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Research Article

NOVEL INTERVENTION TO IMPROVE ADHERENCE TO MEDICATION IN DIABETIC PATIENTS: FORMULATION AND EVALUATION OF METFORMIN HCL NOVEL DOSAGE FORM

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ABSTRACT

Objective: The aim of the present study was to prepare the chewable Metformin HCl formulation to overcome patient's non-adherence to prescription pattern in diabetes. Chewable tablets provide hassle free approach to diabetic patients to take medication during social gatherings or travelling because of discomfort in carrying or administration.

Method: Chewable Metformin HCl sustained release tablets were prepared using ethyl cellulose and stearic acid/ glycerol monostearate as release retarding agents.Stevia is selected as sweetening agent as its extracts are not absorbed by the digestive tract, so they do not add calories or affect blood glucose levels.

Results: Various evaluation parameters like thickness, hardness, friability weight variation and drug content of the formulations were found to be satisfactory. Among all formulations prepared andevaluated MS-05 appeared to have desired release pattern than others.DSC (Differential Scanning Calorimetry) and IR (Infra-red) studies showed no interaction between drug and excipients in optimized formulation. Formulation MS-05 matches with the innovator product with the similarity factor value 58.65. Release kinetics of optimized formulation follows first order, Higuchi and Kosmeyear- peppas non-fickian diffusion. The optimized tablets found to be stable under accelerated conditions for a period of one month.

Conclusion: The release study of both crushed and intact MS-05 tablet showed similar release rate which supports that even if patient swallows the formulation during chewing, the drug release pattern and thereby the drug absorption may not be affected.

Keywords: Patients non adherence, Chewable tablets, Stevia.

INTRODUCTION

Non-adherence to medication is potentially one of the most serious problems facing diabetes care delivery, particularly in type 2 diabetes. Intervention studies to improve adherence can be developed which include improved patient-centred education, health professional education. Simplest and single most important action that healthcare providers can take to improve adherence is to select medications that permit the lowest daily dose frequency possible [1].

Chewable tablets are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. The advantages of chewable tablets include palatability, stability, precise dosing, portability and ease of delivery. The available literature suggests that chewable tablets provides a safe, well-tolerated alternative to traditional pediatric drug formulations and offer significant advantages in children with two years of age and above [2].

Chewable tablets are sweet in taste, patient may like the dosage form and chances of compliance are more than other dosage forms; this dosage form can be taken without water makes it easier during journey period or in any other situations where availability of water is difficult.

Diabetic patientsmay have reservation in exposing themselves to the society as diabetic patient and may feel more conscious to take medication during social gathering. As chewable formulation is quite handy to carry and easy to take patients need not reveal it to others. Diabetics have to control their intake of sugar/sweets and psychologically they have moretendencytowards sweets and thereby the chewable tablet may be more acceptable by the patients. Metformin chewable tablets formulation may provide more palatable and acceptable dosage form for diabetic patients and improve medication adherence.

Metformin is a popular oral drug for treating Type II diabetes. It is a member of class of drugs called biguanides. Metformin HCl enhances insulin sensitivity of both hepatic and peripheral (muscle) tissues. This allows for increased uptake of glucose into these insulin-sensitive tissues [3].

This work is focussed on chewablesustained release Metformin HCl tablets using stevia a natural sweetening agent. Commonly used sweetening agents in chewable tablet are carbohydrates and are not appropriate for diabetic people. So in the present work stevia is selected as sweetening agent as stevia extracts are not absorbed by the digestive tract, so they do not add calories or affect blood glucose levels, making them a good addition to blood glucose levels[4]. Stevia also has mild anti-hyperglycaemic, antihypertensive activity [4] and its presence in the formulation may help in delaying the onset of hypertension which is common with type 2 diabetes.Formulation consists of (i) an active ingredient, (ii) a primary sustained release agent, (iii) a wax-like agent, and (iv) bulking or spheronizing agent; here ethyl cellulose [5] is primary sustained release agent, stearic acid and glycerylmonostearate as wax like agents, HPMC, avicel 101 and mannitol as bulking agents.

MATERIALS AND METHODS

Metformin HCl is was obtained fromAurobindopharma Ltd, mannitol, lactose anhydrous were procured from merckSpecialities Pvt. Ltd, ethyl cellulose was obtained from Sigma-Aldrich, stearic acid and vanilla flavour was obtained from S d fine Chem Ltd, glycerylmonosterarate procured from National chemicals, stevia was obtained from Procarvit food products Pvt. Ltd.

Method

In the preparation of chewable metformin HCl sustained release tablet, initial granules were prepared by conventional wet granulation method. Granulation was done manually with a solution of calculated quantity of ethyl cellulose in sufficient solvent blend containing isopropyl alcohol and methylene chloride in 1:1 ratio. The wet masses were passed through a 12 mesh sieve and the wet granules produced were first air dried for 10 min and finally at 45-50 ºC in hot air oven for 1 hour. The dried granules were sized by a 22 mesh sieve and mixed with 15% of fines (granules passed

through a 20 mesh sieve). Molten wax was prepared by heating at constant temperature of 75°C and above granules was gradually added to the molten mass with continuous stirring.The molten mixture was then allowed to cool and solidify at room temperature. And these granules were passed through mess 12 and then magnesium stearate and flavour were added and mixed uniformly. The obtained granules were evaluated for flow property and then the granules were compressed using a single punch tableting machine (Cadmach machinery Co. Pvt. Ltd) equipped with 15mm round flat and plain punch and compressed to obtain required hardness. The composition of chewable sustained release metformin tablets are given in table 1.

Table 1: Composition of Metformin HCl Sustained release chewable tablets

Ingredients (mg/kg)	MS-01	MS-02	MS-03	MS-04	MS-05
Metformin HCl	500.0	500.0	500.0	500.0	500.0
Ethyl cellulose (10cps)	60.0	60.0	60.0	60.0	60.0
Avicel-101	145.0	145.0	145.0	---	---
Mannitol	150.0	150.0	150.0	150.0	100.0
Stearic acid	100.0	---	50.0	100.0	100.0
Glyceryl Monostearte	---	100.0	50.0	---	---
Starch	20.0	20.0	20.0	20.0	20.0
Stevia	20.0	20.0	20.0	20.0	40.0
Vanillin	5.0	5.0	5.0	5.0	5.0
HPMC	---	---	---	145.0	175.0
Magnesium Stearate	0.5%	0.5%	0.5%	0.5%	0.5%
Tatal Weight(mg)	1000	1000	1000	1000	1000

Drug excipients compatibility studies

Literature survey [6] shows there as such no interaction between metformin and excipients selected for our formulation and in addition the physical mixture may not show any incompatibility under normal storage conditions. So preformulation screening of drug-excipient interaction was not carried out in our research work. But the final optimized formulations were screened for drug-excipient interaction. (DSC and IR)

Characterization of granules

Prior to compression, blends of were evaluated for their characteristic parameters, such as angle of repose, bulk density, tapped density, compressibility index and Hausner Ratio. Carr's index was calculated from the bulk and tapped densities using a digital tap density apparatus (Electrolab Ltd, india).

Tablet Characterization

The tablets were characterized immediately after preparation.The weight variation of the tablets was evaluated on 20 tabletsusing an electronic balance (Essae-Teraoka Ltd. Bangalore). Friability wasdetermined using 10 tablets in a Roche friabilator for 4 minutesat a speed of 25 rpm (rotations per minute). The hardness of10 tablets for each formulation batch was evaluated using a Monsanto hardness tester (Secor India PVT ltd). The thickness of the tablets wasmeasured on 10 tablets with VernierCalipers (Mitutoyo,Japan).

Drug content: For determination of drug content, three tablets were crushed and powder was dissolved in 50ml of 0.1Nbuffer. The solution was then filtered through whatmann (No.1) filter and analysed spectrophotometrically at 233 nm after sufficient dilution with buffer. Drug content was calculated from calibration curve of metformin in the same buffer.

Disintegration [7, 8]

This test initially may not appear appropriate for chewable tablets as these tablets are to be chewed before being swallowed. However, patients, especially pediatric and geriatric, have been known to swallow these chewable dosage forms. This test would thus indicate the ability of the tablet to disintegrate and still provide the benefit of the drug if it is accidentally swallowed. Tablets should preferably pass the USP disintegration test for uncoated tablets.

Dissolution studies [7]

Chewable tablets should preferably be tested in two forms: intact (in case the dosage form is accidentally swallowed) and partially crushed (to simulate chewing). The study was carried in 900ml of 0.1N HCl for a duration of 2 hours (rpm is set to 100) and followed by pH 6.8 buffer for next 10 hours (rpm was set to 75); the temperature was maintained at 37±0.5˚C. Aliquots of 5.0 ml were withdrawn at specific time intervals. At each time of withdrawal, 5ml of fresh corresponding medium pre-warmed to 37 ± 0.5°C was replaced into the dissolution flask.

Dissolution study was also conducted for innovator product and compared with the release profile of prepared formulations.

Characterization of the Release Profile [9]

In order to describe the kinetics drug dissolution process, various equations were used as shown below:

Zero order Release Equation which describes where the drug release rate is independent of concentration of dissolved substance.

First Order Release Equation which describes the drug release rate depends on the concentration.

Higuchi's Square Root of Time Equation which describes the drug release as a diffusion process based on the Fick's law.

Korse-Meyer Peppas Equation which describes the drug release is Fickian diffusion or Non- Fickian transport (it is a combination of both diffusion and erosion controlled rate release) or Case II transport or Super case II transport (erosion of polymeric chain).

Similarity factor calculation(f_2)

To evaluate and compare dissolution data, the similarity factor f2 [8] was calculated using the formula

$$f_2 = 50log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where,

n is number of observations

R_t is percentage drug dissolved from reference formulation (Obimet SR)

T_t is percentage drug dissolved from test formulation

The ƒ2 value between 50 and 100 suggest that the dissolution is similar. The ƒ2 values of 100 suggest that the test and reference profile are identical and as the value becomes smaller, the dissimilarity between releaseprofile increases.

Stability studies [10]

The optimized tablet formulation were packed in the aluminium foil and kept in stability chamber at 40˚C and 75% RH (relative humidity) for a period of one month and evaluated for physical appearance and drug content.

RESULTS AND DISCUSSION

Characterization of powder flow properties: The granule flow properties were analysed and the results of the above parameters are given in table 2. It was observed that all formulations showed good flow properties with Carr's index ranging from 14 to 17. Hausner's ratio below 1.25 indicates good compressibility and flowability of all granules. The granules were further analysed for angle of repose which was below 30˚ which also supports its good flow property.

Table 2: Characterisation of flow property of Metformin HCl sustained release granule blends

Batch no.	Bulk density (g/cc)	Tapped density (g/cc)	Carr's compressibility index (%)	Angle of repose	Hausner's ratio
MS-01	0.445	0.529	15.8	28.1	1.18
MS-02	0.457	0.533	14.2	27.9	1.16
MS-03	0.462	0.555	16.7	29.1	1.20
MS-04	0.469	0.548	14.4	28.7	1.16
MS-05	0.455	0.549	17.1	28.2	1.20

Characterization of tablet properties of optimized batches

All the parameters were evaluated in triplicates and the results of the above parameters are given in table 3. A total of five optimized formulations were prepared using different levels of concentration of Avicel pH101, stearic acid, glycerol monosterarate and HPMC described above in table no.1. All the formulations passed weight variation and content uniformity test. The hardness of all the tablets was found in the range of 5-5.5 kg/cm^2. Friability was found to be below 1% which was an indication of good resistance of tablets. Disintegration time of intact tablets was found to be in range of 27.43 to 28.76 minutes. As these formulations are chewable sustained release tablets with waxy excipients, the disintegration time might have been increased little higher than conventional tablets. This slight higher disintegration value may support sustained release of the metformin from the formulation without causing discomfort during chewing.

Release profile

In order to simulate the environmental conditions in the human gastrointestinal tract, *in vitro* drug release tests of the optimal formulations were conducted in 0.1 N HCl (pH 1.2) for the first 2 hours followed by pH 6.8 phosphate buffer for10 hours. Figure 3 and 4 shows the release profiles of crushed and intact chewable metformin sustained release tablets respectively with release data of innovator formulation. The crushed formulations of MS-01, 02, 03 showed 100% release at the end of 6 hours. Though MS-01, 02, 03 formulations consists of ethyl cellulose as primary sustained release and stearic acid and /or glycerol monostearate as secondary sustained release agent, it could not achieve required release rate. So to retard the drug release further, HPMC was included in the further formulation MS-04. MS-04 formulation showed slight improvement in release pattern but the formulation failed to sustain the release as that of innovator product. The HPMC (Hydroxy Propyl methyl Cellulose) 50cps concentration was further increased and mannitol concentration was decreased in the next formulation MS-05 to achieve the *in vitro* drug release as that of innovator formulation.MS-05 formulation showed 93.23% and 92.74% drug release by 12hrs from crushed and intact tablet respectively which is better than release profile of innovator product. The release study of both crushed and intact MS-05 tablet showed similar release rate which supports that even if patient swallows the formulation during chewing, the drug release pattern and thereby the drug absorption may not be affected. Comparative dissolution profile of MS-01 to MS-05 crushed and intact tablets with innovator release profile are given in figure 1 and 2 respectively.

Table 3: Post compression parameters of Metformin HCl sustained release tablets

Batch no	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Drug content (%)	Disintegration time(min)
MS-01	5.59±0.005	4.6±0.17	0.45±0.085	99.55±0.11	98.66±1.55	28.33±0.57
MS-02	5.61±0.01	4.73±0.11	0.51±0.081	99.62±0.06	97.29±0.84	27.43±0.51
MS-03	5.6±0.015	4.76±0.05	0.48±0.046	99.52±0.09	97.23±0.94	28.76±1.07
MS-04	5.61±0.011	5.26±0.11	0.61±0.06	99.52±0.12	97.96±1.4	28.33±0.57
MS-05	5.6±0.03	5.13±0.15	0.45±0.083	99.51±0.14	98.04±0.84	28.66±1.15

*all values are expressed as mean ± SD (n=3)

Drug-Excipient compatibility studies

a) The DSC thermograms of pure Metformin and optimised formulation of sustained release formulations MS-05 is given in figure no. 3. Pure Metformin HCl shows sharp endotherm at 238.4˚C corresponding to its melting point/transition temperature. Lowering of melting point of MS-05 was observed in the formulation.

As the optimized formulation consists of mannitol, avicel, ethyl cellulose, HPMC which have multifunctional hydroxyl groups, forms weak physical interactions like vanderwall forces and H-bonding with Metformin and causes lowering of melting point as shown in DSC thermogram. This weak interaction between excipients and drug may not affect drug release from the formulation. Stearic acid does not interact with drug as such, but may possess physical barrier in drug release.

b) Major peaks for pure drug were 3370.72, 1628.94, 1061.85 cm^{-1} and which are well in the support to theoretical prediction. The optimized formulation did not produce major shift in peaks, indicating no interaction as shown in figure no.4.

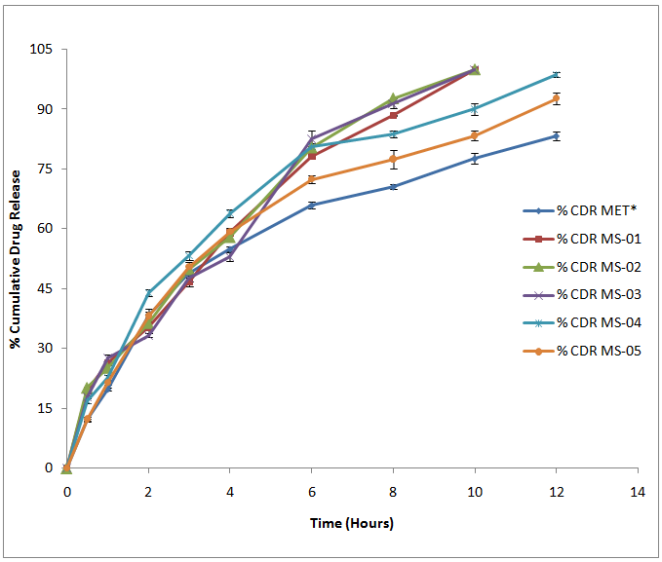

Fig. 1: Comparative dissolution profile of MS-01 to MS-05 (crushed tablets) batches with innovator product

% CDR MET*- Percentage Cumulative Drug Release of metformin innovator product

% CDR MS-01- Percentage Cumulative Drug Release of formulation MS-01

% CDR MS-02- Percentage Cumulative Drug Release of formulation MS-02

% CDR MS-03- Percentage Cumulative Drug Release of formulation MS-03

% CDR MS-04- Percentage Cumulative Drug Release of formulation MS-04

% CDR MS-05- Percentage Cumulative Drug Release of formulation MS-05

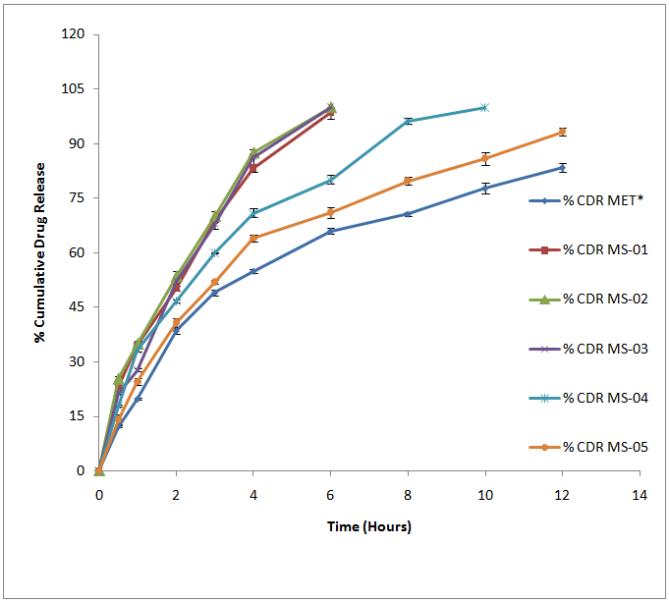

Fig. 2: Comparative dissolution profile of MS-01 to MS-05 (intact tablets) batches with innovator product

% CDR MET*- Percentage Cumulative Drug Release of metformin innovator product

% CDR MS-01- Percentage Cumulative Drug Release of formulation MS-01

% CDR MS-02- Percentage Cumulative Drug Release of formulation MS-02

% CDR MS-03- Percentage Cumulative Drug Release of formulation MS-03

% CDR MS-04- Percentage Cumulative Drug Release of formulation MS-04

% CDR MS-05- Percentage Cumulative Drug Release of formulation MS-05

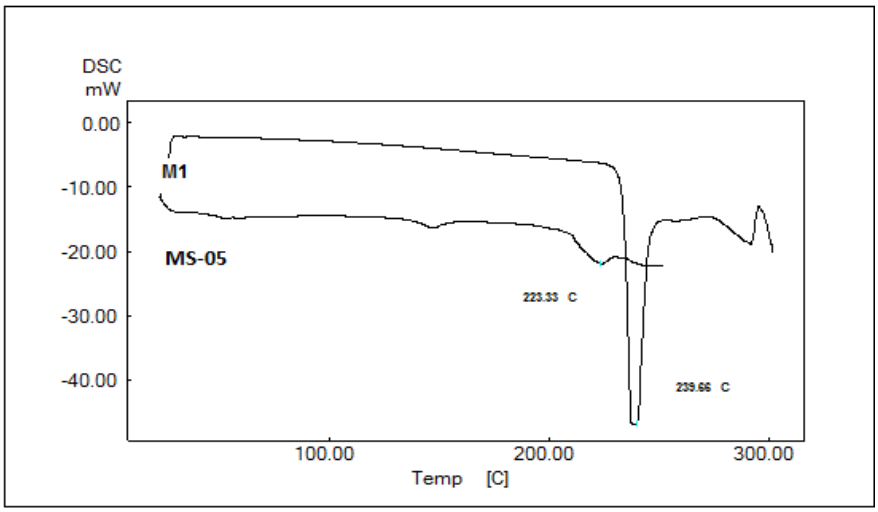

Fig. 3: DSC thermograms of pure Metformin (M1) and optimized formulation MS-05.

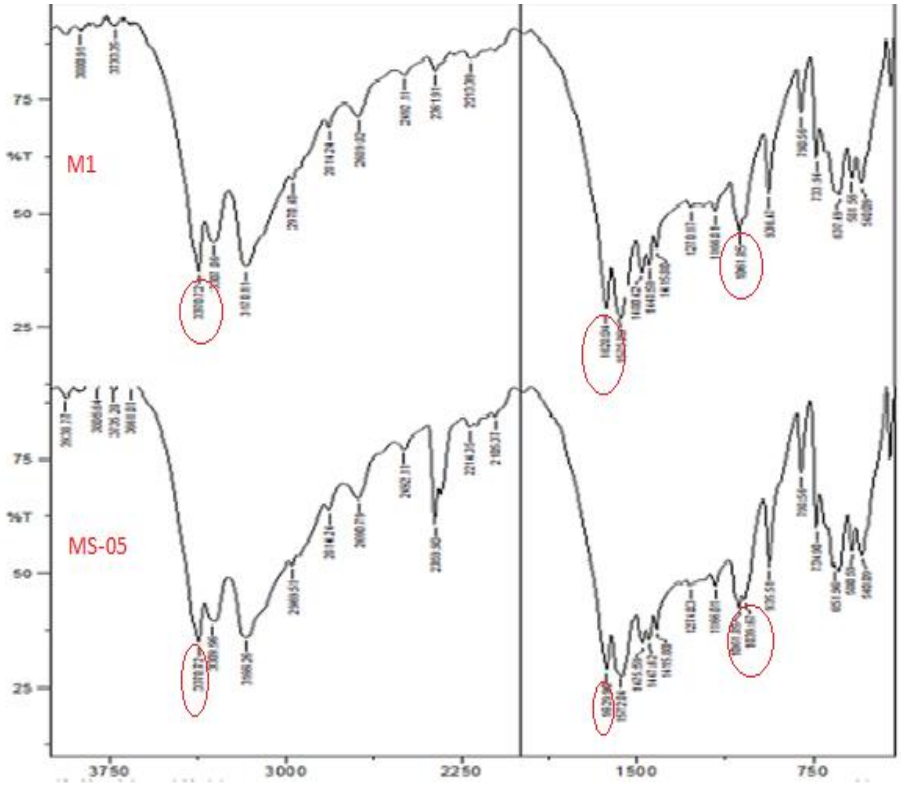

Fig. 4: IR peaks of pure metformin HCl (M 1) and optimized formulation MS-05

Calculation of similarity factor (f_2) of optimized formulation MS-05

MS-05 matches with release rate of innovator product as similarity factor was found to be 58.65 which is above 50.As the release rate of optimized formulation was higher and better than innovator; the similarity factor could not be on higher side but is within the limit.

Release kinetics of optimized formulation and Innovator product (Table no. 4)

Both optimized formulation MS-05 and innovator product release data fits better with first order model and Higuchi release kinetics indicating the drug release process is directly proportional to the drug concentration and by diffusion mechanism.

The release kinetic data of optimized formulation indicates the drug release from the melt granulation by a diffusion mechanism initially from the primary sustained release layer (ethyl cellulose) followed by secondary sustained release layer (steric acid) which forms non-porous a partition. The drug particles might partition into the lipid phase followed by diffusion through it.

In Kosmeyer and Peppas model if n=0.45 it indicates fickian diffusion, if it is 0.45<n<0.89 it indicates non fickian or anomalous diffusion. Drug which is embedded with in polymer coating followed by wax coating under goes erosion followed by diffusion.

When we compare the release kinetics of innovator product (Matrix formulation) and optimized formulation (chewable formulation) both followed similar release kinetics.

Table 4: Release kinetic data of optimized formulation and innovator product

Formulation	First order	Zero order	Higuchi model	Kosmeyer and Peppas	
	R^2	R^2	R^2	R^2	N
MS-05(crushed)	0.9856	0.8752	0.9839	0.7316	0.5235
Innovator	0.9793	0.8675	0.9793	0.7414	0.5473

Stability studies

On storage under accelerated conditions the tablets did not show any physical changes. The percentage drug content of optimized formulation is given in the table 5 which is within the limit.

Table 5: Stability study data

Days	% Drug remained at different time interval for MS-05
0	98.04±0.84
15	98±0.76
30	98±0.53

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CONCLUSION

Chewable Metformin HCl sustained release tablets were prepared using ethyl cellulose as primary release retarding agent and stearic acid/ glycerol monostearate as secondary release retarding agent. In conclusion, the present study demonstrated the successful formulation and evaluation of chewable Metformin HCl sustained release tablets.

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