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Methylphenidate Fast Dissolving Films: Development, Optimization Using Simplex Centroid Design and *In-Vitro* Characterization

Short title: Mouth Dissolving Film of Methylphenidate Hydrochloride

Biswajit Basu[1], Ankur Mankad[2], Ayon Dutta[1]
[1]Bengal School Of Technology, Sugandha, Delhi Road, Hooghly, Pin – 712 102, West Bengal, India
[2]Atmiya Institute Of Pharmacy, Yogidham Gurukul, Kalawad Road, Rajkot – 360 005, Gujarat, India

Corresponding Author Information
Biswajit Basu
9724142699
bbasu.pharma@gmail.com
https://orcid.org/0000-0001-8442-801X
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ABSTRACT
Objectives: The main focus of this study to design and optimize Methylphenidate Hydrochloride mouth dissolving film that can be beneficial in an acute condition of attention deficit hyperactivity disorder (ADHD) and Narcolepsy.
Materials & methods: Solvent casting method using here for the preparation of this film. Optimization of the effect of independent variables such as the amount of polymers and active pharmaceutical ingredients (API) (HPMC E5, HPMC E15, and Maltodextrin) the % of drug release, disintegration time, the tensile strength of the film done by using Simplex centroid design. The complex formation of the film was tested by using FT-IR and Differential scanning calorimetry study. The multiple regression analysis has got from the equations of the results that adequately describe the influence of the independent variables on the selected responses. Polynomial regression analysis, contour plots, and 3-D surface plots were used to relate the dependent and independent variables.
Results: Results from the experiment indicated that different polymer amounts had complex effects on % drug release from the film, disintegration time as well as the tensile strength of the film. The observed responses were in near alignment with the expected values calculated from the developed regression equations, as shown by the percent relative error. The final formulation was given more than 95% drug release within 2 minutes and showing disintegrating within a minute which had good tensile strength.
Conclusion: These findings suggest that mouth dissolving film containing Methylphenidate Hydrochloride is likely to become one of the choices of Methylphenidate Hydrochloride preparations for treatment in the ADHD and Narcolepsy conditions.

Keywords: HPMC, Maltodextrin, Mouth dissolving film, ADHD, Simplex Centroid Design (SCD)

INTRODUCTION

Oral drug administration has been one of the most convenient and commonly recognized routes of delivery for most medicinal agents since the dawn of time. Oral drug formulations are solid and liquid preparations that are taken orally, chewed or swallowed, and travel into the GI tract for post buccal absorption.[1] Nowadays, The most common solid oral dosage types used today are tablets and capsules, which include traditional tablets, controlled-release tablets, along with hard and soft gelatin capsules.[2,3]

One of the major problems correlated with the use of these oral dosage forms is the time required for the onset of action, which is at least half an hour in the case of the conventional dosage forms and even more in the controlled and sustained release dosage forms. Dysphagia (difficulty swallowing) is a chronic problem in people of all ages, but it is more prevalent in the elderly and paediatric patients due to physiological differences. Uncooperative, mentally ill, and patients suffering from fatigue, vomiting, motion sickness, allergic attack, or coughing are some of the other groups who have issues. This issue affects 35-50 percent of the population, according to reports.[4,5]

These concerns led to the creation of mouth dissolving films, a new kind of solid oral dosage medium. This delivery mechanisms degrade or disintegrate quickly in the mouth, requiring no water to facilitate swallowing. Such technologies make it easier for those with swallowing problems, as well as the general public, to take their drugs. Upon ingestion causes the saliva serves to rapidly disperse/ dissolve the mouth dissolving film. The saliva containing the dissolved medicament is absorbed from the mouth, pharynx, and esophagus. Because of the above-mentioned advantages, the bioavailability of drugs is significantly increased than those observed from conventional dosage forms such as tablets and capsules.[2,3]

Methylphenidate hydrochloride is a psychostimulant drug. The drug is useful in the condition of Attention deficit hyperactivity disorder (ADHD), a condition that requires immediate medication. By blocking dopamine delivery or carrier proteins, this drug prevents dopamine uptake in central adrenergic neurons. It also induces heightened sympathomimetic activity in the central nervous system by operating on the brain stem arousal system and the cerebral cortex. Methylphenidate hydrochloride is a BCS class-I (high permeability and high solubility) drug and its bioavailability is only 11-52% due to hepatic metabolism. So, the main objective of this project was to provide immediate release of the psychostimulant drug Methylphenidate HCl for the immediate action in ADHD condition, to improve patient compliance, and to avoid hepatic first-pass metabolism of the drug [4,5]

Therefore, the current study was carried out to develop mouth dissolving films (MDFs) of Methylphenidate hydrochloride to provide quicker onset of action in the condition of attention deficit hyperactivity disorder.[4]

MATERIALS AND METHODS

The drug methylphenidate hydrochloride was given as a gift sample from Ipca Laboratories Ltd., Mumbai, India. Different HPMC grades were given as a gift sample from Colorcon Asia Pvt. Ltd., Goa, India. Maltodextrin was purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India.

Calibration curve of Methylphenidate HCl

Preparation of standard stock solution

100 mg of Methylphenidate HCl was weighed accurately into a 100 ml volumetric flask and dissolved with phosphate buffer pH 6.8. The volume was made up to 100 ml with the same solution to get a concentration of 1000 µg/ml (1mg/ml).[6]

Scanning of drug

Ultraviolet spectrum was taken of the stock solution between the wavelengths 200-400 nm. It gave a peak at 257.2 nm and the same was selected as λmax. The absorption maxima of Methylphenidate hydrochloride in pH buffer 6.8 is shown in figure 1.[7]

Preparation of calibration curve

The stock solution was diluted with pH buffer 6.8 to get a concentration range of 100 to 1000 µg/ml. The absorbance of these solutions was measured against a blank at 257.2 nm using a UV visible spectrophotometer (Shimadzu Corporation, Japan), and the absorbance values are summarized in table 1. The calibration curve which was plotted against absorbance versus drug concentrations is given in figure 2.[8,9]

Preparation of mouth dissolving film of methylphenidate HCl

Calculation of dose of Methylphenidate HCl

Methylphenidate is an effective attention-deficit/hyperactivity disorder (ADHD) treatment with a good safety profile; evidence show that dose optimization can improve the safety and effectiveness of treatment. Dose optimization is used widely in general medicine and psychiatry to achieve optimum therapeutic impact, thus minimizing the likelihood of adverse effects. Dose optimization is typical with virtually all psychotropic drugs and may be critical, particularly in therapeutic dose–response relationships with high interindividual heterogeneity, such as the use of stimulants to manage ADHD. Genetic diversity, patient weight, age, sex, drug-induced resistance, and associations with other drugs or medical conditions are all considerations that can affect the need for dosage optimization.[10]

The dosage to be used in the film was measured using the equation below.[11]

Drug input = Css × ke × vd

= 133 µg L-1 × 0.3465 hr-1× 2.7 L

= 6872.399 µg hr-1 =6.87 mg

Here, Css = 133 µg L^{-1}

Vd = 2.7 L

Ke = 0.3465

Where Css is the concentration at a steady state.

Ke = elimination rate constant.

Vd = volume of distribution.

The dose of Methylphenidate HCl is 7.17 mg. Therefore 7.17 mg dose of Methylphenidate HCl was required in a film containing 4 cm^2 areas. The total area of 9.4 cm diameter Petri dish was 69.43 cm^2. So, the amount of drug present in 69.43 cm^2 of Petri dish was 124.42 mg for all formulations. Therefore, the amount of Methylphenidate HCl in each film (4 cm^2) was 7.17 mg.[12,13]

Preparation of Film by Solvent Casting Method

Various methods have been used for film preparation. Among all the methods, the solvent casting method was the widely used method to get a good and smooth film. Mouth dissolving film of Methylphenidate HCl was made by the solvent casting method. The aqueous solution was made by dissolving the chosen polymers in 25 mL purified water and allowing it to rest for 1 hour to eliminate any trapped air bubbles. Then API and plasticizer were dissolved in this polymeric solution. After that, the mixture solution was poured into a silicone Petri dish and dried in a 50°C oven for 24 hours. The film was then gently withdrawn from the Petri dish and examined for flaws. The samples were wrapped in butter paper and aluminium foil and stored in a desiccator until further analysis. [14,15,16,17]

Preformulation study

Melting point

The melting point of methylphenidate HCl was measured by digital melting point apparatus. The drug sample was filled in a capillary tube and kept with a mercury thermometer in an aluminium block of apparatus. The block was heated by two elements clamped to the sides in

the apparatus and the sample tube was viewed through the magnifying lens by adjusting a dark or bright background. The temperature was recorded at which the sample started to melt and the point at which it was completely melted.[18,19]

Partition coefficient

Methylphenidate is soluble in alcohol, ethyl acetate and ether. So, ether is chosen for the determination of partition coefficient. To determine the partition coefficients of Methylphenidate HCl, ether and water were saturated with each other for the period of 24 h in a 500 ml volumetric flask. In a 100 ml volumetric flask, 10% w/v of the drug was transferred to the mixture of the above-saturated solution and stirred for 24 hours at room temperature on a rotary shaker. After 24 hours of equilibrium, the system was centrifuged for 15 minutes at 3000 RPM for 15 minutes. The concentration of methylphenidate HCl in ether and water were analyzed by UV visible spectrophotometer at 257.2 nm after appropriate dilution with methanol. The partition coefficient was determined using the equation below. The experiment was replicated three times to ensure that the results were repeatable.[19]

$$\text{Partition coefficients} = \frac{\text{Concentration of drug in ether}}{\text{Concentration of drug in water}}$$

Optimization of Mouth Dissolving Film components

The placebo films were made using polymers like maltodextrin, HPMC E3, HPMC E5, and HPMC E15 by the solvent-casting method. Polymers were selected from the above placebo film by an appearance by visual inspection and disintegration time. An identical approach was used to optimize plasticizers (Glycerin, Propylene glycol) using the previously optimized concentration of respective components. The plasticizer was optimized based on film tensile strength, folding endurance, and disintegration time.[20,21]

Experimental design

Simplex Centroid Design

The use of simplex centroid experimental design in pharmaceutical research is well known. They're especially useful in formulation optimization procedures where the overall number of ingredients being considered must remain constant. In the films, the total amount of polymer, if changed, can lead to a large extent change in the mechanical properties of the film, so simplex centroid is the appropriate design to be applied to the film formulation. The values of dependent and independent variables can be used to develop a polynomial first-order linear interactive model.

$Y= B_1X_1 + B_2X_2 + B_3X_3 + B_{12}X_1X_2 + B_{23}X_2X_3 + B_{13}X_1X_3 + B_{123}X_1X_2X_3$

Where Y is the response parameter and Bi are projected coefficients for factors Xi. The main effects (X_1, X_2, and X_3) represent average results of changing one factor from its low to high value at a time. The interaction terms (X_1X_2, X_2X_3, X_1X_3, $X_1X_2X_3$) show how the response changes when two or more factors are changed simultaneously (table 2 & table 3).[22,23,24]

Other common ingredients used for each formulation

Other ingredients that have been used include propylene glycol, 0.5 ml, as a plasticizer, and brilliant blue as color. Glycerin was used for the lubrication of the Petri dish to facilitate smoother peeling of the film.

EVALUATION PARAMETERS FOR PREPARED FILMS

Scanning of Methylphenidate HCl in UV Spectrophotometer

Scanning of methylphenidate HCl has been performed.[25] A UV spectrum was run between the wavelengths 200-400 nm and it is described in figure 1.

Calibration Curve of Methylphenidate HCl

100 mg of Methylphenidate HCl was weighed accurately into a 100 ml volumetric flask and dissolved with phosphate buffer pH 6.8. The volume was made up to 100 ml with the same solution to get a concentration of 1000 µg/ml. From this, solutions of concentrations ranging

from 100 µg/ml to 1000 µg/ml were prepared and their absorbance was measured at 257.2 nm wavelength in a UV spectrophotometer. [25,26]

Thickness Measurement

A screw gauge was used to measure the thickness of the Mouth dissolving film (2×2 cm2). Each film's thickness was measured in three locations, and the standard deviation was estimated.[27]

Drug Content Uniformity

A 4 cm2 mouth dissolving film was cut into small pieces and placed in a graduated glass stoppered flask with 10 ml of 6.8 pH phosphate buffer. The flask was kept for 24 hrs. The solution from the flask was filtered through Whatman filter paper and the amount of drug present was determined by UV spectrophotometric method at 257.2 nm wavelength.[28]

Weight Variation

Three films of size (2×2 cm^2) from every batch of mouth dissolving film were weighed on an electronic balance (Citizen CY 220C, Mumbai, India) & the average weight with standard deviation was calculated.[29,30]

Tensile Strength

Tensile strength was used to precisely calculate the mechanical properties of the polymeric mouth dissolving film. Using a handcrafted tensile strength instrument, the tensile strength of the mouth dissolving film was measured. The mouth dissolving film was then applied to the assembly, and the weights needed to split it were measured. The following formula was used to measure tensile strength (formula 1).[31,32]

$$T.S. = break\ force / A \qquad (1)$$

Where A = cross-sectional area of the film

Percentage Elongation

After calculating the tensile strength of the film, the percentage elongation was determined using the formula below (formula 2).[32]

$$\text{Percentage elongation} = \frac{(L_F - L_O)}{L_O} X\ 100 \qquad (2)$$

Where, L_F = final length, L_O= initial length

Moisture Content (%)

This measure was also used to determine the film's credibility in dry weather. A film with a surface area of 4 cm2 was cut out, weighed, and placed in a desiccator containing fused anhydrous calcium chloride. The film was removed and re-weighed after 24 hours. Equation 3 was used to calculate the percentage moisture content of the film.[33,34]

$$\%\ \text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \qquad (3)$$

% Moisture Uptake

The formulation was exposed to an atmosphere of 84% RH at 28°C for three days using a saturated solution of NaCl. After three days the films were removed, weighed and the percentage moisture absorbed was calculated. Calculated the average percentage moisture absorption of each film using the following formula 4.[34]

$$\%\ \text{Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \qquad (4)$$

In vitro Disintegration Time

The test was carried out using a slightly modified version of the procedure described by Setouhy et al. A glass petri dish containing 10 ml of distilled water was used to hold the film size needed for dosage distribution (2×2 cm). The time it took to break the film was recorded as *in vitro* disintegration time.[20,35]

Solubility study

The solubility of methylphenidate hydrochloride was determined in different types of solvent like water, methanol, ethanol, 0.1 N HCl, chloroform, ethyl acetate, acetone and pH 6.8 phosphate buffer at room temperature. Saturated solutions were prepared by adding excess drug into the solvents to form a suspension and continuing to stir these for 24 h in the presence of drug particles. The saturated suspensions were filtered (using 0.2 µm PTFE filters) to remove drug particles and the clear solutions were diluted to measure the drug concentration (table 19).

In-vitro Dissolution study

The test was performed with slight modification using the same method as mentioned by Dinge et al. A film of 4 cm^2 was placed in a glass Petri dish and 25 ml of dissolution medium (phosphate-buffered saline pH 6.8) was added. A stirring speed of 100 rpm was selected for dissolution of all the batches. Aliquot of 2.5 ml was withdrawn and replaced with equal volumes of pH buffer 6.8 at regular intervals of 1, 2, 3, 4, 5, 7.5, and 10 minutes to maintain sink condition. The collected samples were filtered through the Whatman filter and using a UV-Visible spectrophotometer, the concentration of dissolved methylphenidate HCl was measured at the required wavelength.[36,37,38]

Folding Endurance

Folding endurance was observed as well as determined by repeated folding of the strip at the same place till the strip breaks due to folding. The number of times the film is folded without breaking was determined as the folding endurance value.[39,40]

Stability Study

Stability testing's goal is to show how the consistency of a drug ingredient or drug product changes over time when exposed to a range of environmental factors including temperature, humidity, and light, allowing for recommended storage conditions, retest times, and shelf-life. ICH specifies the length of study and storage conditions.[41,42,43]

Method:

The sample was wrapped in aluminium foil and subjected to stability studies as per the International Conference on Harmonization (ICH) guidelines. After that, they were held in a stability chamber at 40°C/75°F for 3 months and tested for their physical appearance, drug quality, in-vitro disintegration duration, and drug release at 1-month intervals, with the findings being released.[41,43,44]

Release Kinetics and Mechanisms

Data obtained from dissolution studies were fitted to various kinetic equations. The kinetic models used were zero order (cumulative percentage of drug unreleased vs time in min), first order (log cumulative percentage of drug remaining vs time), Hixon-Crowell model (M01/3 – M1/3 vs time in min) Higuchi's model (cumulative percentage of drug released vs square root of time) and Korsmeyer – peppas model (log cumulative percentage of drug released vs log time) equation. The data were used to find out R^2 value.

Results and discussion

The λmax of the drug was determined by scanning 1000µg/ml concentration solution prepared with pH 6.8 buffer in the range 200-400 nm using a double beam UV visible spectrophotometer. λmax was found to be 257.257 nm (figure 5.1). So, further studies were carried out in a UV spectrophotometer at 257.2 nm.

FTIR and DSC Study

An FTIR spectrophotometer was used to conduct the compatibility tests. A KBr disc was used to investigate the IR spectrum of a pure substance and a physical combination of drug and polymer.[45,46] In different samples, the distinctive peaks of Methylphenidate Hydrochloride were obtained at different wavenumbers. (figure 3, table 4)

The spectra for all formulations are shown below.

In the above spectrum, the characteristic (principal) peaks of Methylphenidate hydrochloride are seen which are as follows.
FTIR spectra of Methylphenidate Hydrochloride+ HPMC E5 (Figure 4) exhibited peaks at 711 cm^{-1} (Monosubstituted Benzene), 1593 cm^{-1} presence of (Aromatic Stretch), 2411-2681 cm^{-1} (Secondary Amine Salt), 1756 cm^{-1} (C=O Stretch), 1182-1201 cm^{-1} (C-O Stretch). Here, all the principal peaks are exhibited in range. FTIR spectra of Methylphenidate Hydrochloride+ HPMC E15 (Figure 5) exhibited peaks at 699 cm^{-1} (Monosubstituted Benzene), 1592 cm^{-1} presence of (Aromatic Stretch), 2411-2588 cm^{-1} (Secondary Amine Salt), 1745 cm^{-1} (C=O Stretch), 1110-1210 cm^{-1} (C-O Stretch). Here, all the principal peaks are exhibited in range. FTIR spectra of Methylphenidate Hydrochloride+ Maltodextrin (Figure 6) exhibited peaks at 701-721 cm^{-1} (Monosubstituted Benzene), 1592 cm^{-1} presence of (Aromatic Stretch), 2419-2633 cm^{-1} (Secondary Amine Salt), 1734 cm^{-1} (C=O Stretch), 1115-1145 cm^{-1} (C-O Stretch). Here, all the principal peaks are exhibited in range. FTIR spectra of mouth dissolving film formulation (Figure 7) exhibited peaks at 713 cm^{-1} (Monosubstituted Benzene), 1595 cm^{-1} presence of (Aromatic Stretch), 2398-2511 cm^{-1} (Secondary Amine Salt), 1731 cm^{-1} (C=O Stretch), 1141-1190 cm^{-1} (C-O Stretch). Here, all the principal peaks are exhibited in range.
In the spectrum of the drug-polymer mixture, all the peaks are present and also in the formulation. This indicates that there is no interaction between drug and the formulation components.

Differential Scanning Calorimetry (DSC):

The DSC thermogram of Methylphenidate Hydrochloride showed an endothermic peak at 229.41^{0}C corresponding to its melting point.[38] The DSC thermograms of drug with other excipients do not show a profound shift in peaks (229.41^{0}C) which indicates compatibility. The DSC thermogram of the individual drug and final formulation show in figure 8 and 9.[47]

Preliminary studies for the selection of polymers

Preliminary research was conducted to identify appropriate polymers and a suitable plasticizer capable of manufacturing films with favourable mechanical properties and disintegration times.[48] The solvent casting process was used to make the casting solution. The composition of various batches, amount of polymers used, and their appearance and disintegration time are given in table 5.

Optimization of Polymer

The placebo films were prepared using Maltodextrin, HPMC E3, HPMC E5, and HPMC E15 as film-forming agents in various amounts.
The placebo films prepared using maltodextrin as a film former in various amounts of 750, 1000, 1250, 1500 mg were not having acceptable physical characteristics. The lowest amount of Maltodextrin (PB 1), when cast in the plastic Petri dish having an area of 70 cm2, was insufficient for making the film. In other batches of Maltodextrin (PB2 to PB4), amounts were sufficient for making the film, the film formed was sticky. So, Maltodextrin alone was not selected as the film-forming polymer.
HPMC is the hydrophilic polymers that are suitable for the mouth dissolving film. Various grades of HPMC were able to make films that were very transparent and having very good mechanical properties. The placebo film of different grades of HPMC E3, HPMC E5, and HPMC E15 were prepared to verify its film-forming capacity and suitability for mouth dissolving film. From all the HPMC batches, PB7 for HPMC E3, PB9 for HPMC E5, and PB11 for HPMC E15 were easily removed from the Petri dish and having good acceptable physical characteristics and low disintegration time in accordance to other batches (table 5). Films prepared from single polymers (PB7, PB9, PB11) were giving good results for disintegration time, but other properties were not so good, so, combinations of different

grades of HPMC were taken which shown better results in terms of disintegration time, folding endurance and tensile strength.
A combination of different grades of HPMC and Maltodextrin was tried and as a result, films having much smoother texture were obtained. The combination yielded smoother films with less disintegration time, and finally, amongst the preliminary batches, PB22 was shown to give the best results (Table 6). So, a combination of HPMC E5, HPMC E15, and Maltodextrin was selected as the film-forming combination for the current work.[49,50]

Optimization of Plasticizer

The films were prepared using propylene glycol and glycerol as plasticizers in different amounts ranging from 0.25 to 1.25ml (table 7). The results show that with the least amount of plasticizer, films were very brittle, and with the highest amount of plasticizer, films could not be dried properly, and peeling off the problem was observed. In between the prepared films, PB24, PB25, PB30, and PB31were good but their disintegration time was much higher than PB29 because of more amount of plasticizer. Based on folding endurance, tensile strength, and disintegration time, 0.5 ml of propylene glycol was selected as the optimum amount of plasticizer.[50,51]

Experimental Design

Simplex centroid design is a type of mixture design that is often used to modify formulation variables with the simple prerequisite of knowing how independent variables interact. Preliminary investigations of the process parameters revealed that factors like the amount of HPMC E5 (X_1), amount of HPMC E15 (X_2), and amount of Maltodextrin (X_3) showed significant influence on the amount of drug dissolved in 2 min (CPR Q_2; R_1), disintegration time(R_2) and tensile strength (R_3) of the drug-loaded fast dissolving film. As a result, they were used in further research. All three chosen dependent variables (X1, X2, and X3) showed large variance in disintegration time, volume of drug released in 2 minutes, and tensile strength for all 7 batches (table 8). The data showed that X1, X2, and X3 had a major effect on those responses (R1, R2, and R3). Since considering the magnitude of coefficients and statistical signals, polynomial equations can be used to determine if the response is positive or negative. The ANOVA results for design batches are shown below.[46,52]

Response 1: CPR Q_2 (R_1)

The magnitude of coefficients and mathematical signs can be used to determine if the polynomial equations express positive or negative information. Statistical analysis was carried out in Design-Expert software (7.1.5), which suggested that a special cubic model (SCM) was followed for % drug release at 2 minutes with a P-value of 0.0385. This indicated that the model was highly significant.

Polynomial equation

R_1 (CPR Q_2) = +104.21*A + 86.83*B + 94.30*C - 9.16*A*B + 8.62*A*C + 23.53*B*C + 55.72*A*B*C

To find out the contribution of each component and their interaction, an Analysis of Variance (ANOVA) for SCM was carried out.

The ANOVA results (Table 9), contour plot, & 3D surface plot for the CPR Q_2 (figure 10) presented the strong effect of the three factors (amounts of HPMC E5, HPMC E15, and maltodextrin). A polynomial equation of Q_2 indicates that the all the three polymer amount has a positive effect on the Q_2. *In vitro* dissolution of the films was found to increase with the increase in the amount of the polymer. It was noted that when the amounts of polymer were selected within the limits of the design, *in vitro* dissolution rate increased to a greater extent with the amount of HPMC E5 and increased to a lesser extent in the case of maltodextrin followed by HPMC E15. As per the equation, better release can be achieved with the combination of all the three polymers, rather than combining any two of them.[53]

Response 2: Disintegration Time (R_2)

Statistical analysis was carried out in Design-Expert software (7.1.5), which recommended that a special cubic model (SCM) was followed for release at $T2_{min}$ with a P-value of 0.0385. This indicated that the model was highly significant.[53]

Polynomial equation

R_2 (Disintegration Time) = +38.50*A + 78.00*B + 35.00*C - 25.00*A*B + 37.00*A*C + 26.00*B*C - 235.50*A*B*C

To find out the contribution of each component & their interaction, an ANOVA for SCM was carried out.

The ANOVA results (Table 10), contour plot, & 3D surface plot for the disintegration time (figure 11) indicated the strong effect of the three factors (amounts of HPMC E5, HPMC E15, and Maltodextrin). A polynomial equation of disintegration time indicates that the all the three polymer amount has a positive effect on the disintegration time. The *in-vitro* disintegration time of the films was observed to increase as the volume of polymer was increased. It was noticed that when the amounts of polymer were selected within the limits of the design, in vitro dissolution rate was decreased the most when more amount of maltodextrin was used in the formulation and it increase gradually with HPMC E5 followed by HPMC E15. As per the equation, a shorter disintegration time can be achieved with the combination of all the three polymers, rather than the single polymer or with the combination of any two of them.

Response 3: Tensile Strength (R_3)

Statistical analysis was carried out in Design-Expert software (7.1.5), which suggested that SCM was followed for release at $T2_{min}$ with a P-value of 0.0385. This revealed that the model was highly significant.

Polynomial equation

R_3 (Tensile Strength) = +2.71*A + 3.43*B + 2.39*C + 0.15*A*B - 0.11*A*C + 0.12*B*C - 0.45*A*B*C

To find out the impact of each component & their interaction, ANOVA for SCM was carried out. The ANOVA results (Table 11), 3D surface plot, & contour plot for the tensile strength (figure 12) indicated the strong effect of the three factors (amounts of HPMC E5, HPMC E15, & Maltodextrin). A polynomial equation of tensile strength indicates that the all the three-polymer amount has a positive effect on the tensile strength. It was observed that when the amounts of polymer were selected within the limits of the design, tensile strength was increased when more amount of HPMC E15 was used in the formulation and it increased to a lesser extent in HPMC E5 followed by Maltodextrin. As per the equation, values of tensile strength were decreased with the combination of all three polymers.[53,54]

Evaluation Parameters of film formulation

Weight variation test

Table 12 summarises the percentage weight difference for all formulations. The percent weight difference was under the pharmacopoeial limits of 7.5 percent, so both of the films passed the weight variation test. It was found to be in the range of 37±2.081 to 81.67±2.081 mg. Films having more amount of maltodextrin exhibited higher weight whereas films having HPMC E5 were lighter in weight. The weight of all the films was uniform.[55]

Thickness

Formulated films were observed to have thicknesses ranging from 0.103±0.015 to 0.207±0.02 mm. Table 12 lists the mean values. In both formulations, the values are almost identical. Films containing maltodextrin resulted in increased thickness which was required for comfortable handling of the film.[56]

Folding Endurance

The films' folding endurance was measured by folding a small strip of film at the same location before it separated, and the average folding endurance of all films was shown in table

12. All of the batches have a folding endurance of 101±2.645 to 177.67±3.51. The folding endurance increases as the concentration of the polymer increases.[57,58]

Drug content

The drug content and uniformity tests were carried out to ensure that the drug was distributed uniformly and accurately. The content uniformity of all nine formulations was determined, and the results are listed in Table 12. A spectrophotometer was used to examine three trials from each formulation. All of the formulations' mean value and standard deviation were calculated. The findings showed that both formulations have the same drug material. In *in vitro* release trials, the total percentage of drug released from each film was calculated using the mean quality of the drug contained in the film. The ranges of drug content in all the formulations were 95.218% to 98.00%.[58]

***In vitro* dissolution study**

In vitro release studies of methylphenidate, hydrochloride films were performed in phosphate buffer (pH 6.8). Cumulative drug release was calculated based on the drug content of Methylphenidate hydrochloride. Rapid drug dissolution was observed in F1, F5, which release 104.44% and 101.41 % respectively, at end of 2 min. Comparatively, slow drug dissolution was observed in F6, F7 with the release of 96.45% and 99.73% respectively at end of 2 min. remaining formulations had slower drug release than the above-mentioned formulations. As the concentration of the polymer HPMC E15 increased, the time for drug release was found to be increasing. This might be due to the higher viscosity of the polymer, which results in the formation of a strong matrix layer resulting in a decrease in mobility of drug particles in swollen matrices, which leads to a delay in drug release.[36]

Table 13 shows the data of the dissolution of the prepared design batches. Figure 13 shows the graph of cumulative percentage release versus time in minutes. The data shown shows the data up to two minutes only so that we can easily compare the dissolution and percentage drug release within our desired time limit. From figure 13 we may conclude that in the first minute, drug release for every batch is almost the same, but for the consecutive minutes, the amount of drug release changes. So we may say that polymer having lower viscosity releases the drug quicker than the polymers of higher viscosity. So, to get a quicker release, lower viscosity grade polymers are desirable.[47]

Optimized Batch Analysis

The optimized formulation was chosen based on criteria, a higher amount of drug release at 2 minutes, shortest disintegration time, and a medium value of tensile strength. The overlay plot was drawn to obtain an optimized batch using Design Expert (7.1.5) (figure 14).

An optimized batch of the film was prepared experimentally using the same procedure/the results of stated parameters were compared with the computed values from the regression equations. When the experimental and theoretical values were compared and % error was found to be less than 8% for all the responses (table 14).

Stability Studies

A stability study has been performed according to ICH guidelines for a short period of time. The developed formulations were tested for stability at 40°C and 75% relative humidity for 6 months & were evaluated for tensile strength, disintegration time, & *in vitro* drug release at 1, 3, & 6 month intervals. The effects of the formulations were considered to be within acceptable limits, as seen in Table 15. The measurable parameters showed no major differences. So, the formulation was found to be stable. [47]

Release Kinetics and Mechanisms

Data of the in vitro release were fit into different equations and kinetic models to explain the release kinetics of methylphenidate from these films. The release kinetics of methylphenidate followed zero order from all the films (table 16). The better fit (highest R^2 values) was observed in case of Higuchi's model than Hixon–Crowel model except film I. Hence

mechanism of drug release from the remaining films followed are diffusion controlled and drug release from film I followed dissolution controlled (table 17).
Application of Hixon – Crowell cube root law, the equation (M01/3 – M1/3) = 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-Peppas model 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 (table 18).
R^2 values are higher for Higuchi's model compared to Hixon – Crowell for all the films except film I. Hence Drug release from film I followed dissolution rate-controlled mechanism and drug release from the remaining films followed diffusion rate-controlled mechanism. According to Korsmeyer-Peppas model, a value of slope between 0.5 and 1 indicates an anomalous behavior (Non-Fickian). So, it indicates that release mechanism from all the films follows non-Fickian diffusion (anomalous behaviour). However, film I follows case II transport.

Conclusions

The prepared film of methylphenidate hydrochloride obtained by the solvent casting method showed the desired % drug release, disintegration time, & tensile strength. The prepared film was having a very smooth surface because of maltodextrin and without any interactions between drug and polymer. The optimization of the film was done by simplex centroid design. The multiple regression analysis of the results led to equations that describe adequately the influence of the selected variables on the responses under study. Formulations with a % drug release of more than 95%within 2 minutes were found in a specific region containing having more amount of HPMC E5 resulting in quicker drug release. Formulations with in-vitro disintegration time <60 sec were found in a specific region containing high levels of HPMC E5 and maltodextrin and low levels of HPMC E15. The desired level of tensile strength was achieved when the optimum amount of HPMC E15 was present in the film. The high % drug release of the film in simulated saliva (pH buffer 6.8) indicated that it could be helpful for the treatment of acute attention deficit hyperactivity disorder (ADHD) and Narcolepsy where quick bioavailability of the drug is desired.
So, all designed batches were prepared and their evaluations were carried out which shown acceptable results. Based on the results, we may conclude that the project aim was successfully fulfilled.

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References

1. Arun, A., Amrish, C., Vijay, S. & Kamla, P. Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form. *Int. J. ChemTech Res.* **2**, 576–583 (2010).
2. Biswajit Basu,Kevin Garala, T. J. Formulation and evaluation of Pimozide buccal mucoadhesive patches. *Res. J. Pharm. Technol.* **11**, 4892–4898 (2018).
3. Boateng, J. S. *et al.* Comparison of the in vitro release characteristics of mucosal

freeze-dried wafers and solvent-cast films containing an insoluble drug. *Drug Dev. Ind. Pharm.* **38**, 47–54 (2012).
4. Chinwala, M. Recent Formulation Advances and Therapeutic Usefulness of Orally Disintegrating Tablets (ODTs). *Pharmacy* **8**, 186 (2020).
5. Patel, A. R., Prajapati, D. S. & Raval, J. A. Fast dissolving films (FDFs) as a newer venture in fast dissolving dosage forms. *Int. J. Drug Dev. Res.* **2**, 232–246 (2010).
6. Maheswari, K. M. *et al.* Development and Evaluation of Mouth Dissolving Films of Amlodipine Besylate for Enhanced Therapeutic Efficacy. *J. Pharm.* **2014**, 1–10 (2014).
7. Mahajan, A. Formulation & evaluation of fast dissolving buccal films of Sertraline. *Int. J. Drug Dev. Res.* **4**, 220–226 (2012).
8. Ghorwade, V. *et al.* Formulation and evaluation of Montelukast sodium fast dissolving films by using Gelatin as a film base. *Res. J. Pharm. Biol. Chem. Sci.* **2**, 880–888 (2011).
9. Koland, M., Sandeep, V. P., Charyulu, R. N. & Subrahmanyam, E. V. S. the Design and Characterization of Sublingual Films of Ondansetron Hydrochloride. **7**, 2927–2938 (2009).
10. Huss, M. *et al.* Methylphenidate dose optimization for ADHD treatment: Review of safety, efficacy, and clinical necessity. *Neuropsychiatr. Dis. Treat.* **13**, 1741–1751 (2017).
11. Shelke, P. V. *et al.* Formulation and Evaluation of Rapidly Dis Integrating Film of Amlodipine Bes Ylate. *J. Drug Deliv. Ther.* **2**, 72–75 (2012).
12. Woertz, K., Tissen, C., Kleinebudde, P. & Breitkreutz, J. A comparative study on two electronic tongues for pharmaceutical formulation development. *J. Pharm. Biomed. Anal.* **55**, 272–281 (2011).
13. Patel, R., Shardul, N., Patel, J. & Baria, A. Formulation development and evaluation of mouth melting film of Ondansetron. *Arch. Pharm. Sci. Res.* **1**, 212–217 (2009).
14. Irfan, M. *et al.* Orally disintegrating films: A modern expansion in drug delivery system. *Saudi Pharm. J.* **24**, 537–546 (2016).
15. Kalyan, S. & Bansal, M. Recent trends in the development of oral dissolving film. *Int. J. PharmTech Res.* **4**, 725–733 (2012).
16. Meghana, R. & Velraj, M. An overview on mouth dissolving film. *Asian J. Pharm. Clin. Res.* **11**, 44–47 (2018).
17. Shimoda, H. *et al.* Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. *Eur. J. Pharm. Biopharm.* **73**, 361–365 (2009).
18. VARINDER KUMAR, FOZIYAH ZAKIR, GEETA AGARWAL, A. C. Formulation and evaluation of buccal patches of venlafaxine. *Int. J. Pharm. Biol. Sci.* **1**, 170–182 (2011).
19. Chaurasia, G. A review on pharmaceutical preformulation studies in formulation. *Int. J. od Pharm. Sci. Res.* **7**, 2313–2320 (2016).
20. Mishra, R. & Amin, A. Formulation and characterization of rapidly dissolving films of cetirizine hydrochloride using pullulan as a film forming agent. *Indian J. Pharm. Educ. Res.* **45**, 71–77 (2011).
21. Gunjan, J. P. & Darshan, A. M. Formulation, optimization and evaluation of levocetirizine dihyrochloride oral thin strip. *J. Pharm. Bioallied Sci.* **4**, 35–36 (2012).
22. Khairnar, A., Jain, P., Baviskar, D. & Jain, D. Developmement of mucoadhesive buccal patch containing aceclofenac: In vitro evaluations. *Int. J. PharmTech Res.* **1**, 978–981 (2009).
23. jadhav et.al, 2012. Research Article FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF LEVOCETIRIZINE DIHYDROCHLORID. *Int. J. Pharm. Res.* **7**, 95–99 (2015).
24. Khan, S., Shahi, S., Borde, S. & Shaikh, S. Formulation and evaluation of methylphenidate hydrochloride fast dissolving tablet by QbD approach. *Asian J. Pharm.*

Pharmacol. **5**, 33–42 (2018).
25. Bhupinder et.al, 2010. Formulation and evaluation of fast dissolving sublingual films of Rizatriptan Benzoate Bhyan. **4**, 133–143 (2012).
26. bukka et.al, 2010. Preparation and evaluation of microporous drug delivery system. *Int. J. Pharma Bio Sci.* **1**, 294–301 (2010).
27. Choudhary, D. R., Patel, V., Patel, H. & Kundawala, A. J. Exploration of film forming properties of film formers used in the formulation of rapid dissolving films. *Int. J. ChemTech Res.* **3**, 531–533 (2011).
28. Cilurzo, F. *et al.* Nicotine fast dissolving films made of maltodextrins: A feasibility study. *AAPS PharmSciTech* **11**, 1511–1517 (2010).
29. Jyoti, A., Gurpreet, S., Seema, S. & Rana, A. C. Fast Dissolving Films: a Novel Approach To Oral Drug Delivery. *Int. Res. J. Pharm.* **2**, 69–74 (2011).
30. S, K. A., A, D. H., S, M. M. & M, G. D. Exploration of different polymers for use in the formulation of oral fast dissolving strips. *J. Curr. Pharm. Res. JCPR* **2**, 33–35 (2010).
31. Dixit, R. P. & Puthli, S. P. Oral strip technology: Overview and future potential. *J. Control. Release* **139**, 94–107 (2009).
32. Choudhary, D. R., Patel, V. A., Patel, H. V. & Kundawala, A. J. Formulation and evaluation of quick dissolving film of levocetirizine dihydrochloride. *Int. J. Pharm. Technol.* **3**, 1740–1749 (2011).
33. Sudhakar, Y., Kuotsu, K. & Bandyopadhyay, A. K. Buccal bioadhesive drug delivery - A promising option for orally less efficient drugs. *J. Control. Release* **114**, 15–40 (2006).
34. Senthilkumar, K. & Vijaya, C. Formulation Development of Mouth Dissolving Film of Etoricoxib for Pain Management. *Adv. Pharm.* **2015**, 1–11 (2015).
35. smitha et.al, 2011. Development of Taste Masked Fast Dissolving Orally Consumable Films of Seldinafil Citrate. *IJPI's J. Pharm. Cosmetol.* **2**, 30–39 (2012).
36. Xia, Y., Chen, F., Zhang, H. & Luo, C. A new method for evaluating the dissolution of orodispersible films. *Pharm. Dev. Technol.* **20**, 375–379 (2015).
37. Sharma, D., Kumar, D., Singh, M., Singh, G. & Rathore, M. S. Fast Disintegrating Tablets: A New Era In Novel Drug Delivery System And New Market Opportunities. *J. Drug Deliv. Ther.* **2**, 74–86 (2012).
38. Dinge, A. & Nagarsenker, M. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. *AAPS PharmSciTech* **9**, 349–356 (2008).
39. Kunte, S. & Tandale, P. Fast dissolving strips: A novel approach for the delivery of verapamil. *J. Pharm. Bioallied Sci.* **2**, 325 (2010).
40. Lai, K. L. *et al.* Orally-dissolving film for sublingual and buccal delivery of ropinirole. *Colloids Surfaces B Biointerfaces* **163**, 9–18 (2018).
41. Morales, J. O. & McConville, J. T. Manufacture and characterization of mucoadhesive buccal films. *Eur. J. Pharm. Biopharm.* **77**, 187–199 (2011).
42. Murata, Y., Isobe, T., Kofuji, K., Nishida, N. & Kamaguchi, R. Preparation of fast dissolving films for oral dosage from natural polysaccharides. *Materials (Basel).* **3**, 4291–4299 (2010).
43. Gupta, M. M., Patel Mitul, G. & Kedawat, M. Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of meclizine hydrochloride with β-cyclodextrine. *J. Appl. Pharm. Sci.* **1**, 150–153 (2011).
44. Prabhu, P. *et al.* Formulation and evaluation of fast dissolving films of levocitirizine di hydrochloride. *Int. J. Pharm. Investig.* **1**, 99 (2011).
45. Langoth, N. & Kalbe, J. Development of buccal drug delivery systems based on a thiolated polymer. *Int. J. Pharm.* **252**, 141–148 (2003).
46. Narasimha Rao R, Sindhu Reddy Kandhadi, Swapna D, Sushma Devi Konasree, S. E. Formulation and Evalution of Rapidly Dissolving Buccal Patches. *Int. J. Pharm. Biol. Sci.* **1**,

145–159 (2011).
47. Mashru, R. C., Sutariya, V. B., Sankalia, M. G. & Parikh, P. P. Development and Evaluation of Fast-Dissolving Film of Salbutamol Sulphate. *Drug Dev. Ind. Pharm.* **31**, 25–34 (2005).
48. Saini, S., Samta, Rana, A. C. & Gupta, S. Optimization of formulation of fast dissolving films made of pullulan polymer. *Int. J. Pharm. Sci. Rev. Res.* **9**, 127–131 (2011).
49. dahiya et.al, 2009. A Review on Mouth Dissolving Films. *Indian Drugs* **50**, 5–14 (2013).
50. swarbrick et.al. Drug delivery to the oral cavity molecules: To market. *Drug Deliv. to Oral Cavity Mol. to Mark.* 1–397 (2005).
51. Gavaskar, B., Kumar, S. V., Sharan, G. & Madhusudan Rao, Y. Overview on fast dissolving films. *Int. J. Pharm. Pharm. Sci.* **2**, 29–33 (2010).
52. sapkal et.al, 2011. Development of fast dissolving oral thin films of ambroxol hydrochloride: Effect of formulation variable. **2**, 102–109 (2011).
53. Samprasit, W., Akkaramongkolporn, P., Kaomongkolgit, R. & Opanasopit, P. Cyclodextrin-based oral dissolving films formulation of taste-masked meloxicam. *Pharm. Dev. Technol.* **23**, 530–539 (2018).
54. Patel, V. F., Liu, F. & Brown, M. B. Advances in oral transmucosal drug delivery. *J. Control. Release* **153**, 106–116 (2011).
55. Narang, N. & Sharma, J. Sublingual mucosa as a route for systemic drug delivery. *Int. J. Pharm. Pharm. Sci.* **3**, 18–22 (2011).
56. Patel, H. A., Patel, J. K., Patel, K. N. & Patel, R. R. Studies on formulation and in vitro evaluation of fast dissolving tablets of domperidone. *Int. J. Pharm. Sci.* **2**, 470–476 (2010).
57. Hearnden, V. *et al.* New developments and opportunities in oral mucosal drug delivery for local and systemic disease. *Adv. Drug Deliv. Rev.* **64**, 16–28 (2012).
58. nandy et.al, 2011. AN OVERVIEW ON FAST DISSOLVING DRUG DELIVERY SYSTEM. **1**, 10–15 (2011).

Table 1: Calibration data of drug in pH 6.8 phosphate buffer at 257.2 nm.

Concentration (µg/ml)	Absorbance			Mean absorbance*
	I	II	III	
0	0	0	0	0
100	0.056	0.084	0.068	0.0693±0.014
200	0.119	0.140	0.131	0.13±0.013
300	0.186	0.214	0.205	0.2017±0.014.
400	0.251	0.289	0.271	0.2703±0.019
500	0.327	0.369	0.349	0.3483±0.021
600	0.402	0.443	0.414	0.4197±0.021
700	0.456	0.485	0.471	0.4707±0.014
800	0.544	0.559	0.552	0.5517±0.017
900	0.602	0.649	0.623	0.6247±0.023
1000	0.664	0.682	0.673	0.673±0.014

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

Table 2: Independent variables and their respective levels

Independent variables	**0**	**0.33**	**0.5**	**1**
HPMC E5 (X1)	217	250	267	317
HPMC E15 (X2)	150	183	200	250
Maltodextrin (X3)	300	333	350	400

Table 3: Simplex centroid design

Formulations*	**CODED VALUES**			**ACTUAL VALUES (mg)**		
	X_1	X_2	X_3	X_1	X_2	X_3
F1	1	0	0	317	150	300

F2	0	1	0	217	250	300
F3	0	0	1	217	150	400
F4	0.5	0.5	0	267	200	300
F5	0.5	0	0.5	267	150	350
F6	0	0.5	0.5	217	200	350
F7	0.33	0.33	0.33	250	183	333

Table 4: FTIR characteristic (principal) spectral details

Pure Methylphenidate Hydrochloride	**Stretching**
701, 733	Monosubstituted Benzene
1599	Aromatic Stretch
2412 – 2698	Secondary Amine Salt
1736	C=O Stretch
1146 - 1169	C-O Stretch

Table 5: Characteristics of Placebo Film Prepared Using Different Polymers

Batch	Polymer	Amount (mg)	Remarks	Disintegration Time* (sec)
PB1	Maltodextrine	750	Insufficient	--
PB2		1000	Sticky	--
PB3		1250	Sticky	--
PB4		1500	Very Sticky	--
PB5	HPMC E3	500	Insufficient	--
PB6		750	Good	32±1.732
PB7		1000	Very Good	44.67±1.527
PB8	HPMC E5	500	Average	38.67±2.081
PB9		750	Very Good	42.67±0.577
PB10		1000	Good	51.67±2.081
PB11	HPMC E15	500	Very Good	36.67±1.527
PB12		750	Good	56.33±1.527
PB13		1000	Average	66±2.645

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

Table 6: Optimization of Mixture of Polymers

PB14	E3 + E5	500+375	Good	56.33±0.577
PB15	E3 + E15	500+250	Good	57.33±1.527
PB16	E5 + E15	375+250	Good	50.33±1.154
PB17	E3 + Maltodextrin	500+500	Good and Smooth	43.67±1.154
PB18	E5 + Maltodextrin	375+500		41.33±0.577
PB19	E15 +Maltodextrin	250+500		35.33±0.577
PB20	E3 + E5+Maltodextrin	333+250+333	Very Good and Smooth	42.67±2.081
PB21	E3+E15+Maltodextrin	333+166+333		39.33±1.527

PB22	E5+E15+Maltodextrin	250+166+333		34.67±1.154

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

Table 7: Characteristics of Placebo Films Prepared Using Different Plasticizer

Batch[#]	Plasticizer	Amount (ml)	Folding Endurance	Disintegration Time * (sec)	Tensile strength* (N/cm2)
PB23	Glycerin	0.25	142	Brittle	--
PB24		0.5	156	66.33±2.081	3.11±0.061
PB25		0.75	--	74.66±4.167	3.18±0.017
PB26		1	--	Peel off problem	--
PB27		1.25	--	Peel off problem	--
PB28	Propylene Glycol	0.25	--	Brittle	--
PB29		0.5	148	46±1.73	2.42±0.023
PB30		0.75	152	59.66±3.055	2.74±0.068
PB31		1	156	64.33±2.516	2.96±0.066
PB32		1.25	--	Peel off problem	--

[#] Each formulation contains HPMC E5, HPMC E15 and Maltodextrin (250+166+333)

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

Table 8: Design Summary

Formulation code	R1	R2	R3
	$Q_{2\ min}$*	Disintegration time (sec) *	Tensile strength (N/cm^2) *
F1	104.44±2.91	38±0.57	2.7±0.02
F2	97.08±2.89	78±1.15	3.43±0.06
F3	99.80±0.80	35±2.01	2.39±0.03
F4	98.12±1.62	52±2.64	3.1±0.07
F5	101.41±1.89	46±1.73	2.52±0.01
F6	98.86±3.18	63±2.31	2.94±0.04
F7	99.73±1.78	46±2.64	2.84±0.02
F1(R)	103.94±0.27	39±1.52	2.72±0.02

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

R_1: Response 1, R_2: Response 2, R_3: Response 3.

Table 9: ANOVA for special cubic model (% release at 2 min)

Source	Sum of squares (SS)	DF	Mean square (MS)	F value	Prob > F
Model	253.82	6	42.30	395.44	0.0385
Linear mixture	210.05	2	105.02	981.76	0.0226
AB	3.81	1	3.81	35.62	0.1057
AC	3.38	1	3.38	31.60	0.1121
BC	23.06	1	23.06	215.56	0.0433

ABC	2.62	1	2.62	24.52	0.1269
Pure error	0.11	1	0.11		
Cor total	253.92	7			

Table 10: ANOVA for special cubic model (Disintegration time)

Source	**Sum of squares**	**DF**	**Mean square**	**F value**	**Prob > F**
Model	1477.38	6	246.23	492.46	0.0345
Linear mixture	1320.95	2	660.48	1320.95	0.0195
AB	28.41	1	28.41	56.82	0.0840
AC	62.23	1	62.23	124.45	0.0569
BC	28.17	1	28.17	56.33	0.0843
ABC	46.86	1	46.86	93.72	0.0655
Pure error	0.50	1	0.50		
Core total	1477.88	7			

Table 11: ANOVA for special cubic model (Tensile Strength)

Source	Sum of squares	DF	Mean square	F value	Prob > F
Model	0.77	6	0.13	450.86	0.0360
Linear mixture	0.76	2	0.38	1348.51	0.0193
AB	9.924E-004	1	9.924E-004	3.51	0.3122
AC	5.767E-004	1	5.767E-004	2.04	0.3889
BC	5.709E-004	1	5.709E-004	2.02	0.3905
ABC	1.690E-004	1	1.690E-004	0.60	0.5811
Pure error	2.828E-004	1	2.828E-004		
Cor total	0.77	7			

Table 12: Evaluation parameters of experimental design batches

Batches	Weight variation ± SD* (mg)	Thickness ± SD* (mm)	Folding Endurance ± SD*	Drug content ± SD* (%)
F1	37.33±2.081	0.117±0.011	108±3.51	95.21±0.52
F2	72.66±1.527	0.167±0.005	101±2.645	95.41±0.63
F3	81.67±2.081	0.207±0.02	116±3.05	96.41±0.46
F4	54.33±1.527	0.137±0.011	103±2.0	98.00±0.87
F5	80.33±2.081	0.17±0.02	117.67±4.15	95.41±0.56
F6	76.33±2.301	0.103±0.015	109±5.03	97.40±0.58
F7	62.66±1.527	0.133±0.011	115±5.291	96.01±0.48
F1(R)	37.66±2.31	0.17±0.10	108±3.60	95.41±0.52

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

Table 13: Cumulative percentage drug release from film formulations

Time (min)	0	1	2	3	4
F1	0.0±0.0	75.19±2.30	104.44±2.91	-	-
F2	0.0±0.0	73.34±1.04	86.83±1.00	89.64±3.40	97.08±2.89
F3	0.0±0.0	72.62±3.88	94.30±2.04	99.80±0.80	-
F4	0.0±0.0	78.60±2.98	93.23±2.02	98.12±1.62	-
F5	0.0±0.0	80.12±2.27	101.41±1.89	-	-
F6	0.0±0.0	81.40±2.53	96.45±2.81	98.86±3.18	-
F7	0.0±0.0	77.46±1.42	99.73±1.78	-	-
F1(R)	0.0±0.0	75.74±0.378	103.94±0.27	-	-

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

Table 14: Evaluation of Optimized Batch

Responses	Predicted value	Experimental value*	Relative error (%)
$Q_{2\ min}$	99.01	98.45±0.99	-0.56

Disintegration time(sec)	45.73	49±3	7.15
Tensile strength(N/mm^2)	2.90	2.98±0.14	2.75

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

Table 15: Results of accelerated stability studies

Evaluation parameters	**Time period for sampling***			
	Initial	**After 1 month**	**After 3 months**	**After 6 months**
CPR at 2 min(%)	98.45±0.99	98.06±5.44	98.15±4.78	98.42±2.35
Disintegration time(sec)	49±3	47±1	48±0.57	49±0.57
Tensile strength(N/cm^2)	2.98±0.14	2.95±0.081	3.01±0.07	2.99±0.14

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

Table 16: Comparison of orders of *in vitro* release from all the patches.

Batches	***In vitro* release in Phosphate buffer pH 6.8 Regression equations**	
	Zero order	**First order**
I	y = - 1.6731x + 90.129 R^2 = 0.9799	Log y = -0.0227x + 2.1477 R^2 = 0.8944
II	y = - 1.1987x + 86.842 R^2 = 0.9817	Log y = -0.0247x + 2.2969 R^2 = 0.6074
III	y = - 0.8962x + 96.53 R^2 = 0.9944	Log y = -0.014x + 2.2549 R^2 = 0.6323
IV	y = - 1.0745x + 93.923 R^2 = 0.9933	Log y = -0.0166x + 2.223 R^2 = 0.6606
V	y = - 1.356x + 91.964 R^2 = 0.9921	Log y = -0.0236x + 2.2586 R^2 = 0.6991
VI	y = - 0.7912x + 86.63 R^2 = 0.9944	Log y = -0.0146x + 2.1439 R^2 = 0.6421
VII	y = - 1.0745x + 93.923 R^2 = 0.9947	Log y = -0.0214x + 2.2547 R^2 = 0.6666

Table 17: Comparison of regression equations of *in vitro* release from all the patches

Batch	***In vitro* release of drug in phosphate buffer pH 6.8**		
	Hixon-Crowell model	**Higuchi's model**	**Korsmeyer Peppas model**

I	y = 0.0159x - 0.0399 R^2 = 0.9762	y = 13.552x - 11.116 R^2 = 0.9744	y = 1.0295x + 0.255 R^2 = 0.9464
II	y = 0.014x - 0.0571 R^2 = 0.8862	y = 11.717x - 8.1596 R^2 = 0.9733	y = 0.9141 + 0.3521 R^2 = 0.9074
III	y = 0.0092x - 0.0988 R^2 = 0.8606	y = 10.24x - 18.435 R^2 = 0.9239	y = 0.8815x + 0.2008 R^2 = 0.9688
IV	y = 0.0111x - 0.0775 R^2 = 0.8668	y = 11.012x - 14.728 R^2 = 0.9397	y = 0.9136x – 0.2446 R^2 = 0.9561
V	y = 0.0149x - 0.0777 R^2 = 0.9094	y = 12.606x - 13.274 R^2 = 0.9624	y = 0.979x + 0.2519 R^2 = 0.9524
VI	y = 0.0261x - 0.0411 R^2 = 0.9662	y = 12.255x – 12.111 R^2 = 0.9777	y = 0.9812x + 0.522 R^2 = 0.9644
VII	y = 0.012x - 0.0617 R^2 = 0.9288	y = 11.177x – 9.634 R^2 = 0.9755	y = 0.9144 + 0.5312 R^2 = 0.9047

Table 18: Slope of Korsmeyer-Peppas Equation and Proposed Release Mechanisms

Slope (n)	**Mechanism**
<0.5	Fickian diffusion (Higuchi Matrix)
0.5 < n < 1	Non-Fickian diffusion
1	Case II transport

Table 19: Solubility data of methylphenidate HCl

Solvent	**Solubility (mg/ml)**
Water	> 100
Methanol	> 100
Ethanol	> 25
0.1 N HCl	> 100
Chloroform	> 100
Ethyl acetate	0.08

Acetone	0.9
Phosphate buffer pH 6.8	> 100

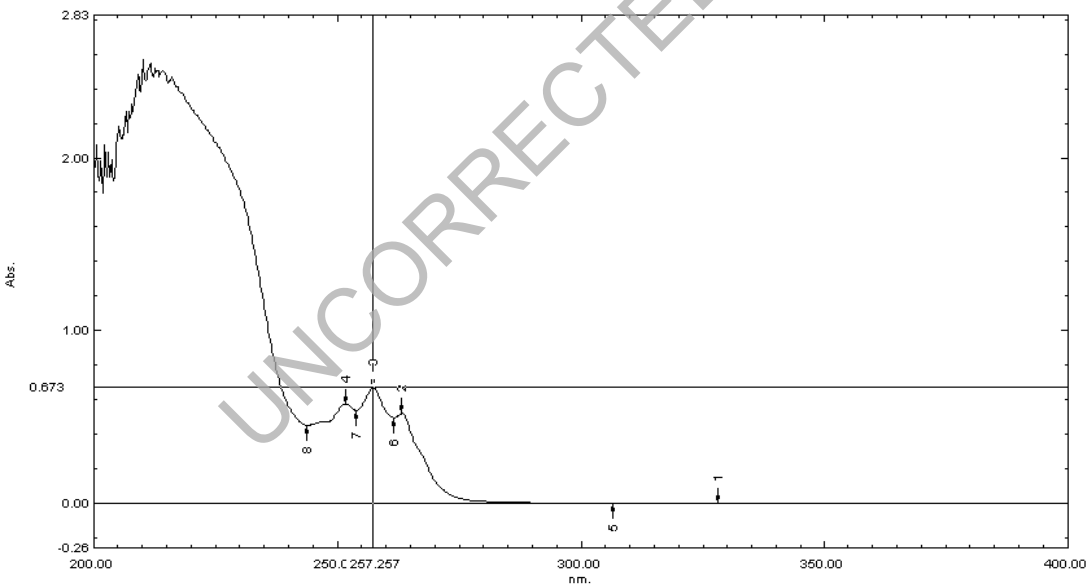

Figure 1: Absorption maxima of Methylphenidate HCl in pH 6.8 phosphate buffer

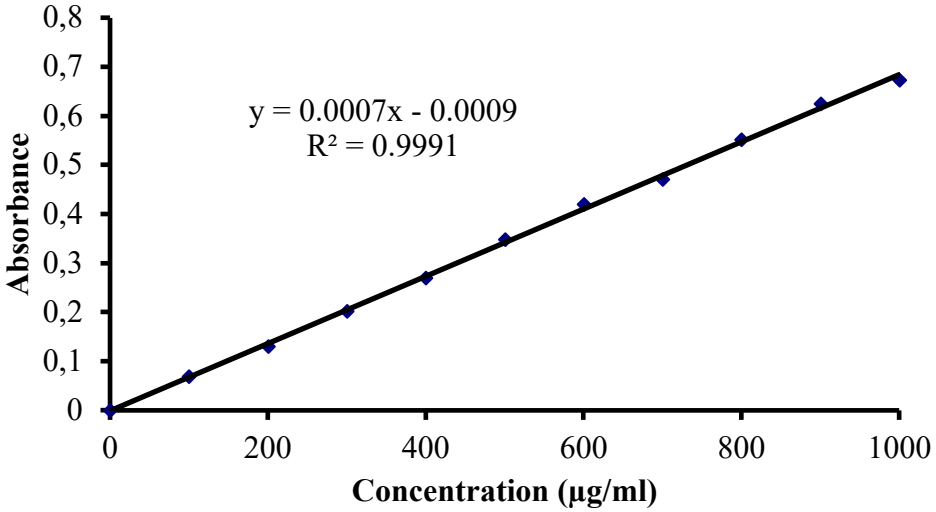

Figure 2: Standard Curve of Methylphenidate HCl in pH 6.8 phosphate buffer.

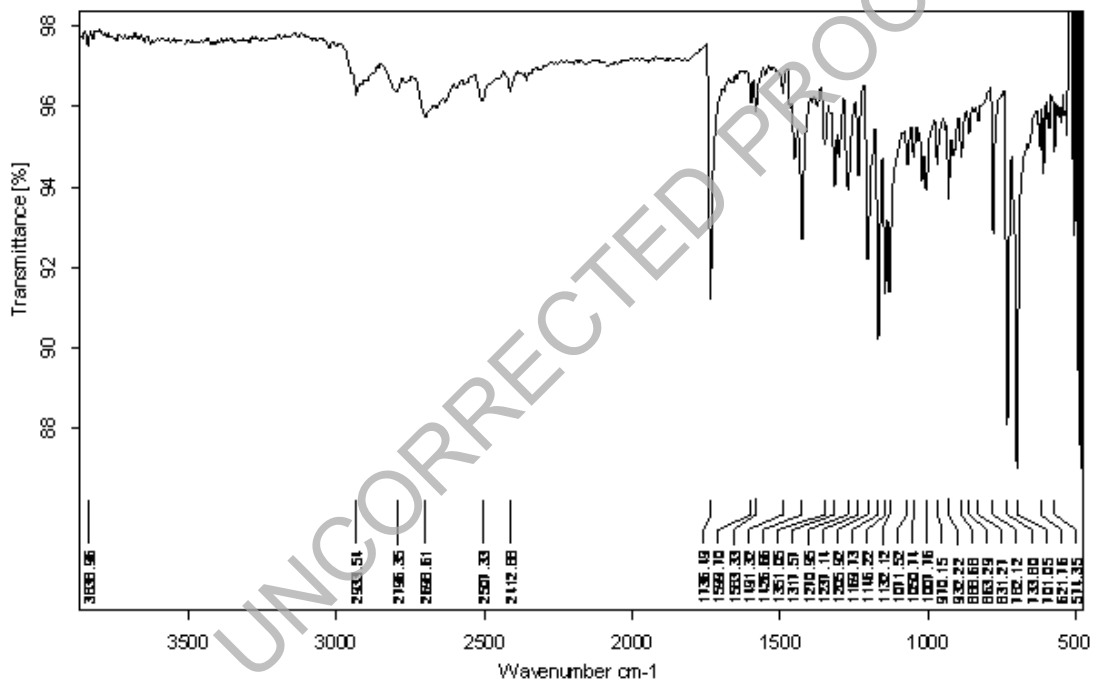

Figure 3: FTIR spectrum of pure Methylphenidate Hydrochloride

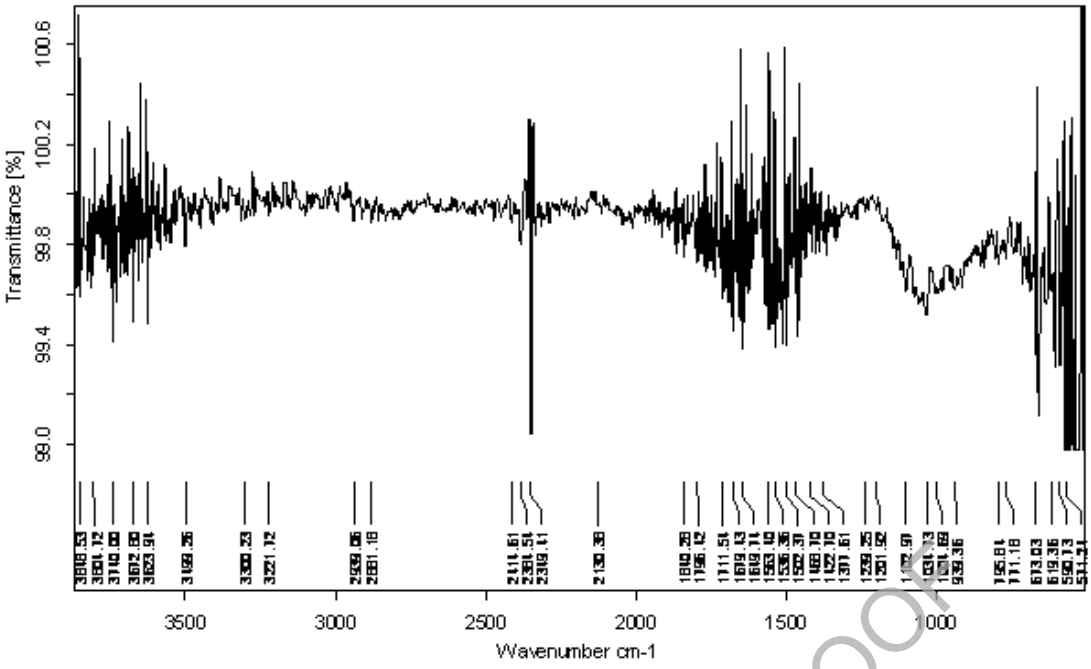

Figure 4: FTIR Spectrum of Methylphenidate HCl + HPMC E5

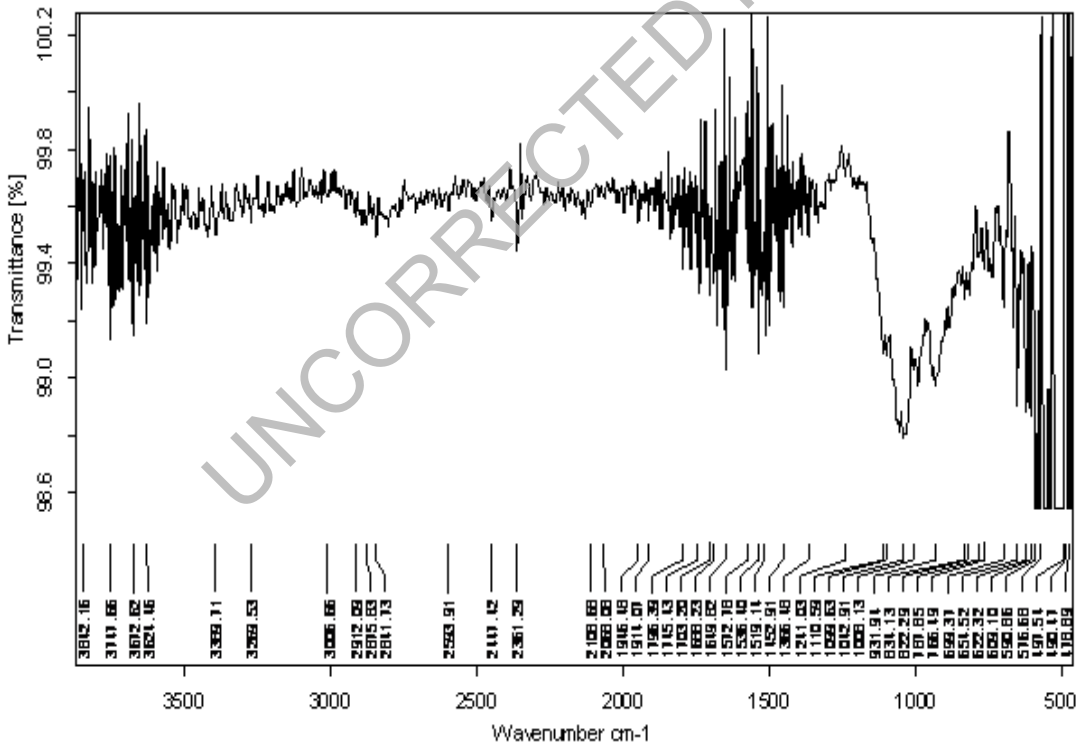

Figure 5: FTIR spectrum of Methylphenidate HCl + HPMC E15

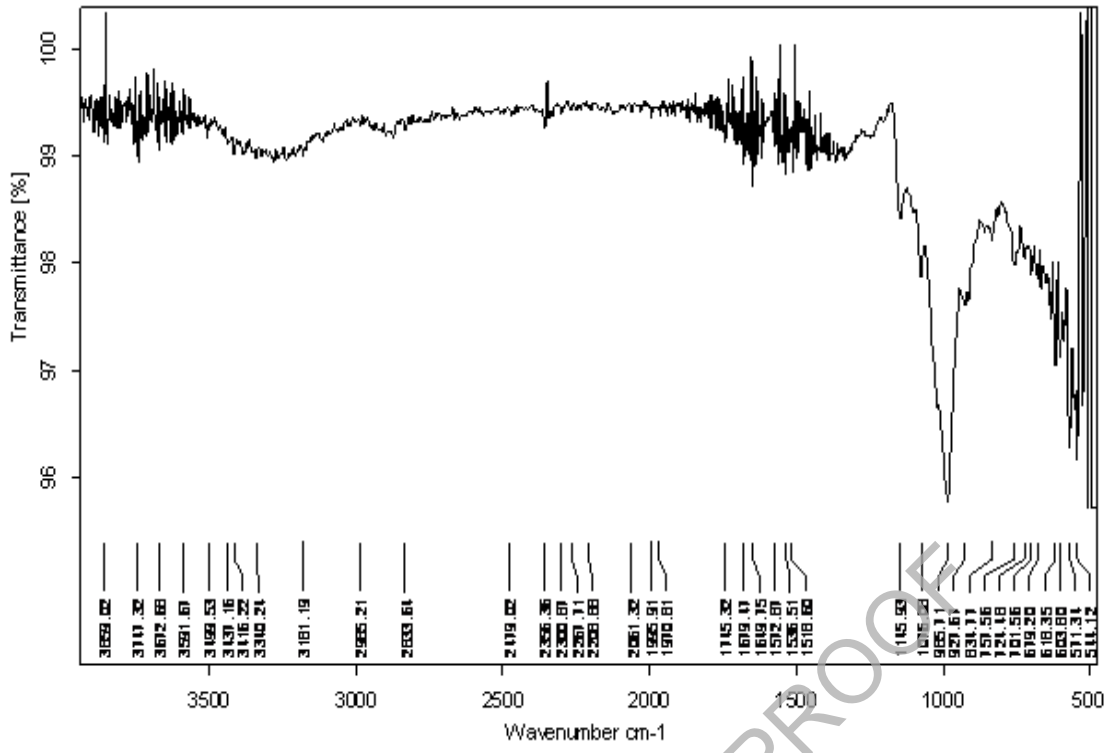

Figure 6: FTIR Spectrum of Methylphenidate HCl + Maltodextrin

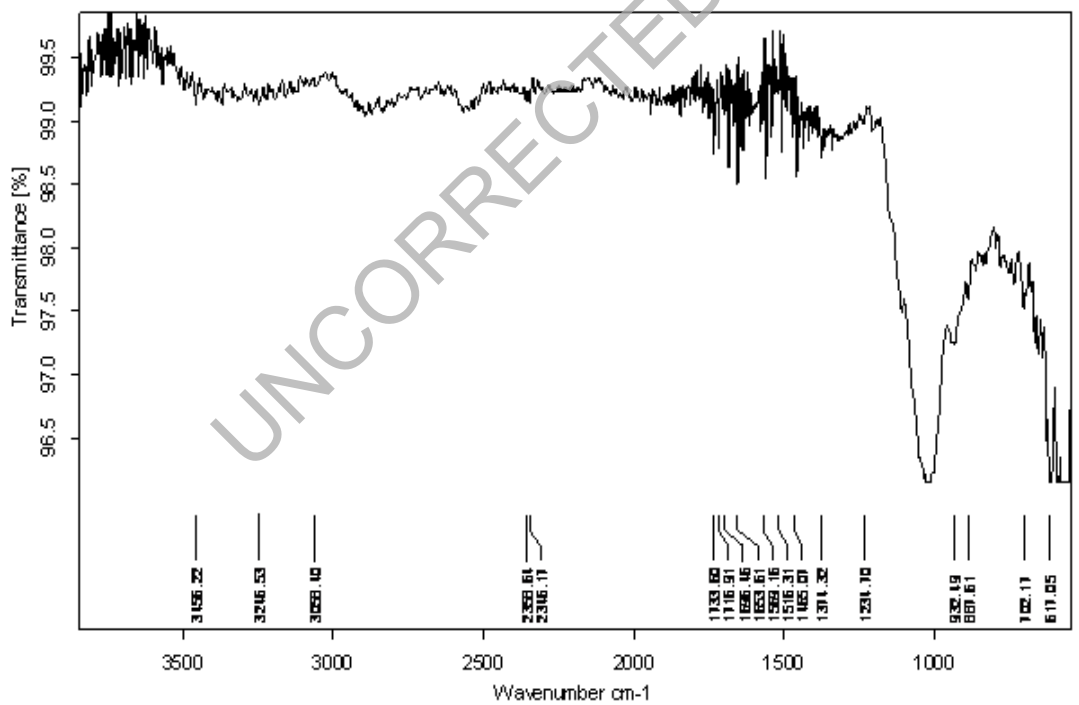

Figure 7: FTIR of Mouth Dissolving Film Formulation

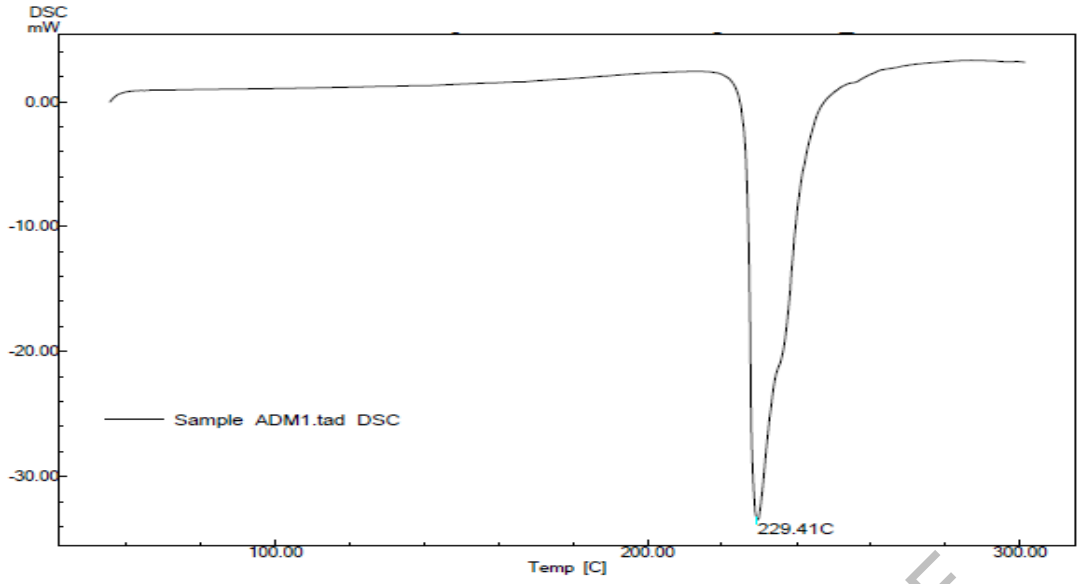

Figure 8: DSC of pure drug

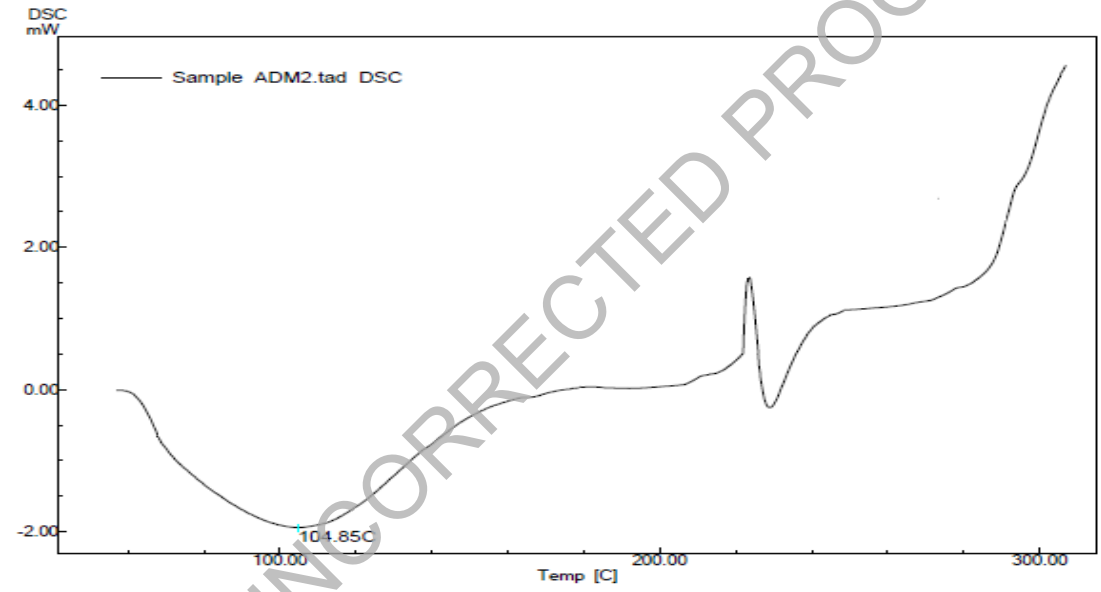

Figure 9: DSC of formulation

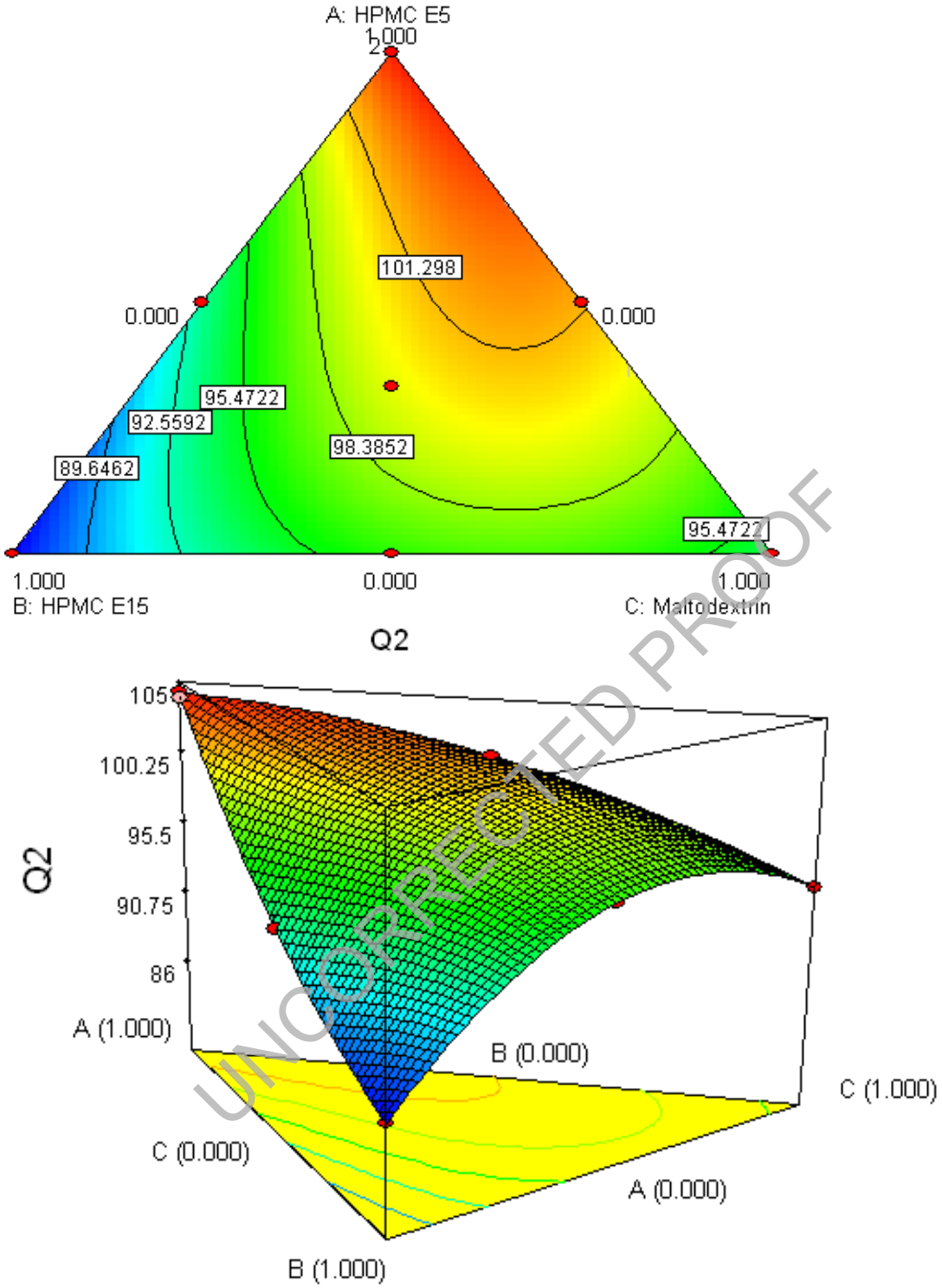

Figure 10: Contour plot and 3D Surface Plot of CPR Q_2 (%) against amounts of HPMC E5, HPMC E15 and Maltodextrin.

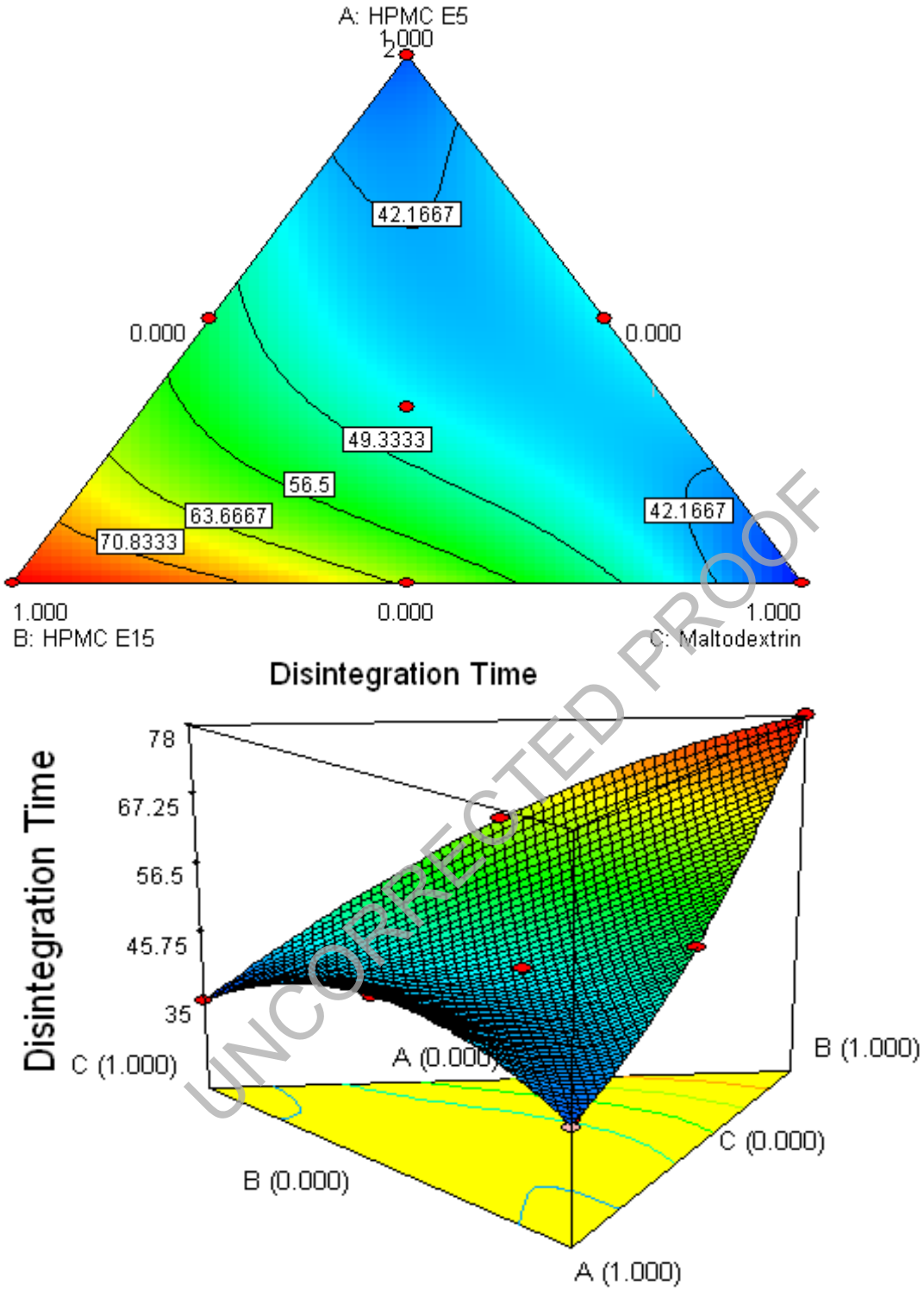

Figure 11: Contour plot and 3D surface plot of disintegration time (seconds) against amounts of HPMC E5, HPMC E15 and maltodextrin.

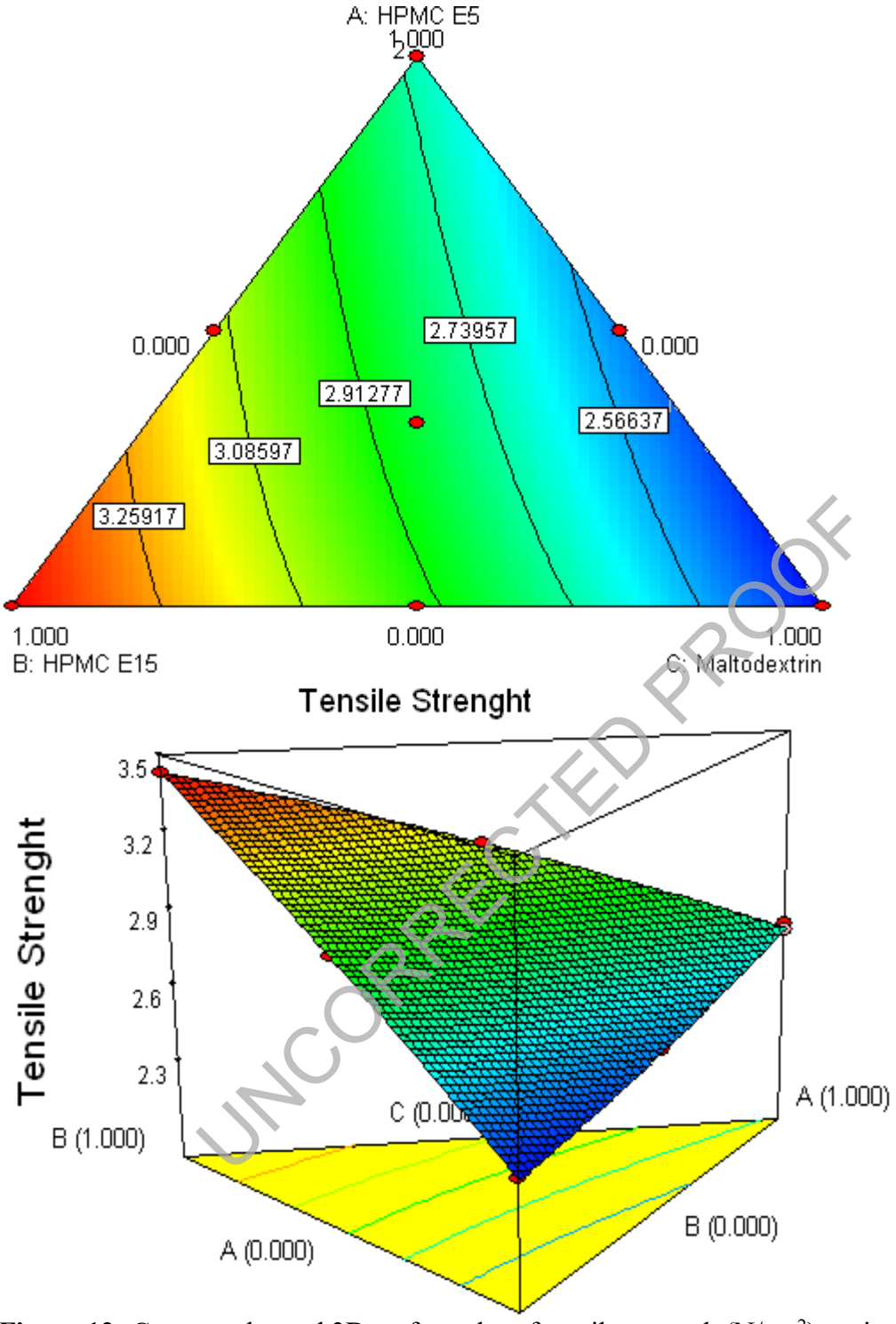

Figure 12: Contour plot and 3D surface plot of tensile strength (N/cm^2) against amounts of HPMC E5, HPMC E15 and maltodextrin.

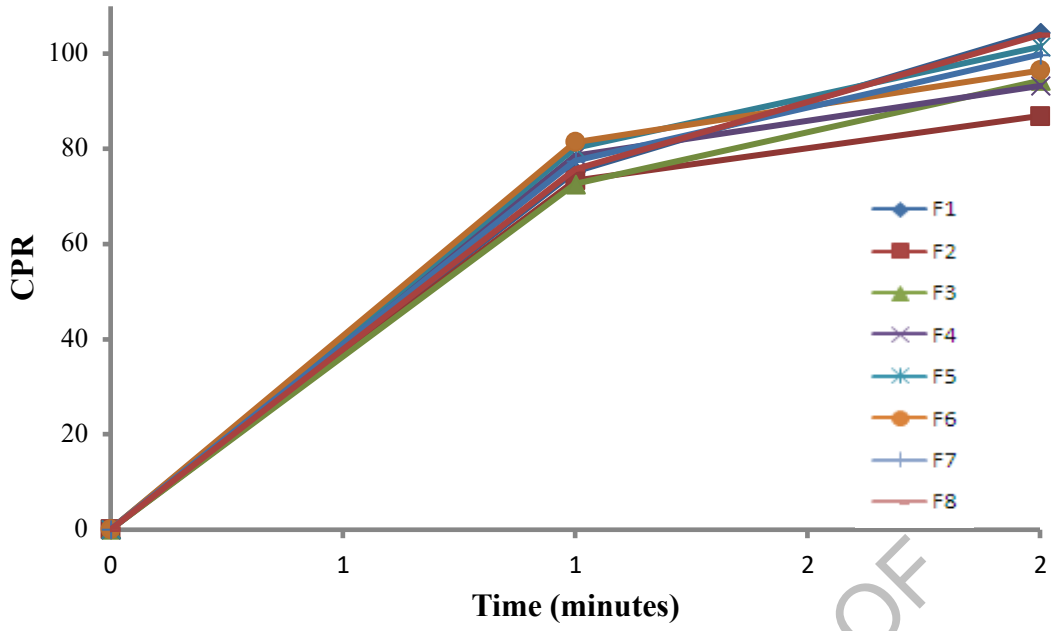

Figure 13: *In vitro* release of methylphenidate hydrochloride in phosphate buffer (pH 6.8) from film formulation.

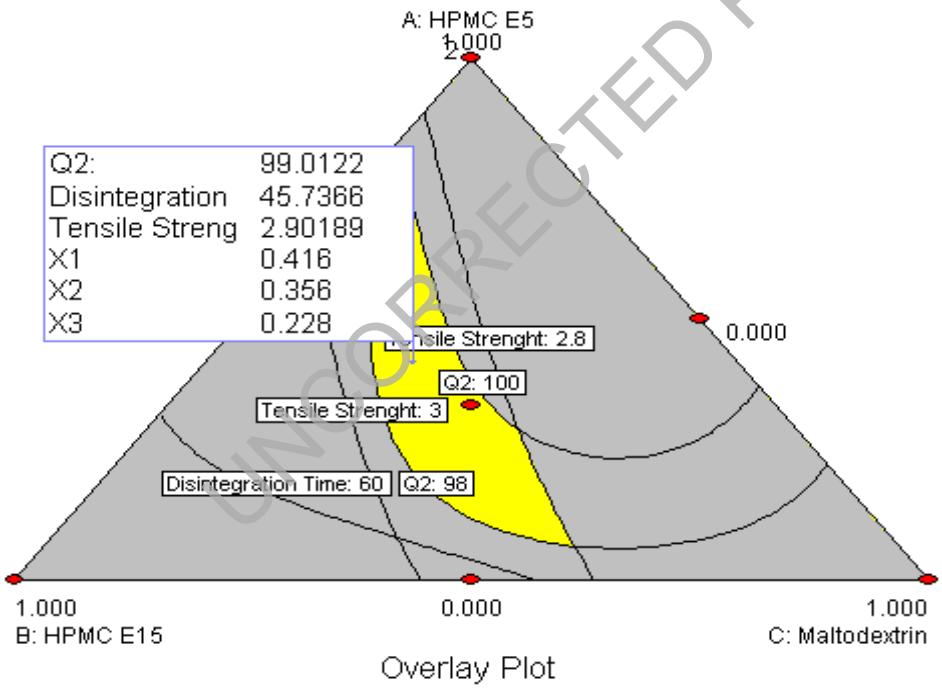

Figure 14: Overlay Plot