International Journal of Multidisciplinary Research and Growth Evaluation.

Design, prepare, and characterization of methylphenidate controlled release tablets

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Article Info

ISSN (online): 2582-7138
Impact Factor: 5.307 (SJIF)
Volume: 05
Issue: 01
January-February 2024
Received: 10-12-2023;
Accepted: 12-01-2024
Page No: 603-607

Abstract
The present work aims to develop and characterize the controlled release of Methylphenidate matrix tablets used for the treatment of attention deficit hyperactivity disorder (ADHD). Development of CR Methylphenidate is proposed considering the adverse event profile and high fluctuation index of Methylphenidate observed with IR dosage forms. In the present work, attempts were made to formulate and evaluate the controlled release of matrix tablets of Methylphenidate. Methylphenidate was subjected to preformulation studies; based on the results obtained Methylphenidate controlled-release tablets were successfully formulated. Formulations prepared by direct compression technique. Set of trials were formulated for which Methylphenidate evaluated parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) was found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in pH 6.8 phosphate buffer. From the results of the in vitro study it appears that the release of the Methylphenidate was significantly influenced by the characteristics of the polymer used.

Keywords: Methylphenidate, polymers, FTIR studies, direct compression technique, *in vitro* drug release studies, zero order kinetics

Introduction
Oral drug delivery system is the most popular route, which is due to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes [1]. Controlled-release (CR) formulations have been introduced into drug therapy with two main purposes: to reduce the number of single doses per day improving patient compliance of treatments and to decrease the fluctuations of plasma levels, in order to obtain better therapeutic efficacy and lower toxicity [2]. Controlled release dosage form covers a wide range of prolonged action formulation which provides continuous release of their active ingredient at a predetermined rate and time. Sustained or controlled drug delivery system is to reduce the frequency of dosing [3]. Methylphenidate hydrochloride, also known as methyl-phenyl-2-piperidine acetate hydrochloride. The drug taken for the present study is among the atypical anti-psychotic group, with the strength of 20mg for therapeutic response against treatment of attention-deficit hyperactivity disorder (ADHD), postural orthostatic tachycardia syndrome and narcolepsy. Methylphenidate blocks dopamine uptake in central adrenergic neurons by blocking dopamine transport or carrier proteins [4]. Hence, in the present work, an attempt has been made to formulate the controlled release matrix tablets of Methylphenidate using various polymers to evaluate the *in vitro* release characteristics and to predict the release behavior.

Materials
Methylphenidate was obtained from Hetero lab, HYD. HPMC and Ethyl cellulose were procured from Synpharma Research Labs, Hyderabad, and other chemicals, and the reagents used were of analytical grade.

Methodology

Fourier Transform Infrared Spectroscopy (FTIR) [5]

The compatibility studies were carried out by taking a mixture of drug and excipients. A part of mixture can be exposed to different storage conditions like 400C±20C / 75% RH ±5% and control samples were to be kept at 2-8 0C. They were tested with respect to their physical and chemical aspects. These samples were collected at regular intervals and subjected to FT-IR.

Formulation Development

Table 1: Formulation table

S.NO.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Methylphenidate	10	10	10	10	10	10	10	10
2	HPMC k 4M	50	100	150	200	-	-	-	-
3	Ethyl cellulose	-	-	-	-	50	100	150	200
4	Microcrystalline Cellulose	335	285	235	185	335	285	235	185
5	Magnesium stearate	3	3	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2	2	2
7	Total Weight	400	400	400	400	400	400	400	400

Method of Preparation: [6]

The drug, polymer/s, and diluent were screened through # 40 and preblended using a lab-scale double cone blender. The lubricant was added and the blend was mixed again prior to compression. The tablet blends were directly compressed by using a Elite 10 station minipress with 6mm flat round punches. To avoid processing variables all batches of matrix tablets were compressed under identical conditions. All the matrix tablets prepared were further evaluated for physical parameters such as weight uniformity, hardness, friability and uniformity of drug content.

Evaluation Studies

Weight variation [7]

A total of 20 tablets were individually weighed and then their average weight was calculated. The average weight was compared with the individual tablet weights, and the weight variation was calculated.

Hardness [8]

The hardness of the prepared tablets was determined using Monsanto tablet hardness tester.

Friability Test [9]

This test was performed by using Roche Friabilator. This test was performed on twenty tablets from a batch were weighed and placed in the friabilator chamber. The chamber was allowed to rotate 100 revolutions. During each revolution these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were collected 71 from the chamber dedusted and weighed. The loss in weight indicates friability.

Drug Content Uniformity [10]

A matrix tablet of Methylphenidate was taken at random from each batch and crushed to fine powder. The powdered material was transferred in to a 100 ml volumetric flask containing 70 ml of distilled water. The flask was shaken occasionally for 30 minutes and the volume was made up to 100 ml mark with distilled water. About 10 ml of the solution was taken and filtered. The filtrate was suitably diluted and the absorbance was measured at 277 nm using UV spectrophotometer (Elico model SL-218). This test was repeated with six tablets from each batch. The amount of Methylphenidate estimated from different batches of tablets

In vitro release profile [11]

The in vitro drug release studies of the tablets were performed using a dissolution test apparatus (USP 24 Type II, Model TDT6P) with the peddle rotating at 50 rpm in dissolution media maintained at 37±0.5°C. The dissolution media used were 0.1 N HCl/pH 6.8 buffer (1000 mL). The media were 750 mL of 0.1 N HCl for 2 h then for the remaining intervals 250 mL of trisodium phosphate buffer was added to adjust the pH to 6.8.10 mL aliquots of dissolution media were withdrawn at suitable time intervals and replaced with the same volume of fresh dissolution media after each withdrawal. Aliquots were filtered through Whatman filter paper no. 5 and then the absorbance of samples was measured at 306 nm against the corresponding reagent blank.

Kinetics of drug release [12]

To study kinetices data obtained from invitro releasase were plotted in various kinetic models.

- **Zero-order equation**

$\%R = Kt$

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.

- **First order equation**

$\text{Log}\%\text{ unreleased} = Kt / 2.303$

This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

- **Higuchi equation**

$\%R=Kt^{0.5}$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

- **Korsmeyer-Peppas equation**

$\%R=Kt^{n}$

This model is widely used, when the release phenomenon could be involved. The end value could be used to characterize different release mechanisms as:

Stability studies: [13]
Selected formulations of Methylphenidate were subjected to accelerated stability studies as per ICH guidelines. The matrix tablet formulations were subjected to accelerated stability studies.

Results and Discussion

Compatibility Study
Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied.
The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

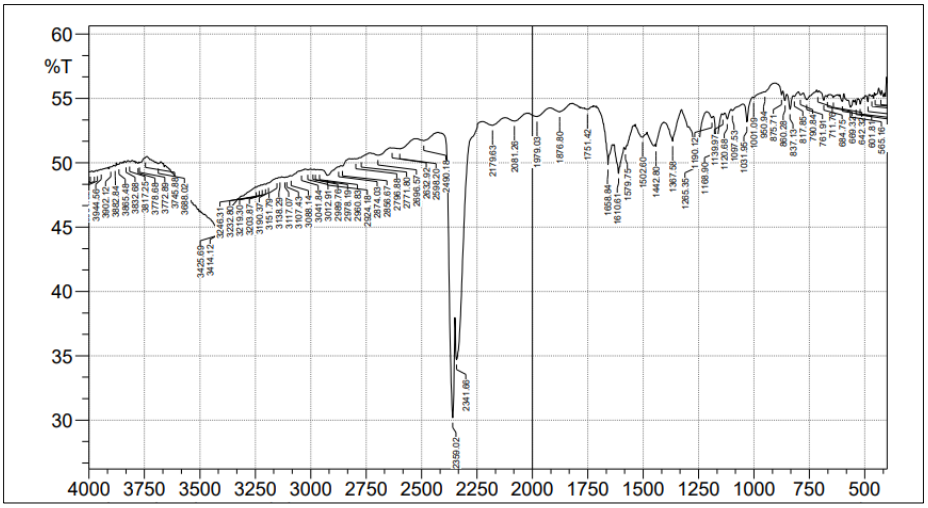

Fig 1: FTIR Spectra of Methylphenidate

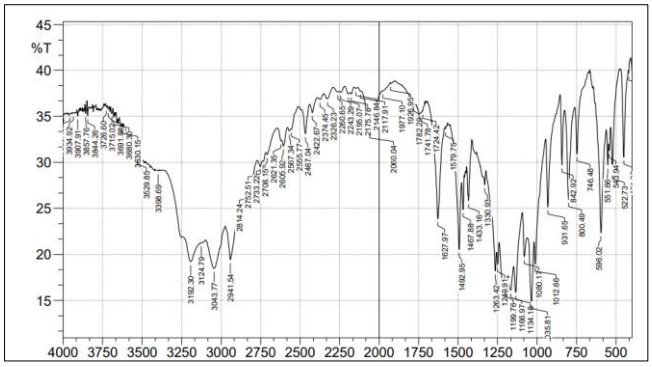

Fig 2: FTIR Spectra of Optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients

Evaluation parameters
Weight variation
All the formulated (F1 to F8) tablets passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness
Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 3.17mm to 3.23 mm.

Hardness
The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm^2. This ensures good handling characteristics of all batches.

Friability
The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity
The percentage of drug content for F1 to F8 was found to be between 90.22 % and 97.58 % of Methylphenidate it complies with official specifications.

Table 2: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	400	3.22	6.12	0.40	93.70
F2	400	3.19	6.14	0.42	94.50
F3	399	3.22	6.22	0.40	95.24
F4	398	3.23	6.16	0.39	91.15
F5	400	3.20	6.10	0.43	97.58
F6	399	3.17	6.15	0.42	90.22
F7	400	3.23	6.17	0.38	95.90
F8	399	3.39	6.20	0.38	91.48

In-vitro Dissolution Study

Table 3: *In vitro* release data of tablet F_1 to F_8

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0		0
1	23.30	25.50	20.41	22.30	28.50	23.65	20.40	26.41
2	34.62	31.15	32.81	32.42	33.72	35.20	29.72	30.85
3	40.92	38.65	39.90	41.18	42.70	41.28	32.70	40.28
4	52.65	48.23	53.41	50.90	56.65	52.62	49.65	51.27
5	61.25	59.95	65.50	63.82	65.38	60.74	52.38	62.32
6	73.12	72.82	74.84	73.86	73.72	78.56	68.72	71.63
7	80.19	81.84	83.90	84.82	85.09	81.68	75.09	82.75
8	91.16	92.32	93.25	94.12	94.50	91.62	88.25	89.90

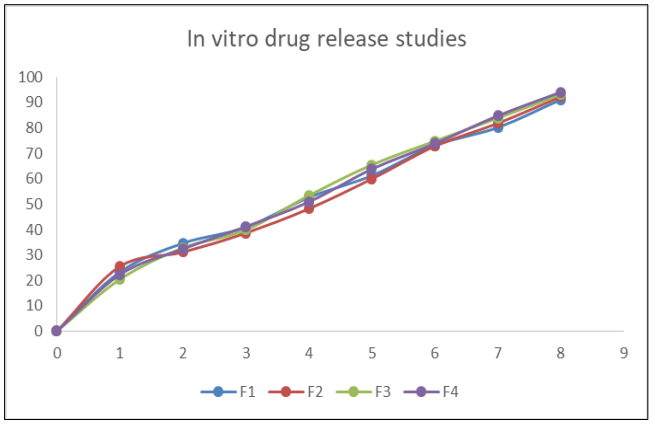

Fig 3: In vitro drug release studies (F1-F4)

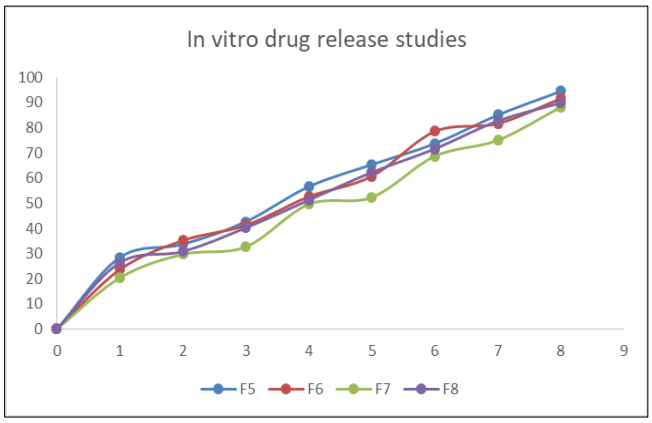

Fig 4: In vitro drug release studies (F5-F8)

Kinetic modelling of drug release

All the 8 formulation of prepared matrix tablets of Methylphenidate were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)

Zero order kinetics

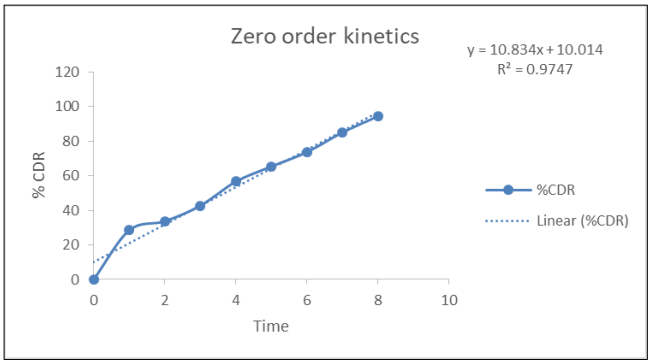

Fig 5: Zero order kinetics of Optimized formulation

First order kinetics

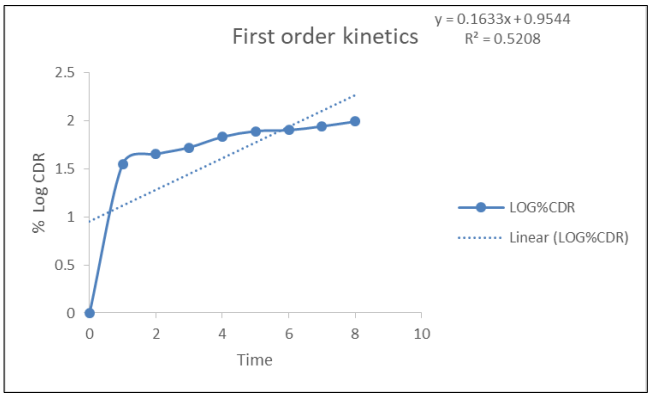

Fig 6: First order kinetics of Optimized formulation

Higuchi model

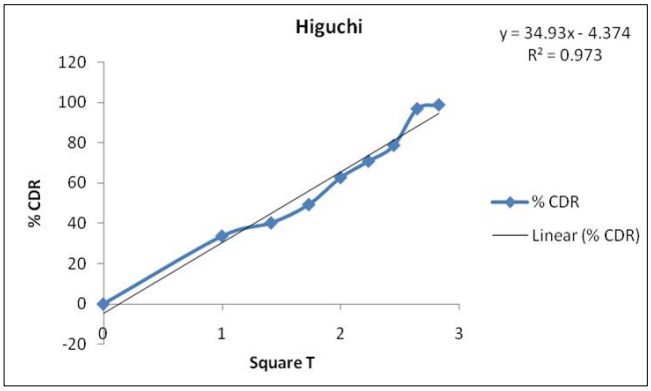

Fig 7: Higuchi model of Optimized formulation

Korsmeyer Peppas

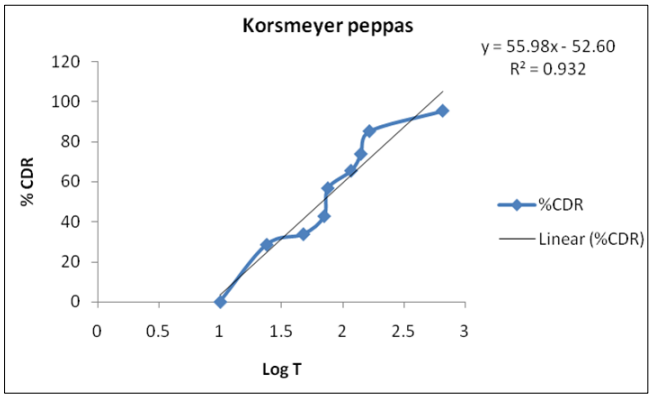

Fig 8: korsmeyer peppas of Optimized formulation

The kinetic values obtained for formulation F5 were shown. The values of in vitro release were attempted to fit into various mathematical models. Regression values are higher with Zero order release kinetics. Therefore all the Methylphenidate tablets Zero order release kinetics. Therefore all the Methylphenidate tablets follow first order release kinetics.

Table 4: Regression equations of Methylphenidate tablets F5

Film code	In vitro release in phosphate buffer P^H 7.4 Regression values			
	Zero order	First order	Higuchi Plot	Korsmeyer peppas
F_5	0.974	0.520	0.973	0.932

The table indicates that r^2 values are higher for Higuchi's model compared for all the tablets. Hence Methylphenidate release from all the tablets followed dissolution rate controlled mechanism.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-5 after 3 months. Parameters quantified at various time intervals were shown

Table 6: Results of stability studies of optimized formulation F5

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	25^0C/60%RH	94.4	93.56	92.32	91.49	Not less than
F-5	30^0C/75% RH	94.4	93.48	92.25	91.5	Not less than
F-5	40^0C/75% RH	94.4	93.12	92.36	91.42	Not less than

Conclusion

In the present work, attempts were made to formulate and evaluate controlled release Methylphenidate matrix tablets. Methylphenidate was subjected to preformulation studies, based on the results obtained Methylphenidate controlled release tablets were successfully formulated. Formulations prepared by direct compression technique using HPMC and ethylcellulose as control release polymers. Set of trials were formulated for which physical parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications Dissolution study was performed in USP type II apparatus at 100 RPM in pH 6.8 phosphate buffer upto 8 hr. From the results of the in vitro study it appears that the release of the Methylphenidate was significantly influenced by the characteristics of the polymer used.

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