissolving film formulation

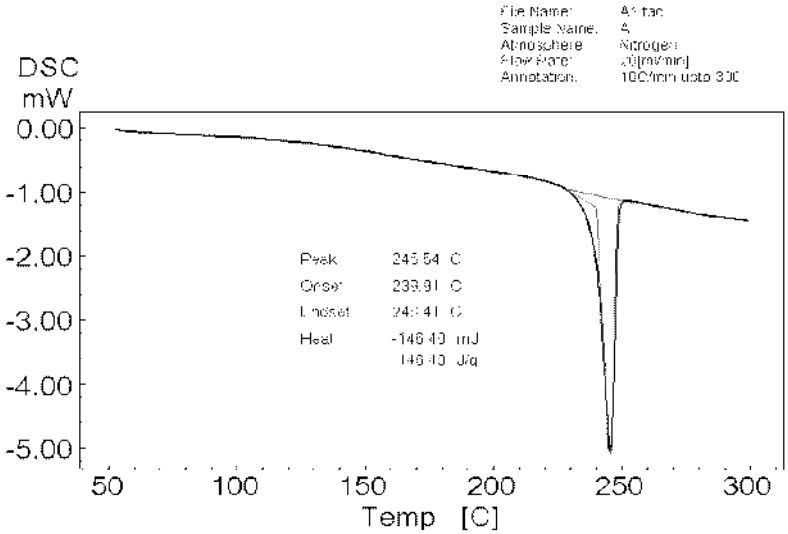

Fig 3: DSC of Pure drug

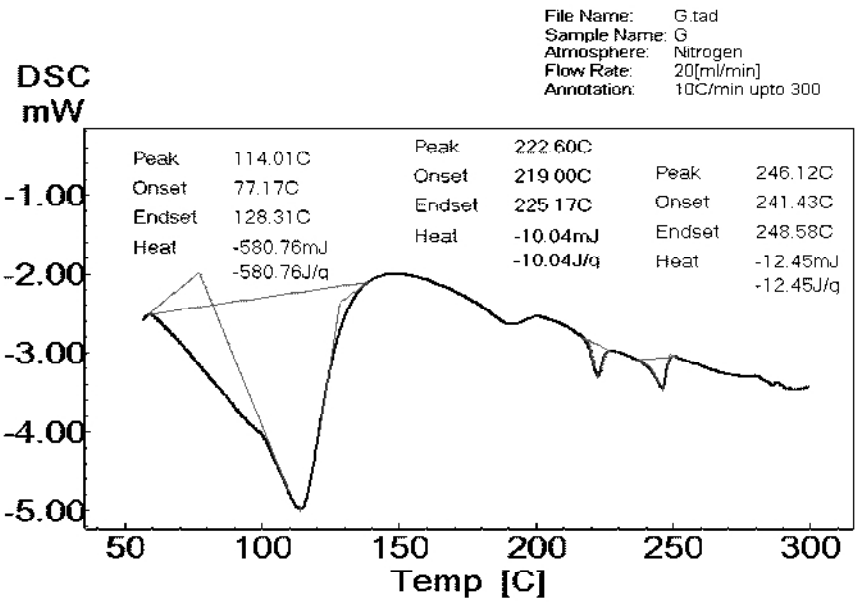

Fig. 4: DSC of optimized fast dissolving film

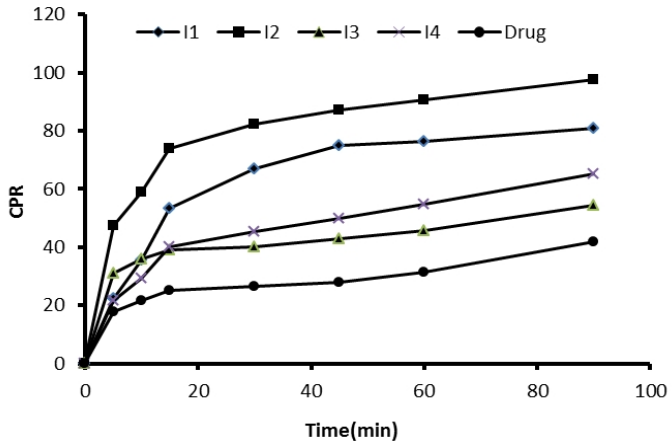

Fig. 5: *In vitro* release of domperidone in phosphate buffer (pH 6.8) from inclusion complex.

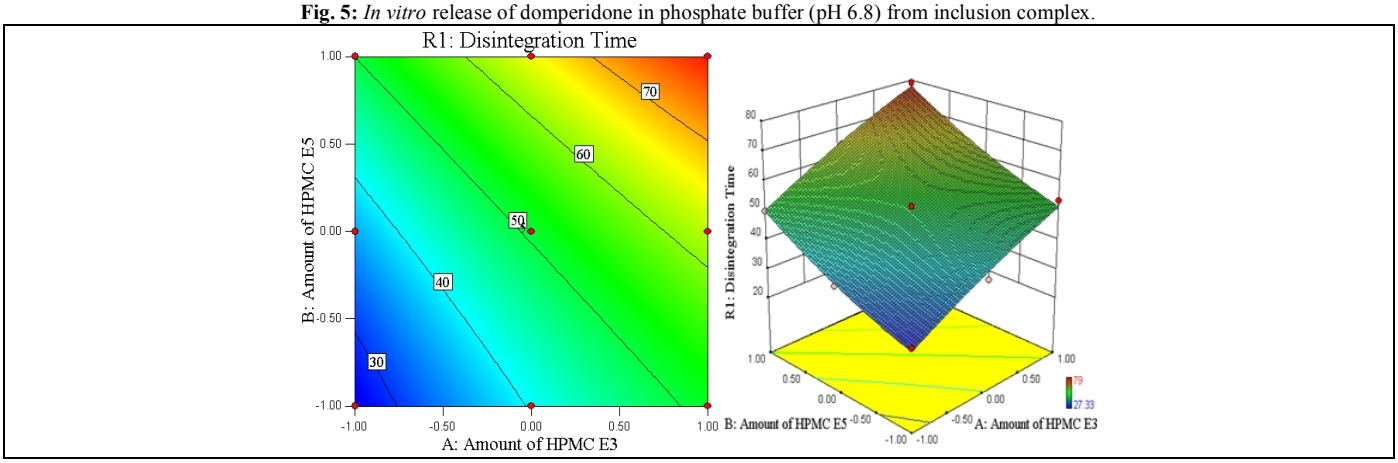

Figure 6: Contour plot and 3D Surface Plot of disintegration time (sec) against amount of HPMC E3 (%w/v) and amount of HPMC E5 (%w/v)

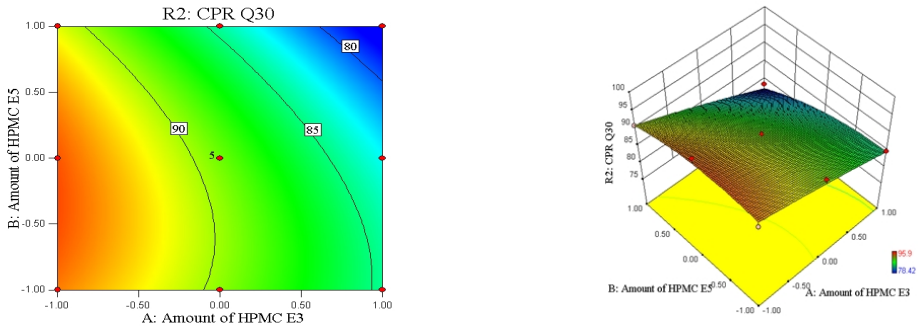

Figure 7: Contour plot and 3D Surface Plot of CPR_{30} (%) against amount of HPMC E3 (%w/v) and amount of HPMC E5 (%w/v)

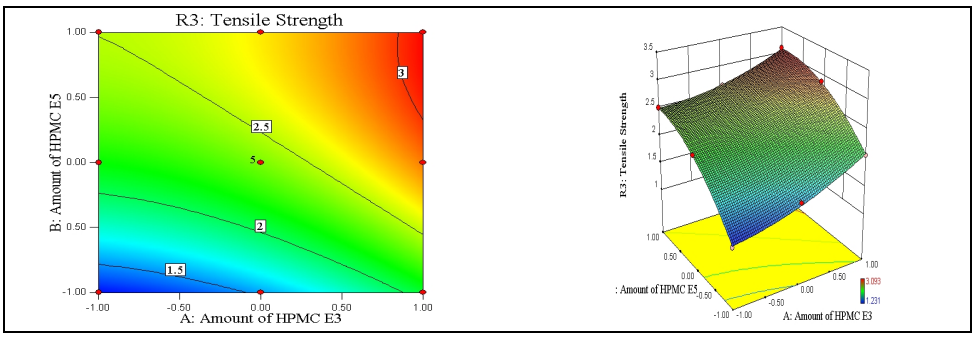

Figure 8: Contour plot and 3D Surface Plot of tensile strength (N/cm^2) against amount of HPMC E3 (%w/v) and amount of HPMC E5 (%w/v)

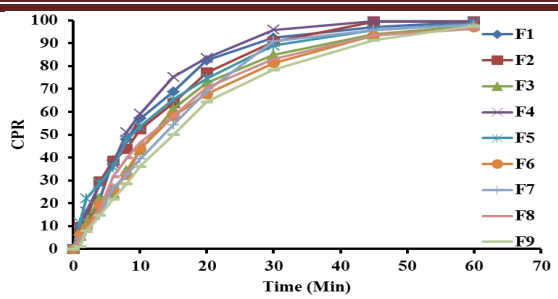

Figure 9: *In vitro* release of domperidone in phosphate buffer (pH 6.8 +20 % v/v PG) from film formulation**.**

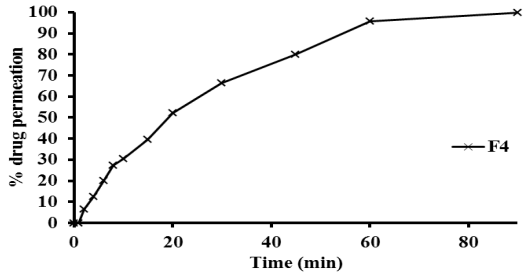

Figure 10: *In vitro* permeation of Domperidone from film formulation.

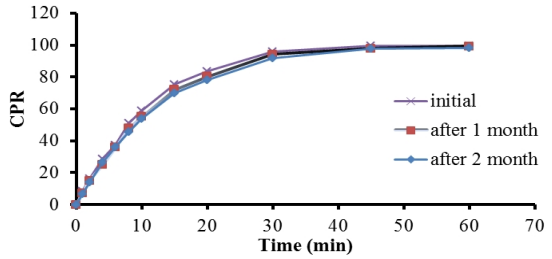

Figure 11: *In vitro* drug release of Domperidone from optimized formulation after and before stability study

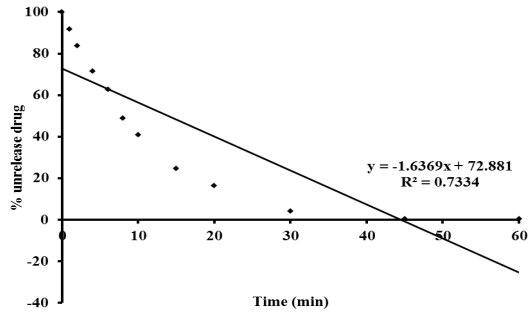

Figure 12: *In vitro* release of domperidone from F4 in phosphate buffer (pH 6.8) formulation. Zero order release.

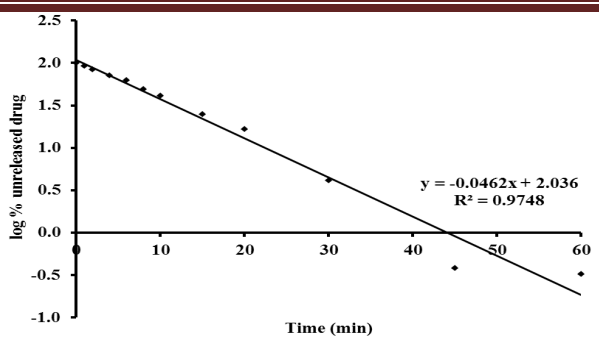

Figure 13: *In vitro* release of domperidone from F4 in phosphate buffer (pH 6.8). First order release.

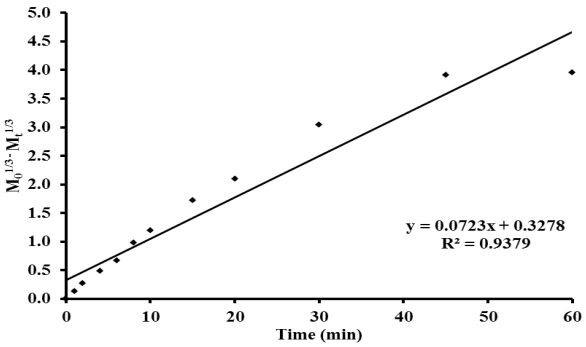

Figure 14: *In vitro* release of Domperidone from F4 in phosphate buffer (pH 6.8) formulation. Hixon Crowell.

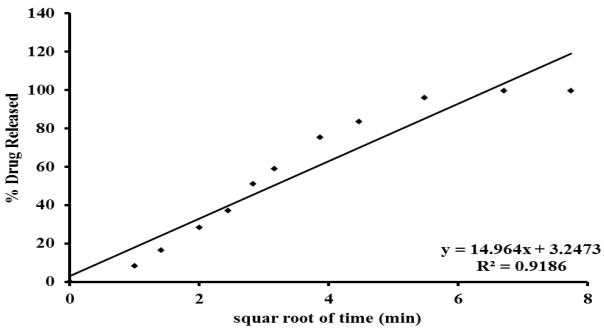

Figure 15: *In vitro* release of Domperidone from F4 in phosphate buffer (pH 6.8) formulation. Higuchi's release model.

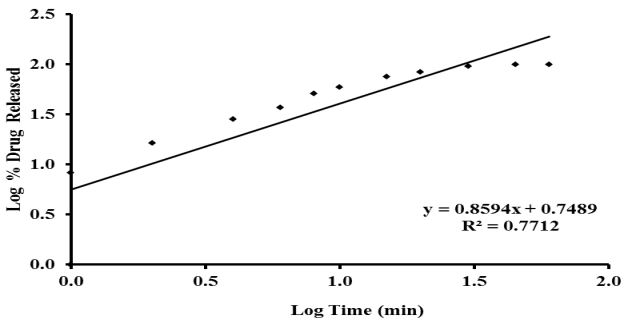

Figure 16: *In vitro* release of Domperidone from F4 in phosphate buffer (pH 6.8) formulation. Korsmeyer-Peppas model.

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