ORIGINAL ARTICLE

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

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ABSTRACT

Objectives: The focus of this study was to design and optimize methylphenidate hydrochloride mouth dissolving film (MDF) that can be beneficial in an acute condition of attention deficit hyperactivity disorder (ADHD) and narcolepsy.

Materials and Methods: Solvent casting method was used for the preparation of this film. Optimization of the effect of independent variables such as the number of polymers and active pharmaceutical ingredients [hydroxypropyl methyl cellulose (HPMC) E5, HPMC E15, and maltodextrin], % of drug release, disintegration time, and tensile strength of the film done using simplex centroid design. Complex formation of the film was tested using fourier-transform infrared spectroscopy and differential scanning calorimetry study. The multiple regression analysis was obtained from equations of the results that adequately describe influence of the independent variables on the selected responses. Polynomial regression analysis, contour plots, and 3-D surface plots were used to relate dependent and independent variables.

Results: Experimental results 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 expected values calculated from the developed regression equations as shown by percentage relative error. Final formulation showed more than 95% drug release within 2 min and was shown to disintegrate within a minute that had good tensile strength.

Conclusion: These findings suggest that MDF containing methylphenidate hydrochloride is likely to become a choice of methylphenidate hydrochloride preparations for treatment in ADHD and narcolepsy conditions.

Key words: HPMC, maltodextrin, mouth dissolving film, ADHD, simplex centroid design

INTRODUCTION

Oral drug administration has been most convenient and commonly recognized routes of delivery of 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 gastrointestinal 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 use of these oral dosage forms is the time required for onset of action, which is at least half an hour in case of conventional dosage forms and even more in the controlled and sustained release dosage forms. Dysphagia (difficulty in swallowing) is a chronic problem in people of all ages, but it is more prevalent in the elderly and pediatric 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% of the population according to reports.[4,5]

These concerns created mouth-dissolving films (MDF), a new kind of solid oral dosage medium. These delivery mechanism degrades or disintegrates quickly in mouth, requiring of water

to facilitate swallowing. Such technologies make it easier for those with swallowing problems as well as the public to take their drugs. Upon ingestion, saliva serves to rapidly disperse/dissolve the MDF. The saliva containing dissolved medicament is absorbed from mouth, pharynx, and esophagus. Because of the above-mentioned advantages, 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 a heightened sympathomimetic activity in central nervous system by operating on brain stem arousal system and cerebral cortex. Methylphenidate hydrochloride is a biopharmaceutics classification system class-I (high permeability and solubility) drug and its bioavailability is only 11-52% due to its hepatic metabolism. Therefore, main objective of this work was to provide immediate release of the psychostimulant drug methylphenidate HCl for immediate action in ADHD condition in order to improve patient compliance and to avoid hepatic first-pass metabolism of the drug.[4,5]

Therefore, the current study was conducted to develop MDFs of methylphenidate hydrochloride to provide quicker onset of action in the condition of ADHD.[4]

MATERIALS AND METHODS

Methylphenidate hydrochloride was given as a gift sample from Ipca Laboratories Ltd., Mumbai, India. Different hydroxypropyl methyl cellulose (HPMC) grades were gifted 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 solutions

Methylphenidate HCl (100 mg) 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 (1 mg/mL).[6]

Scanning of drugs

Ultraviolet (UV) spectrum was taken of the stock solution between wavelengths of 200-400 nm. It gave a peak at 257.2 nm and the same was selected as λ_{max}. The absorption maxima of methylphenidate hydrochloride in a pH buffer of 6.8 are shown in Figure 1.[7]

Preparation of calibration curve

The stock solution was diluted with a pH buffer of 6.8 to get a concentration range of 100 to 1000 µg/mL. 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 drug against ADHD treatment with a good safety profile; evidence shows 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 individual heterogeneity, such as the use of stimulants to manage ADHD. Genetic diversity, patient's 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]
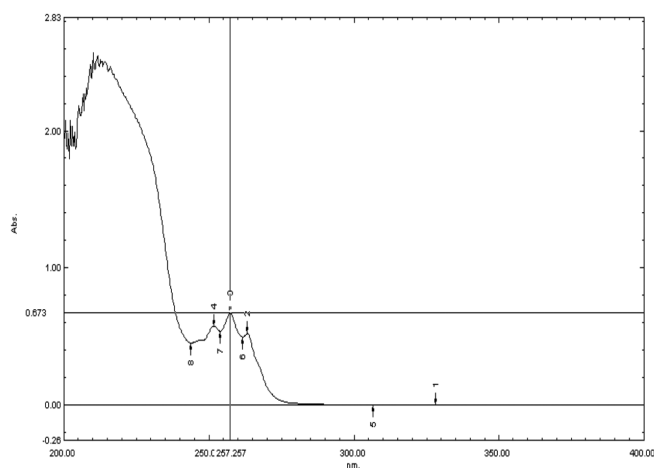

Figure 1. Absorption maxima of methylphenidate HCl in pH 6.8 phosphate buffer

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 ± SD (n= 3), SD: Standard deviation

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

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

= 133 µg L-1 × 0.3465 hr-1 × 2.7 L

= 6872.399 µg hr-1=6.87 mg

Here, C_{ss}= 133 µg L^{-1}

V_d= 2.7 L

K_e= 0.3465, where C_{ss} is the concentration at a steady state.

K_e= Elimination rate constant

V_d= Volume of distribution

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 area. 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 the methods, the solvent casting method is the widely used method to get a good and smooth film. MDF of methylphenidate HCl was made by the solvent casting method. The aqueous solution was prepared by dissolving the chosen polymers in 25 mL purified water and allowed to rest for 1 hour to eliminate any trapped air bubbles. Then, the active pharmaceutical ingredients 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 aluminum foil and stored in a desiccator until further analysis.[14-17]

Preformulation study

Melting point

Melting point of methylphenidate HCl was measured by digital melting point apparatus. The drug sample was filled in a capillary tube and stored using a mercury thermometer in an aluminum block of the 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. 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. Hence, ether is chosen for determination of partition coefficient. For this purpose, 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 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. Concentration of methylphenidate HCl in ether and water was analyzed by a UV-visible spectrophotometer at 257.2 nm after appropriate dilution with methanol. Partition coefficient was determined using the equation below. The experiment was replicated thrice.[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 solvent-casting method. Polymers were selected from the abovementioned placebo film by an appearance *via* 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]

Statistical analysis

Statistical analysis has been performed using simplex centroid design.

Simplex centroid design

The use of simplex centroid experimental designs in pharmaceutical research is well known. They are 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 the projected coefficients for factor X_i. 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,
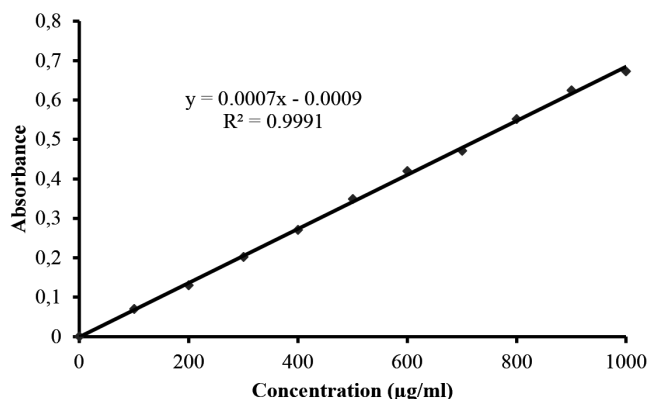

Figure 2. Standard curve of methylphenidate HCl in phosphate buffer (pH 6.8)

y = 0.0007x - 0.0009
R² = 0.9991

$X_1X_2X_3$) show how the response changes when two or more factors are changed simultaneously (Tables 2, 3).[22-24]

Other common ingredients used for each formulation
Other ingredients used include propylene glycol, 0.5 mL, as a plasticizer, and brilliant blue as color. Glycerin was used to the lubrication 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 is described in Figure 1.

Calibration curve of methylphenidate HCl
Methylphenidate HCl (100 mg) 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 MDF (2×2 cm^2). Each film's thickness was measured in three locations and the standard deviation (SD) was estimated.[27]

Drug content uniformity
A 4 cm^2 MDF 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 MDF were weighed on an electronic balance (Citizen CY 220C, Mumbai, India) and the average weight with SD was calculated.[29,30]

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

$$T.S.= Break force/A \tag{1}$$

where A= Cross-sectional area of the film

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

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

Here, 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 cm^2 was cut-out, weighed, and placed in a desiccator containing fused anhydrous calcium chloride. The films were removed and re-weighed after 24 hours. Formula 3 was used to calculate the percentage moisture content of the film.[33,34]

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

% 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

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

HPMC: Hydroxypropyl methyl cellulose

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

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 Mishra and Amin[20]. A glass petri dish containing 10 mL of distilled water was used to hold the film size needed for dosage distribution (2 × 2 cm). Time that took to break the film was recorded as the 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 continued stirring 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 4).

In vitro dissolution study

The test was performed with a slight modification using the same method as mentioned by Dinge and Nagarsenker[38] A film of 4 cm² 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 the dissolution of the batches. An 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.[36-38]

Folding endurance

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

Table 4. 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

Stability study

Stability testing's goal was 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. International Conference on Harmonization (ICH) specifies the length of study and storage conditions.[41-43]

Method

The sample was wrapped in aluminum foil and subjected to stability studies as per the 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), the 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. These data are used to find R^2 value.

RESULTS AND DISCUSSION

λ_{max} of the drug was determined by scanning 1000 μg/mL concentration solution prepared with pH 6.8 buffer in range 200-400 nm using a double beam UV-visible spectrophotometer. λ_{max} was found to be 257.257 nm (Figure 1). Therefore, further studies were conducted in a wavelenght of 257.2 nm.

Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) studies

An FTIR spectrophotometer was used to conduct the compatibility tests. A KBr disc was used to investigate 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 5)

The spectra for all formulations are shown below.

In the above spectrum, the characteristic (principal) peaks of methylphenidate hydrochloride are presented as follows.

FTIR spectra of methylphenidate hydrochloride+ HPMC E5 (Figure 4) exhibited peaks at 711 cm⁻¹ (monosubstituted benzene), 1593 cm⁻¹ in the 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 the 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 the 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 the range. FTIR spectra of MDF 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 exhibit in the range.
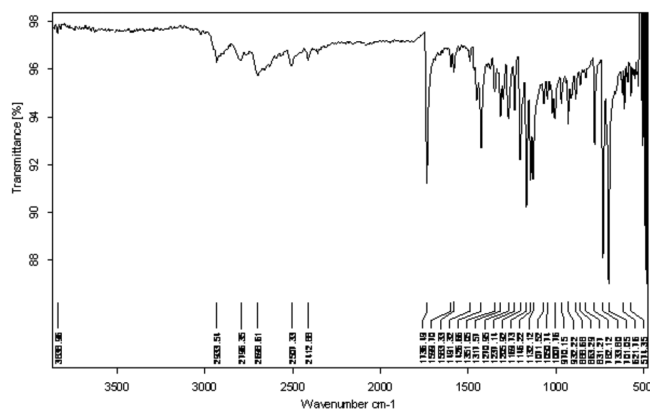

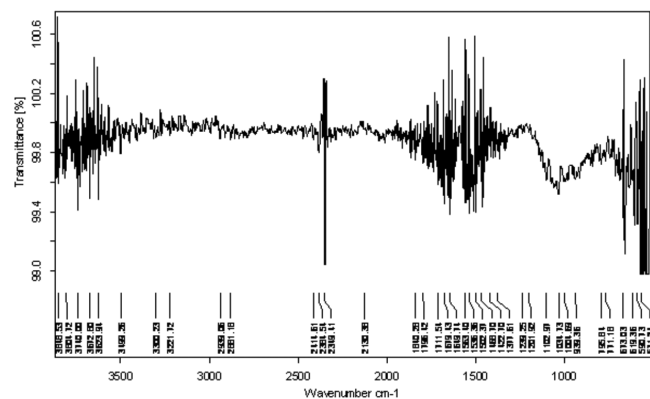Figure 3. FTIR spectrum of pure methylphenidate hydrochloride

Figure 4. FTIR spectrum of methylphenidate HCl + HPMC E5

Table 5. 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

FTIR: Fourier-transform infrared spectroscopy

In the spectrum of the drug-polymer mixture, all the peaks are present and in the formulation. This indicates that there is no interaction between the drug and the formulation components.

DSC

DSC thermogram of methylphenidate hydrochloride showed an endothermic peak at 229.41°C corresponding to its melting
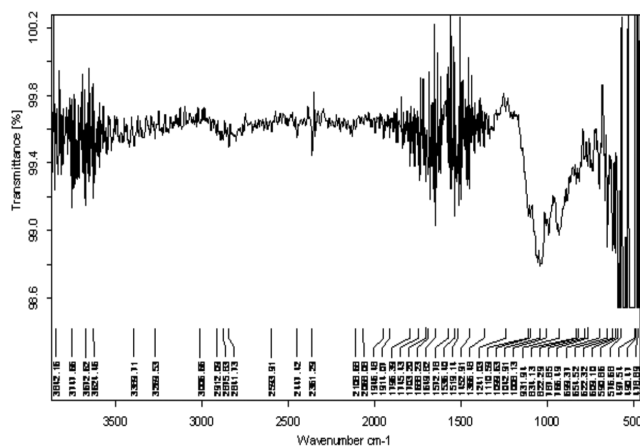

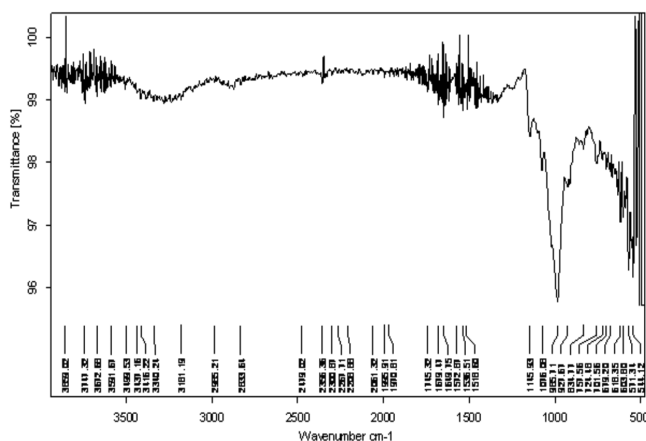Figure 5. FTIR spectrum of methylphenidate HCl + HPMC E15

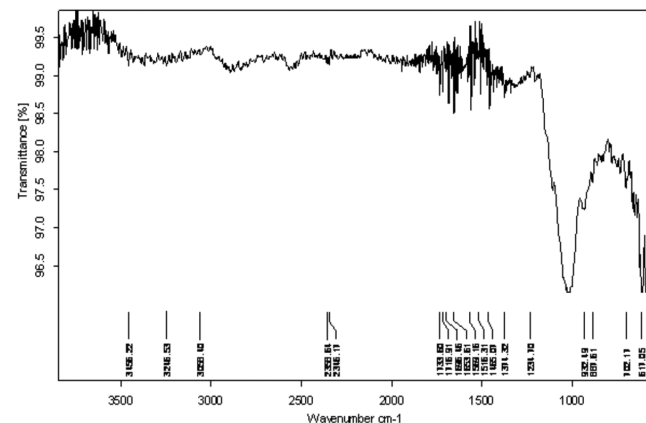Figure 6. FTIR spectrum of methylphenidate HCl + maltodextrin

Figure 7. FTIR of mouth dissolving film formulation

point.[38] DSC thermograms of the drug with other excipients do not display a profound shift in peaks (229.41°C), which indicates compatibility. DSC thermograms of the individual drug and final formulation are shown in Figure 8 and 9.[47]
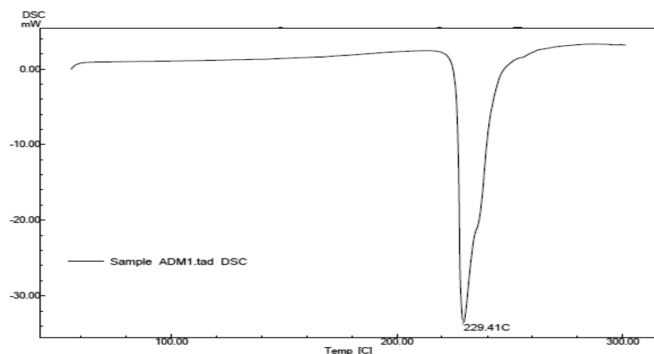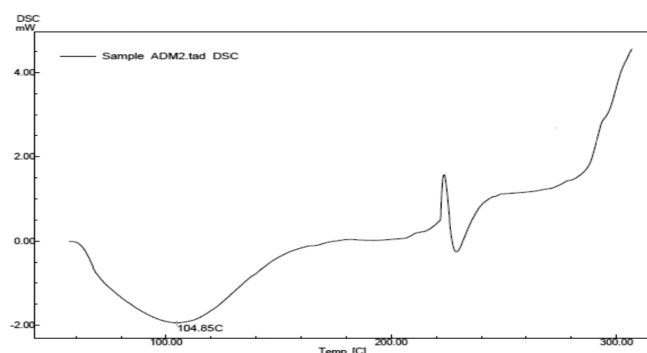

Figure 8. DSC of pure drug

Figure 9. DSC of formulation

Preliminary studies on the selection of polymers

A preliminary research was conducted to identify appropriate polymers and a suitable plasticizer capable of manufacturing films with favorable mechanical properties and disintegration times.[48] The solvent casting process was used to make the casting solution. The composition of various batches, number of polymers used, and their appearance and disintegration time are given in Table 6.

Optimization of polymer

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, and 1500 mg were not having acceptable physical characteristics. The lowest amount of maltodextrin (PB1), when cast in the plastic petri dish having an area of 70 cm^2, was insufficient for making the film. In other batches of maltodextrin (PB2 to PB4), amounts were sufficient for making the film, which was sticky. Thus, maltodextrin alone was not selected as the film-forming polymer.

HPMC is a hydrophilic polymer that is suitable for the MDF. Various grades of HPMC could make films that were very transparent and had excellent mechanical properties. Placebo films of different grades of HPMC E3, HPMC E5, and HPMC E15 were prepared to verify their film-forming capacity and suitability for MDF. From all HPMC batches, PB7 for HPMC E3, PB9 for HPMC E5, and PB11 for HPMC E15 were easily removed from the petri dish and had good acceptable physical characteristics and low disintegration time in accordance with other batches (Table 6).

Films prepared from single polymers (PB7, PB9, PB11) gave good results for disintegration time, but other properties were not so good, so, combinations of different grades of HPMC were

Table 6. 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 ± SD (n= 3), SD: Standard deviation, HPMC: Hydroxypropyl methyl cellulose

taken, which exerted 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 a much smoother texture were obtained. The combination yielded smoother films with less disintegration time, and finally, among the preliminary batches, PB22 was shown to give the best results (Table 7). Therefore, 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 1.25 mL (Table 8). The results indicated 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. Amongst the prepared films, PB24, PB25, PB30, and PB31 were 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]

Statistical analysis

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 such the amount of HPMC E5 (X_1), amount of HPMC E15 (X_2), and amount of maltodextrin (X_3) showed a 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, it was used in further research. All three chosen dependent variables (X_1, X_2, and X_3) showed large variance in disintegration time, volume of drug released in 2 minutes, and tensile strength for all 7 batches (Table 9). The data showed that X_1, X_2, and X_3 had a major effect on those responses (R_1, R_2, and R_3). Since considering the magnitude of coefficients and statistical signals, polynomial equations can be used to determine, whether the response is positive or negative. The statistical analysis (ANOVA) results for the design batches are shown below.[46,52]

Table 7. 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		43.67 ± 1.154
PB18	E5 + maltodextrin	375 + 500	Good and smooth	41.33 ± 0.577
PB19	E15 + maltodextrin	250 + 500		35.33 ± 0.577
PB20	E3 + E5 + maltodextrin	333 + 250 + 333		42.67 ± 2.081
PB21	E3 + E15 + maltodextrin	333 + 166 + 333	Very good and smooth	39.33 ± 1.527
PB22	E5+E15 + maltodextrin	250 + 166 + 333		34.67 ± 1.154

*Results are shown in mean ± SD (n= 3), SD: Standard deviation

Table 8. Characteristics of placebo films prepared using different plasticizer

Batch[#]	Plasticizer	Amount (mL)	Folding endurance	Disintegration time* (sec)	Tensile strength* (n/cm²)
PB23		0.25	142	Brittle	-
PB24		0.5	156	66.33 ± 2.081	3.11 ± 0.061
PB25	Glycerin	0.75	-	74.66 ± 4.167	3.18 ± 0.017
PB26		1	-	Peel off problem	-
PB27		1.25	-	Peel off problem	-
PB28		0.25	-	Brittle	-
PB29		0.5	148	46 ± 1.73	2.42 ± 0.023
PB30	Propylene glycol	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 ± SD (n= 3). SD: Standard deviation, HPMC: Hydroxypropyl methyl cellulose

Response 1: CPR Q$_2$ (R$_1$)

The magnitude of coefficients and mathematical signs can be used to determine whether 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 % in 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 determine contribution of each component and their interaction, an ANOVA for SCM was carried out.

The statistical analysis (ANOVA) results (Table 10), contour plot, and 3D surface plot for cumulative percentage release (CPR), Q$_2$ (Figure 10) presents a strong effect of three factors (amounts of HPMC E5, HPMC E15, and maltodextrin). A polynomial equation of Q$_2$ indicates that three polymer amounts have a positive effect on the Q$_2$. *In vitro* dissolution of the films increased with the increase in 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 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 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 the contribution of each component and their interaction, an ANOVA for SCM was carried out.

ANOVA results (Table 11), contour plot, and 3D surface plot for the disintegration time (Figure 11) indicates the strong effect of the three factors (amounts of HPMC E5, HPMC E15, and maltodextrin). A polynomial equation of disintegration time indicates that the three polymers amounts have a positive effect on the disintegration time. *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

Table 9. Design summary

Formulation code	R$_1$	R$_2$	R$_3$
	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 ± SD (n= 3), SD: Standard deviation, R$_1$: Response 1, R$_2$: Response 2, R$_3$: Response 3

Table 10. ANOVA for special cubic model (% release at 2 min)

Source	Sum of squares	DF	Mean square	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	-	-	-

DF: Degree of freedom

were selected within the limits of the design, *in vitro* dissolution rate decreased the most, when more amounts of maltodextrin were used in the formulation, which increased gradually with HPMC E5 followed by HPMC E15. As *per* the equation, a shorter disintegration time can be achieved with the combination of the three polymers, rather than the single polymer or with the combination of any two of them.
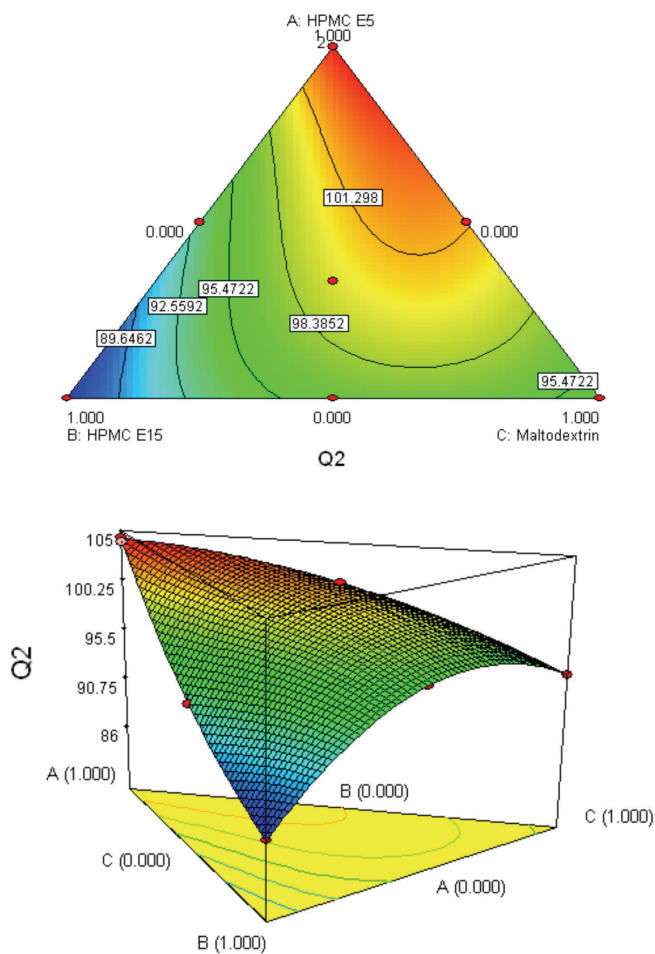
Response 3: Tensile strength (R_3)
Statistical analysis was carried out in Design-Expert software (7.1.5), which suggested that SCM was followed for release at $T2_{min}$ with a *p* value of 0.0385. It revealed that the model was highly significant.

Figure 10. Contour plot and 3D surface plot of CPR Q_2 (%) against amounts of HPMC E5, HPMC E15, and maltodextrin
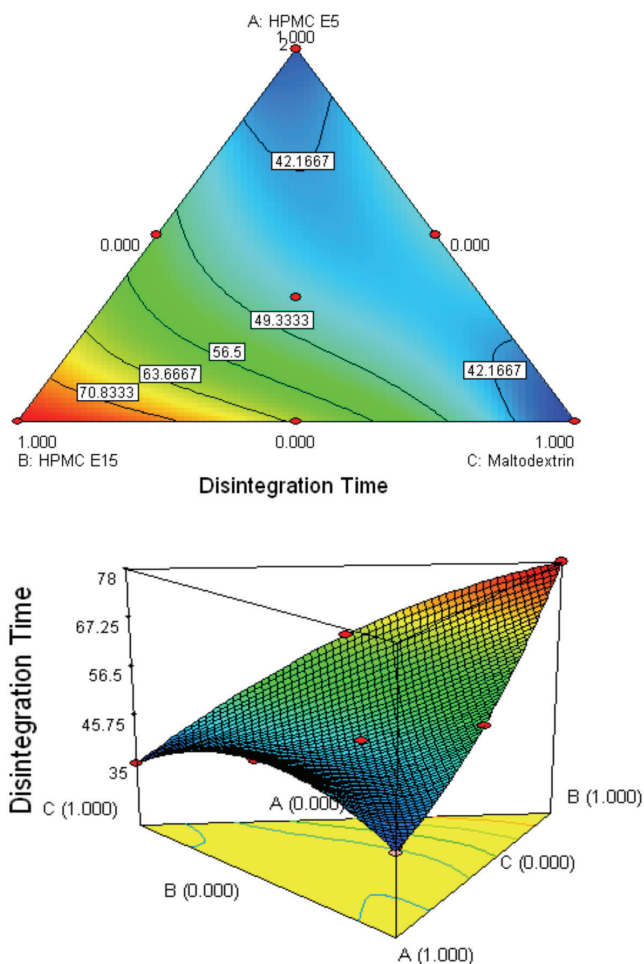

Figure 11. Contour plot and 3D surface plot of disintegration time (seconds) against amounts of HPMC E5, HPMC, E15, and maltodextrin

Table 11. 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	-	-	-

DF: Degree of freedom

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 determine impact of each component and their interaction, ANOVA for SCM was carried out. The ANOVA results (Table 12),
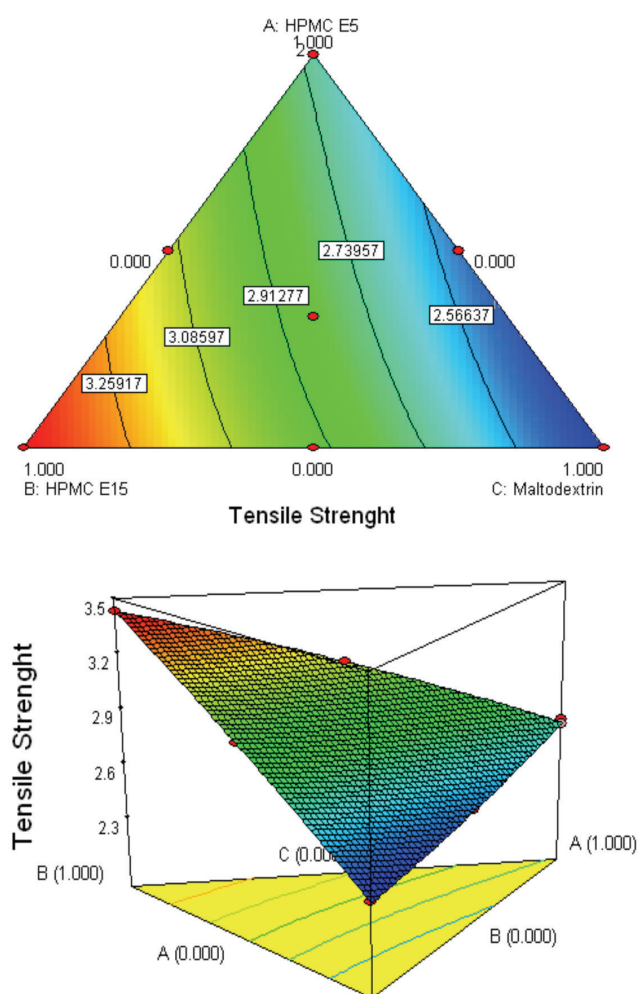

Figure 12. Contour plot and 3D surface plot of tensile strength (n/cm²) against amounts of HPMC E5, HPMC, E15 and maltodextrin

3D surface plot, and contour plot for the tensile strength (Figure 12) indicated the strong effect of the three factors (amounts of HPMC E5, HPMC E15, and maltodextrin). A polynomial equation of tensile strength indicates that all the all the three-polymer amount have 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 amounts of HPMC E15 were 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 for film formulation

Weight variation tests

Table 13 summarizes weight difference % for all formulations. They were under the pharmacopeial limits of 7.5%, so both of the films passed 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. Weight of the films was uniform.[55]

Thickness

The formulated films were observed to have thicknesses ranging from 0.103 ± 0.015 to 0.207 ± 0.02 mm. Table 13 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 is shown in Table 13. All the batches have folding endurance of 101 ± 2.645 to 177.67 ± 3.51. The folding endurance increases as concentration of the polymer increases.[57,58]

Drug content

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, where the

Table 12. 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	-	-	-

DF: Degree of freedom

results are listed in Table 13. A spectrophotometer was used to examine three trials for each formulation. Mean values of all the formulations and SDs were calculated. The findings showed that both formulations had the same drug material. In *in vitro* release trials, the total % of drug released from each film was calculated using the mean quality of the drug contained in the film. Ranges of drug content in 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 released 104.44% and 101.41%, respectively, at the 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 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 decreasing mobility of drug particles in swollen matrices, which leads to a delay in drug release.[36]

Table 14 shows the data of dissolution of prepared design batches. Figure 13 shows the graph of CPR *versus* time in minutes. The data indicated the data up to 2 min only, so that, we can easily compare the dissolution and % of 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, number of drug release changes. So, we may say that polymers having a lower viscosity release the drug quickly than the polymers with higher viscosity. Thus, in order to get a quicker release, lower viscosity-grade polymers are desirable.[47]

Optimized batch analysis by statistical analysis

The optimized formulation was chosen based on criteria, a higher amount of drug release in 2 minutes, shortest disintegration time, and a medium value of tensile strength.

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 regression equations. When the experimental and theoretical values were compared, error % was found to be less than 8% for the responses (Table 15).

Stability studies

A stability study was conducted according to the ICH guidelines for a short time. The developed formulations were tested for stability at 40°C and 75% relative humidity for 6 months and were evaluated for tensile strength, disintegration time, and *in vitro* drug release at 1, 3, and 6 month intervals. Effects of the formulations were deemed within acceptable limits as seen in Table 16. The measurable parameters showed no major differences. So, the formulation was found to be stable.[47]

Release kinetics and mechanisms

Data of *in vitro* release were fit into different equations and kinetic models to explain release kinetics of methylphenidate from these films. Release kinetics of methylphenidate followed zero order from the films (Table 17). A better fit (highest R^2 values) was observed in the case of Higuchi's model than Hixon-Crowel model except film I. Hence, mechanism of drug release
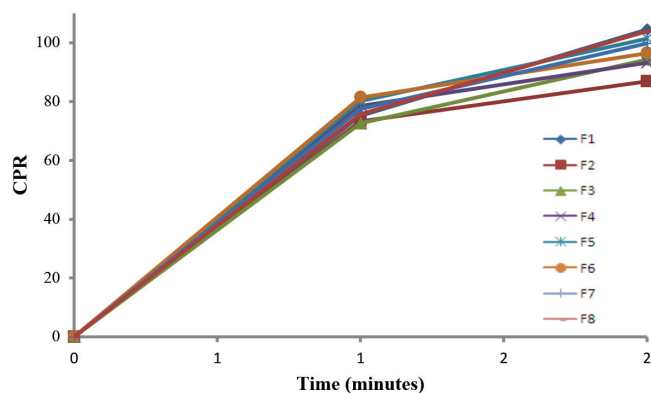

Figure 13. *In vitro* release of methylphenidate hydrochloride in phosphate buffer (pH 6.8) from the film formulation

Table 13. 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 ± SD (n= 3), SD: Standard deviation

from the remaining films followed is diffusion controlled and drug release from film I followed dissolution controlled (Table 18).
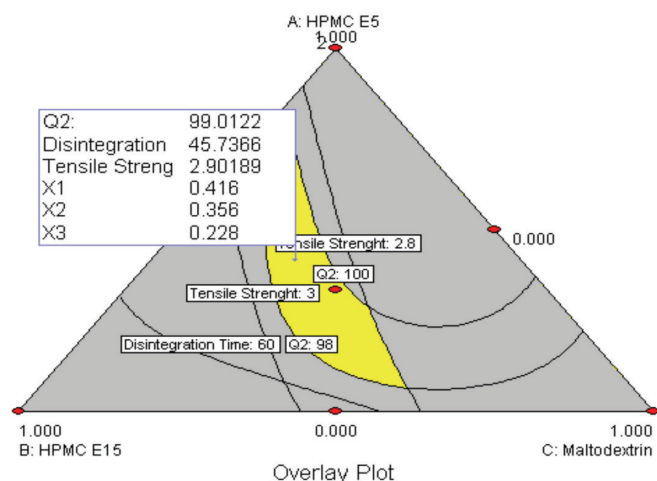

Figure 14. Overlay plot

Application of the Hixon-Crowell cube root law, the equation (M01/3-M1/3)= kt, provides information about the release mechanism, namely the dissolution rate limited. Application of Higuchi's equation (M= K $t_{1/2}$) provides information about the release mechanism, namely the diffusion rate limited. Korsmeyer-Peppas model indicates that the release mechanism is not well-known or that more than one type of release phenomenon could be involved. The "n" value could be used to characterize different release mechanisms (Table 19).

R^2 values are higher for Higuchi's model compared to Hixon-Crowell for the films except film I. Hence, drug release from film I followed a dissolution rate-controlled mechanism and drug release from the remaining films followed a diffusion rate-controlled mechanism.

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

Table 14. Cumulative% of 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 ± SD (n= 3), SD: Standard deviation

Table 15. 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/mm²)	2.90	2.98 ± 0.14	2.75

*All results are shown in mean ± SD (n= 3), SD: Standard deviation

Table 16. 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/cm²)	2.98 ± 0.14	2.95 ± 0.081	3.01 ± 0.07	2.99 ± 0.14

*All results are shown in mean ± SD (n= 3), SD: Standard deviation
CPR: Cumulative percentage release

Table 17. 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 18. 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 19. 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

CONCLUSION

The prepared film of methylphenidate hydrochloride obtained using the solvent casting method showed the desired % drug release, disintegration time, and tensile strength. The prepared film had a very smooth surface because of maltodextrin and without any interactions between the 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 adequately describe 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 more amounts 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. High drug release % of the film in simulated saliva (pH buffer 6.8) indicated that it could be helpful for treating acute ADHD and narcolepsy, where quick bioavailability of the drug is desired.

Therefore, all designed batches were prepared and their evaluations were carried out which showing acceptable results. Based on the results, we may conclude that aim of the current work was successfully fulfilled.

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Ethics

Ethics Committee Approval: There is no requirement for ethical approval.

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.B., Design: B.B., Data Collection or Processing: B.B., A.M., A.D., Analysis or Interpretation: B.B., A.M., A.D., Literature Search: A.M., A.D., Writing: B.B.

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