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ORIGINAL ARTICLE

Formulation And Evaluation of Sustained Release Mucoadhesive Tablet of Methyldopa

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ABSTRACT
An aim of the present study was formulation and evaluation of sustained release mucoadhesive tablets of methyldopa using mucoadhesive polymers to impart mucoadhesion. Methyldopa is a drug used in hypertension and also used in heart failure. Methyldopa is also used for hypertension in pregnancy. But the drug having half-life 1-2 hours and it given with a dose 250 mg 3 to 4 times a day and that favors development of sustained release formulation. The present study is for developing sustained released mucoadhesive tablet of methyldopa using carbopol and HPMC at various concentrations as release controlling polymers. There were total 9 batches formulated by direct compression method and evaluated by parameters such as precompression studies such as bulk density, tapped density, compressibility index, hausner's ratio, and post compression studies such as hardness, thickness, Invitro drug release, swelling index etc. Among this MCH 3 batch was found to be optimized batch. This study includes that sustained release mucoadhesive tablets of methyldopa can provide a good mucoadhesion property and increase the bioavailability, improve the half life and reduce the dosing frequency of methyldopa.
Key Words: *Mucoadhesion, sustained release, methyldopa, HPMC, carbopol, evaluation, matrix tablet, In vitro drug release, U.V. spectrophotometry.*

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INTRODUCTION

Mucoadhesion describes the attractive forces between a biological material and mucous membrane [1]. Mucous membranes adhere to epithelial surfaces such as the gastrointestinal tract (GI-tract), the vagina, the lung, etc. They are generally hydrophilic as they contain many hydrogen macromolecules due to the large amount of water (approximately 95%) within its composition. However, mucin also contains glycoprotein that enable the formation of a gel-like substance [1]. Understanding the hydrophilic bonding and adhesion mechanisms of mucus to biological material is of most importance in order to produce the most efficient applications. For example, in drug delivery systems, the mucus layer must be penetrated in order to effectively transport micro or nano sized drug particles into the body [2].

Mucoadhesion involves various types of bonding mechanisms, and it is the interaction between each process that allows for the adhesive process such as wetting theory, adsorption theory, diffusion theory, electrostatic theory, and fracture theory [3]. Specific processes include mechanical interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes [4].

Methyldopa is a antihypertensive drug used in treatment of hypertension and heart failure. methyldopa belongs to a class of drugs called Alpha2 Agonists, Central-Acting. Methyldopa lower blood pressure by stimulating central inhibitory alpha-adrenergic receptors, false neurotransmission, and/or reduction of plasma renin activity. It works by relaxing the blood vessels so that blood can flow more easily through the body [5].

The short biological half-life of drug favors development of sustained release formulation. And also it given with a dose 250 mg 3 to 4 times a day, therefore it become necessary to formulate oral dosage form

to deliver methyldopa to increase the efficiency of drug and provide sustain action with reduced dosing frequency.

Mucoadhesive tablets are the oral and most convenient dosage form. The present research was aimed to formulate and evaluate oral sustained release mucoadhesive matrix tablets of methyldopa which is completely absorb by gastrointestinal tract.

MATERIAL AND METHODS

Material

Methyldopa and Carbopol971P was received as gift sample. HPMC K100M (Research lab fine chemical industries, Mumbai, India), Magnesium stearate (HILAB chemicals, Shrirampur, India), Talc (Thermosil fine chem. Khed, Pune, India), Lactose (G.S. lab, India).

Method

Sustained release mucoadhesive tablet of methyldopa was prepared by direct compression method. Sustained release layer was prepared by using HPMC K100m and Carbopol 971P at different concentrations and combination.

Methyldopa mucoadhesive tablets was prepared by direct compression method. Methyldopa, Carbopol 971P, HPMC K100M, lactose was weigh accurately and mixed and blended in mortar. Then the mixture was passed through 60 sieve, then add talc and magnesium stearate. Then the mixture was compressed in rotary tablet compression machine (make-CREATE INDUSTRIES, MODEL-LP-8GMP).

Table 1. Formulation Table For Development Of Mucoadhesive Tablets

Ingredients	MC1 (Mg)	MC2 (Mg)	MC3 (Mg)	MH1 (Mg)	MH2 (Mg)	MH3 (Mg)	MCH1 (Mg)	MCH2 (Mg)	MCH3 (Mg)
Methyldopa	250	250	250	250	250	250	250	250	250
Carbopol 971P	50	80	110	-	-	-	25	25	25
HPMC K100M	-	-	-	50	80	110	25	50	75
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Lactose	80	50	20	80	50	20	80	55	30

Preformulation study

Identification by U.V. visible spectrophotometer

50 mg of methyldopa was weighed accurately and transferred it into 50 ml volumetric flask. Dissolve it into 0.1N HCL1.2 pH and make the volume up to 50 ml with respective solvent. This was a stock solution (1000mcg/ml). Further dilutions were made by using this stock solution and scanned in the range of 200-400 nm using U.V. spectrophotometer (SHIMADZU U.V.1800) [6, 7]

Melting point

Melting point of methyldopa was determined by using melting point apparatus by capillary method [6].

Solubility

The solubility of drug was done by dissolving 10 mg of drug in 10 ml of solvent such as acetone, methanol, ethanol, isopropyl alcohol, chloroform, ether, distilled water etc [8].

Compatibility study by FT-IR

The compatibility study of methyldopa with excipients was studied by FTIR spectroscopy. The method used for study is pressed KBr pellet method and the ratio of sample is should be 1:100, where 1 is a part of drug sample and 100 is a part of KBr. The scanning range was 400-4000cm^{-1} at ambient temperature. (Perkin Elmer Spectrum-65) [6, 7].

Pre-compression study: - [6, 7]

Bulk density and tapped density

The measured quantity of drug was introduced into the measuring cylinder and initial volume was noted. Then the cylinder was allow to tap. The tapping was continue until no any change in volume was observed.

The bulk density and tapped density was determined by using formula,

Bulk density= mass/ bulk volume

Tapped density= mass/ tapped volume

Hausner's ratio

Hausner's ratio was calculated by formula, tapped density/bulk density. It is the number that is correlated to the flow ability of powder.

Carr's index [9]

Carr's index was calculated by formula:

$$Carr's index = \frac{Tapped\ density - Bulk\ density}{tapped\ density} X\ 100$$

Table 2.Relationship between carrs index and their type of flow

SR.NO.	Carr's index	Type of flow
1	5-15	Excellent
2	12-18	Good
3	18-23	Satisfactory
4	23-35	Poor
5	36-38	Very poor
6	>40	Extremely poor

Angle of repose [6, 9]

The angle of repose was determined by fixed funnel method, the funnel was fixed at certain height and allow powder to flow through it. Then measure the height and radius of cone.

Angle of repose was calculated by applying formula

Angle of repose= $\tan^{-1} h/r$

Where,

h= height of cone,

r= radius of cone.

Table 3.The relationship between angle of repose and powder flow is given as follows,

S.no.	Angle of repose	Powder flow
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Post compression evaluation [6, 10]

Weight uniformity

The weight uniformity of tablet was determined by selecting 10 tablets. Then each tablet weigh individually and compared with average weight of tablet.

Thickness

The Vernier calliper is used to measure the thickness of tablet. 5 tablets selected randomly and thickness was measured in mm.

Table 4. Limits for tablet weight variation

Average weight of tablet (mg)	Allowed % difference
130 or less	10%
From 130 to 324	7.5%
>324	5%

Hardness

Hardness is the important parameter and it indicates the ability that resistance of tablet to break under the condition of handling, storage and transportation. The hardness was measured by using Monsanto hardness tester and expressed in terms of $kg/cm^{2.}$

Friability

Friability testing is performed to determine the weight loss of tablets during friction and shock. 6 tablets are weighed and placed in a Roche friabilator. The tablets are falls from 6 inches in each turn. After 100 resolutions the tablets are weighed and compared with initial weight of tablets to determine percentage loss in tablet weight.

$$\%\ loss = \frac{Initial\ weight\ of\ tablet - final\ weight\ of\ tablet}{initial\ weight\ of\ tablet} X\ 100$$

Drug content

Ten tablets were weighed and powdered in mortar and 50 mg equivalent weight of methyldopa was weighed and transferred into a 100 ml volumetric flask. Then it was dissolved and made up the volume

with water. This was filter and suitable dilutions were made and analysed at 280 nm using U.V. Visible spectrophotometer (SHIMADZU U.V.1800)

Swelling Index

Swelling of tablet involves the absorption of a liquid resulting in an increase in volume and weight. The swelling index can be measured in terms of % weight gain by the tablet. For that one tablet from each formulation batch was weighed and placed in a petri plate containing 0.1N HCL of 1.2 pH buffer solution. After 8 hours tablet was removed from plate and remove excess buffer by using filter paper and weigh again.

Swelling index can be calculated by the formula:

$$\text{Swelling index} = \frac{\text{Final weight of tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \text{X } 100$$

Bioadhesive strength determination [11]

In vitro mucoadhesion studies were carried out using goat stomach mucosa. The apparatus used for testing bioadhesion was assembled in laboratory. The mucoadhesion strength of tablet was measured on modified physical balance using rat stomach mucosa. A double beam physical balance used for this method. The left pan was removed and to the left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass vial of 30ml capacity with uniform surface was tied. A clean glass beaker of 500ml was placed below hanging glass vial within which another glass beaker of 100 ml capacity was placed in inverted position. The solution of pH 1.2 was added until it grazed of mucosal surface. The buffer was maintained at 37°c.

The sides of balance were then balanced so that right hand side was exactly 5 g heavier than left.

***In-vitro* drug dissolution studies [6,9]**

In-vitro drug release was studied using USP type II paddle apparatus with 900 ml of 0.1N HCL of pH 1.2 at 37±0.5°c for 8 hours and 50rpm for study. Aquilot volume of 5 ml was withdrawn at specific intervals. Then the samples were replaced with fresh dissolution medium. The samples were analysed by U.V. Visible spectrophotometer at 275nm.

RESULTS AND DISCUSSION

Pre-compression studies [6, 7, 10]

The absorption maxima of methyldopa was found to be 279.76 nm in distilled water.

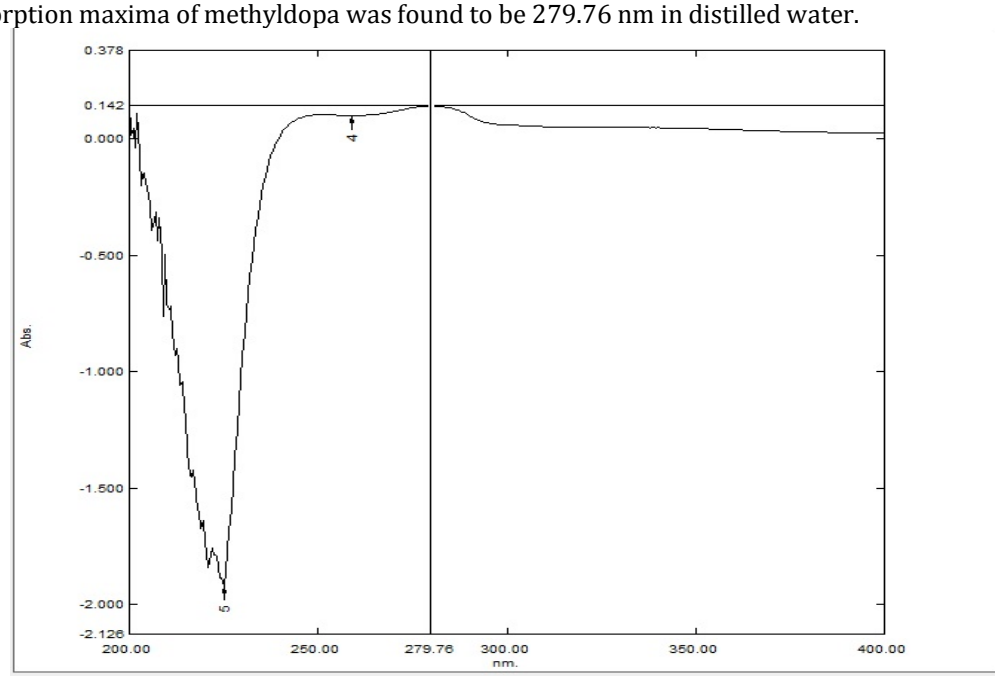


Figure 1. Absorbance Maxima Of Methyldopa

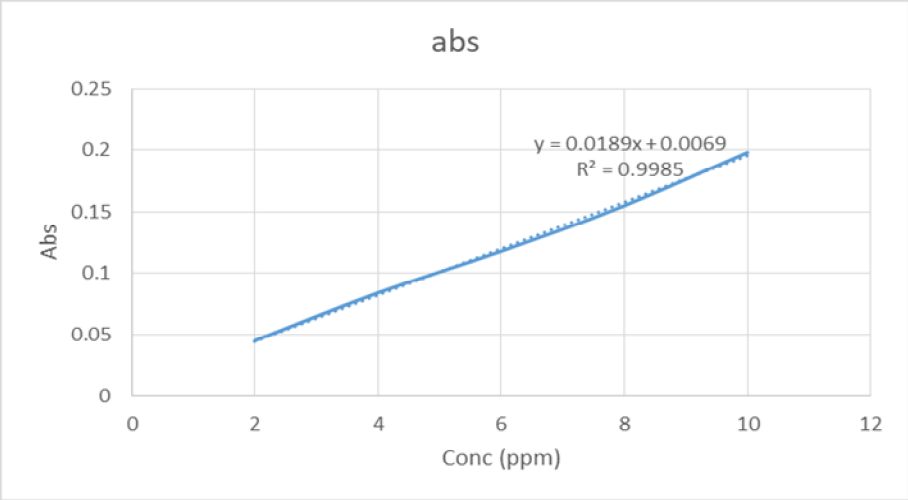
Identification by U.V. visible spectropthotometer [9]

The samples of different concentrations was analysed at 280 nm using U.V. spectrophotometer against distilled water.

Table5. Identification by U.V. visible spectrophotometer

Sr.No	CONCENTRATION	ABSORBANCE
1	2	0.045
2	4	0.084
3	6	0.118
4	8	0.155
5	10	0.198

Figure 2. Calibration curve of methyldopa



Compatibility study by FTIR [6, 7, 9]

Drug polymer interaction was studied by FTIR spectroscopy. The spectra were recorded for pure Methyldopa and with polymer mixture. The spectra were recorded for Methyldopa and physical mixture of drug with polymers using FTIR. And polymers are found compatible with the drug.

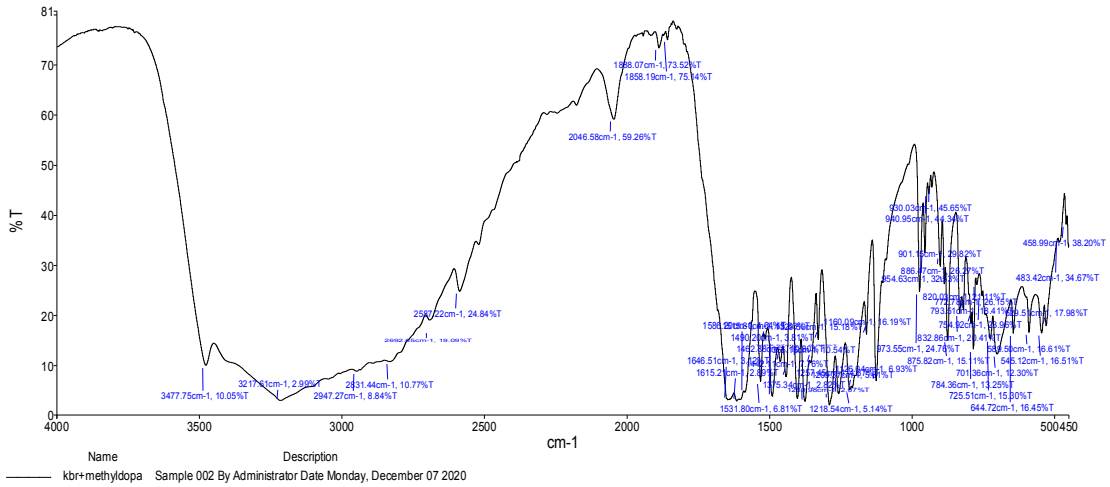


Figure 3. FTIR of Pure drug

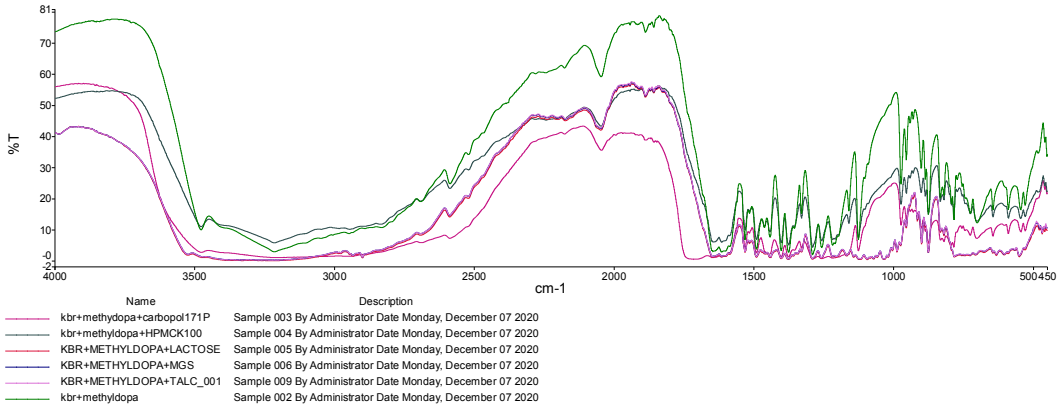


Figure 4. FTIR of Pure drug along with excipients

Table 6. Preformulation study of methyldopa

Sr.No.	Parameter	Methyldopa
1	Identification by UV vis. spectrophotometer	279.76 nm
2	Melting point	298^{o}c
3	Solubility	Soluble in water, slightly soluble in ethanol, practically insoluble in chloroform, ether and most organic solvents.
4	Compatibility study	Compatible

Pre-compression evaluation of powder blend [6, 7, 10]

Precompression parameters such as bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio of sustained release mucoadhesive powder were studied. And overall results are shown in following table.

Table 7. Precompression evaluation of powder blend

Parameter	MC1	MC2	MC3	MH1	MH2	MH3	MCH1	MCH2	MCH3
Bulk density (g/ml)	20.55	23.91	21.48	21.64	22.31	21.85	20.16	19.65	21.38
Tapped density (g/ml)	24.85	28.07	24.45	27.96	27.98	26.87	24.86	23.18	24.18
Compressibility Index (%)	17.30	14.82	12.14	22.60	20.26	18.68	18.90	15.22	11.57
Hausner's ratio	1.20	1.17	1.13	1.29	1.25	1.22	1.23	1.17	1.13
Angle of repose	19.4^{o}	20.6^{o}	21.8^{o}	23.1^{o}	25.4^{o}	27.2^{o}	21.18^{o}	22.49^{o}	23.12^{o}

Post compression evaluation of sustained release mucoadhesive tablet [6, 9, 10]

Prepared tablets was evaluated for weight variation, dissolution test, hardness, thickness, friability, drug content etc . And overall results are shown in following table.

Table 8. Post compression evaluation of sustained release mucoadhesive tablet

Parameter	MC1	MC2	MC3	MH1	MH2	MH3	MCH1	MCH2	MCH3
Uniformity weight (mg)	400.4	398.1	401	401.3	398.6	399	401.2	400.3	399.8
Thickness (mm)	3.8	3.4	3.6	3.5	3.8	3.7	3.8	3.6	3.5
Hardness (kg/cm^2)	6.3	6.8	7.3	5.2	5.6	6.1	6.2	6.4	6.6
Friability (%)	0.60	0.48	0.42	0.89	0.76	0.62	0.47	0.54	0.61
Drug content	98.79	99.58	98.86	99.42	99.89	98.99	98.53	99.18	99.91
% Drug release	77.32	73.42	70.64	99.16	96.84	94.18	92.56	90.46	88.11

Bioadhesion strength [11]

The in vitro bioadhesion study was performed using modified balance and the force required to detach the tablet from mucous membrane was noted. The bioadhesion characteristics was affected by the concentration of bioadhesive polymer used.

Table 9. Bioadhesion strength

Parameter	MC1	MC2	MC3	MH1	MH2	MH3	MCH1	MCH2	MCH3
Bioadhesion strength (gm)	31.6	32.7	33.5	19.9	21.4	23.2	25.4	27.6	30.8

Swelling study [6, 9, 10]

Polymers with higher concentration had lower swelling and this is due to polymers concentration restricts the movement of polymers. Formulation containing guar gum shows more swelling.

Table 10. Swelling study of prepared mucoadhesive tablets of methyldopa

Formulation code	Time (hours) 1	2	3	4	5	6	7	8
MC1	19.37	22.45	25.30	28.49	31.76	34.53	37.18	40.65
MC2	21.84	24.76	28.1	31.67	35.43	38.86	42.2	45.62
MC3	24.18	27.74	31.14	34.59	37.9	41.43	44.87	48.25
MH1	22.28	25.54	28.12	31.86	34.64	38.10	42.26	45.31
MH2	25.99	28.39	32.46	35.97	38.47	42.53	47.14	51.32
MH3	27.29	30	33.21	36.18	39.43	43.78	48.86	52.67
MCH1	21.18	24	26.76	30.88	34.59	37.58	40.17	42.86
MCH2	23.36	26.67	30.37	35.12	38	41.62	43.21	45.78
MCH3	24.40	30.18	34.59	37.98	41.31	43.14	45.89	48.64

Table 11. Post compression evaluation of mucoadhesive sustained release tablet of MCH3 optimized batch

Sr.No	Parameter	MCH3
1	Uniformity weight (mg)	399.8
2	Thickness (mm)	3.5
3	Hardness (kg/cm^2)	6.6
4	Friability (%)	0.61
5	Drug content	99.91
6	Drug release	88.1
7	Swellin Index	48.64
8	Bioadhesion strength	30.8

***In-vitro* drug dissolution studies [6, 9]**

In-vitro drug release was studied using USP type II paddle apparatus with 900 ml of 0.1N HCL of pH 1.2 at 37±0.5^{o}c for 8 hours and 50rpm for study. Aquilot volume of 5 ml was withdrawn at specific intervals. Then the samples were replaced with fresh dissolution medium. The samples were analysed by U.V. Visible spectrophotometer at 280 nm. From the in vitro dissolution data it was found that the release of methyldopa from the prepared formulations was analyzed by plotting cumulative percentage drug release vs time as shown in figure. From all formulations, over 20% of the methyldopa was release within the first hour of dissolution study. In the present study the formulation MCH3 (HPMC K100M +CARBOPOL 971P) has shown cumulative percent drug release of about 88.1% in 08 h as shown in figure.

Figure 5. % drug release of sustained release tablets

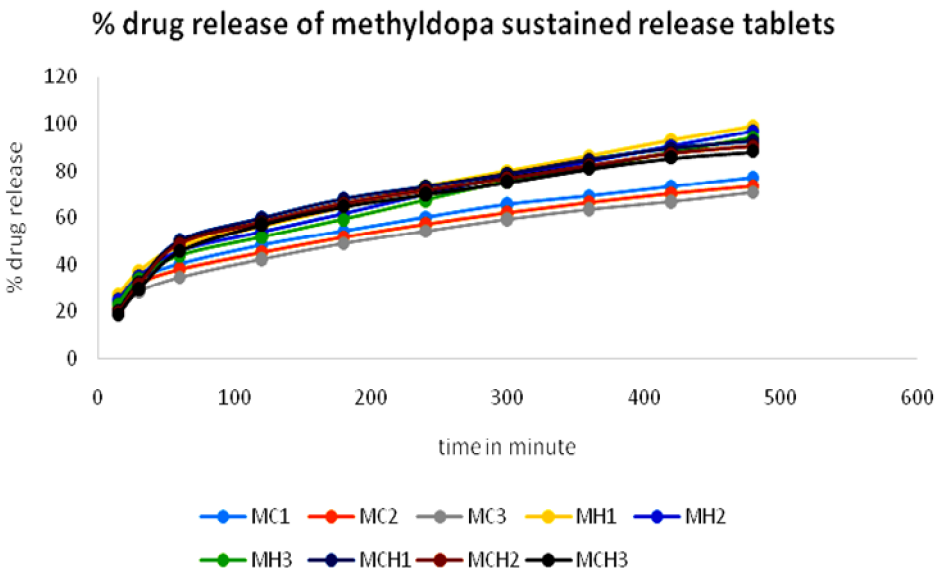


Figure 6. % drug release of optimised formulation MCH3

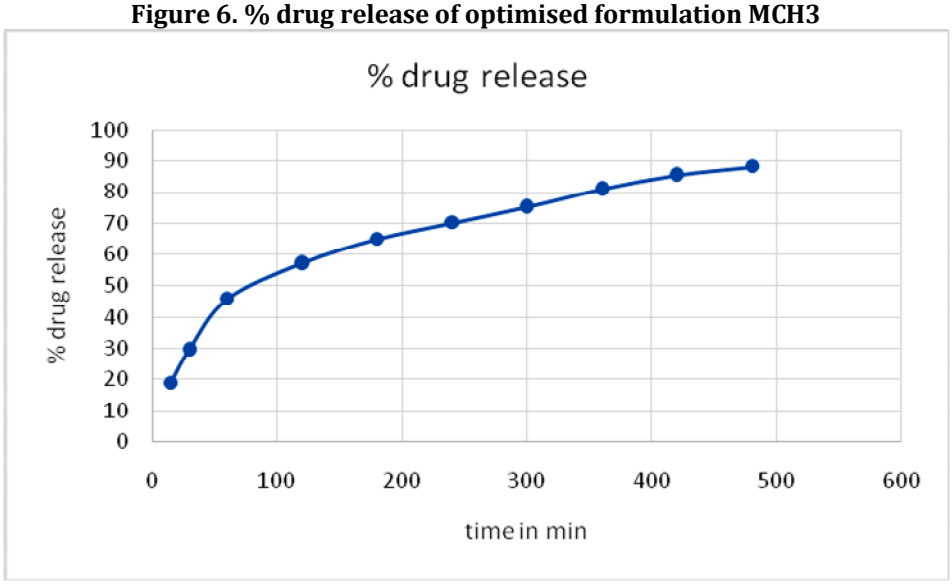


Table 12. Drug release kinetics of sustained release mucoadhesive tablet of methyldopa

Time (Min)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt.)	Wo-Wt.
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
15	18.76	81.24	3.873	1.910	1.176	1.273	18.76	4.331	0.311
30	29.64	70.36	5.477	1.847	1.477	1.472	10.88	4.128	0.514
60	45.73	54.27	7.746	1.735	1.778	1.660	16.09	3.786	0.856
120	57.13	42.87	10.954	1.632	2.079	1.757	11.4	3.500	1.142
180	64.79	35.21	13.416	1.547	2.255	1.812	7.66	3.278	1.364
240	69.99	30.01	15.492	1.477	2.380	1.845	5.2	3.108	1.534
300	75.16	24.84	17.321	1.395	2.477	1.876	5.17	2.918	1.724
360	80.94	19.06	18.974	1.280	2.556	1.908	5.78	2.671	1.971
420	85.46	14.54	20.494	1.163	2.623	1.932	4.52	2.441	2.201
480	88.11	11.89	21.909	1.075	1.000	1.945	2.65	2.282	2.360

Kinetic Models

Dissolution data of above sustained release mucoadhesive tablet was fitted in First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

CONCLUSION

It is proved from this study that mucoadhesive tablet of antihypertensive drug methyldopacan be formulated to increase the gastric residence time and thereby improve its bioavailability. Formulation MCH3 containing carbapol 971P and HPMC K100M at 1:3 ratio which prolonged the release (88.11 % up to 8 hours) of the drug as compared to other prepared formulations. Thus the objective of formulating a sustained release mucoadhesive dosage form of methyldopa has been achieved. And it is proved that carbapol 971P and HPMC K100M at 1:3 ratio acts as good mucoadhesive polymers in matrix tablet.

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