Indo Global Journal of Pharmaceutical Sciences, 2022; 12: 128-133

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Design and Characterization of Sustained Release Tablet Formulation Containing Metformin Hydrochloride and Simvastatin

Shankar Dhobale*, Sayali Nilakh, Suresh Jadhav

VJSM's Vishal Institute of Pharmaceutical Education and Research Ale, Tal – Junnar Dist-Pune (412411), India

Address for Correspondence: Shankar Dhobale, Shankar_dhobale@rediffmail.com

Received: 28.12.2019
Accepted: 18.05.2020
Published: 04.02.2022
Keywords
Sustained release tablet, Simvastatin, Metformin Hydrochloride

ABSTRACT: The aim of the present work was to develop pharmaceutical combinational dosage form for simultaneous treatment of patients with type 2 diabetes with at high-risk of coronary disease associated co-morbidities. Metformin, an antidiabetic drug is used to treat the diabetic patient and combined with Simvastatin which is HMG-CoA reductase inihibitor drug to treat the high-risk coronary disease simultaneously. In this formulation, three batches were prepared by the direct compression method. Preformulation parameters such as identification, solubility, melting point, compatibility studies, Pre-compression parameters such as bulk density, tapped density, angle of repose, Hausner ratio, compressibility index, and Post-compression parameters like weight uniformity, hardness, drug content, thickness, *in-vitro* drug release. *In-vitro* drug release of all formulations, B1, B2, and B3 was carried out in 0.1N HCl for 2hrs and 10 hrs in phosphate buffer (pH 6.8) dissolution media. Among all the formulations, B3 was an optimized batch. B3 formulations showed drug release of 85% for Metformin Hydrochloride and 93% for Simvastatin over a period of 12hrs.

Cite this article as: Dhobale, S.; Nilakh, S.; Jadhav, S. Design and Characterization of Sustained Release Tablet Formulation Containing Metformin Hydrochloride and Simvastatin. Indo Global J. Pharm. Sci., 2022; 12: 128-133. **DOI**: http://doi.org/10.35652/IGJPS.2022.12013 .

INTRODUCTION

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time. Possible therapeutic benefits of properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range profiles attainable, increased convenience and patient compliance [1].

Currently Metformin Hydrochloride available as separate tablet for the treatment of type 2 diabetes. Simvastatin is also currently available as separate tablet for the treatment of hypercholesterolemia. The formulations were prepared by direct compression method. Single tablet containing two drugs such as Simvastatin, Metformin release the compassion typically done by using HPMCK100 and microcrystalline cellulose. The compatibility parameter preformulation study compression parameter and *In vitro* parameters were performed with pharmaceutical expectable [2].

MATERIAL AND METHODS

A. Materials

Simvastatin and Metformin HCl gifted sample (flamingo pharmaceutical) HPMCK4, (Thermmosil fine chem), microcrystalline cellulose (research lab), magnesium stearate (Hilab chemicals) were sample is analytical grade [3, 4].

B. Preparation of Tablet

Combination of Simvastatin and Metformin Hydrochloride were prepared by direct compression method using varying proportion of polymers either alone or combination (**Table 1**). The ingredients were passed through 60 mesh sieve calculated amount of drug polymer (HPMC, and filler microcrystalline) was mixed thoroughly; magnesium stearate was added as lubricant. The appropriate amount of the mixture was weighed and the compression machine (MAKE CREATE INDUSTRIES, MODEL-LP-8GMP).

Table 1: Formulation of Metformin and Simvastatin Combination Tablet:

Sr. No	Ingredients	B1 (mg)	B2 (mg)	B3 (mg)
1	Simvastatin	40	40	40
2	Metformin	500	500	500
3	HPMCK100	100	150	200
4	Microcrystalline cellulose	350	300	250
5	Magnesium stearate	10	10	10
	Total weight	1000	1000	1000

C. Preformulation Study

1. Identification test by UV- Spectrophotometer

a) Metformin

Determination of λ max of Metformin in pH 6.8 phosphate buffers from the stock 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer. Spectrum of this solution was seen from 200-400 nm range on UV-Visible spectrophotometer for determination of λmax. And the λmax was found to be 233.2nm (**Table 2**). From the above-mentioned stock solution subsequent dilutions were made with pH 6.8 phosphate buffers to obtain the series of dilutions containing 2, 4, 6, 8, 10, 12, 14µg/ml of solution. The absorbance of the above dilutions was measured at 233.2nm by using the UV-Spectrophotometer using pH 6.8 phosphate buffers as the blank. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line.

Table 2: Preformulation studies of Metformin

Sr No	Parameter	Observation
1	Identification by UV spectrophotometer	247.6
2	Melting point	223°C
3	Solubility	Freely soluble in ether, Slightly soluble in ethanol, in methanol.
4	Compatibility study(FTIR)	Compatible

Table 3: Preformulation Studies of Simvastatin

Sr. No	Parameter	Observation
1	Identification by UV spectrophotometer	233.20
2	Melting point	139˚C
3	Solubility	Very soluble in dichloromethane, freely soluble in ethanol, soluble in phosphate buffer.
4	Compatibility study(FTIR)	Compatible

b) Simvastatin

Calibration curve of Simvastatin in pH 6.8 phosphate buffer a spectrophotometric method based on the measurement of absorbance at 247.6nm in PH 6.8 phosphate buffer was used in the present study for the estimation of Simvastatin. Preparation of stock solution of Simvastatin weighed accurately 10 mg of Simvastatin and added into a 10ml volumetric flask and dissolved in 10 mL of methanol to get 1000µg/ml. Determination of λ max of in Simvastatin pH 6.8 phosphate buffer from the stock 1 mL was taken and diluted to 100 mL with pH 6.8 phosphate buffer. Spectrum of this solution was seen from 200-400 nm range on UV-Visible spectrophotometer for determination of λ max. And the λ max was found to be 247.6 nm [2].

2. Melting Point Determination [5]

The melting points of Simvastatin and Metformin were determined by melting point apparatus. The melting point was determined by introducing small amount of substance in the capillary attached to graduated thermometer.

3. Determination of Solubility

Qualitative solubility

Qualitative solubility analysis of drugs were done by dissolving 5mg of drug in 5ml solvent such as distilled water, methanol, ethanol, chloroform.

4. Compatibility Study

Fourier Transformation Infra-red (Fourier Transform Infra Red Spectrophometer)

The powdered substance of the tablet were mix, dried potassium bromide ratio of sample is should be 1:100mg, are compressed to form transparent pellets. The sample scanned from 4000 to 400 nm at ambient temperature [6, 7].

D) Pre-compression Evaluation

1. Bulk Density

Bulk density was determined by placing the power blend into measuring cylinder and total volume was measured and also total powder weight was measured and also total powder weight was measured. The bulk density was calculated by using formula.

Bulk density=weight of powder/ bulk volume.

2. Tapped Density

Tapped density was obtained by tapping the cylinder by using tapped density apparatus. Tapped the cylinder up to 100 times and then measure the tapped volume and calculate the tapped density by using formula,

Tapped density= weight of powder/tapped volume

3. Hausner's ratio

Hausner's ratio is the number that is correlated to the flowablity of powder or powder blend. It is calculated using formula,

Hausner's ratio= tapped density –bulk density/tapped density*100.

4. Compressibility Index

Compressibility index was calculated by formula,

Carr's index (%) =Tapped density-bulk density/Tapped density* 100

5. Angle of repose

The angle of repose of powder blend of each layer of each formulation was determined by fix funnel method. The blend was poured through funnel separately until apex of pile so formed just touch the tip of the funnel. The angle of repose was calculated by using formula

$\Theta = \tan^{-1} h/r$

h is height of pile, r is radius of pile

E) Post compression evaluation [8, 9]

1. Uniformity weight

Average weight of the tablet was determined by selecting 20tablet randomly. This selected tablet weighing individually and the weight of individual tablet was compared with average weight.

2. Thickness

Thickness of the tablet was measured by using Vernier Calliper. 5 tablets were selected and thickness was measured in (mm).

3. Hardness

Hardness is important parameter of evaluation of tablet. The resistance of the tablet to break under condition of handling, transportation and storage depend upon hardness. The hardness of tablet was measured by using Monsanto hardness tester. The unit of hardness is expressed in term of kg/cm^2.

4. Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. 20 tablets are weighed and placed in the Roche Friabilator apparatus they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula;

% friability = [initial weight – final weight/initial weight]*100

5. Drug content

5 tablets were taken and powdered. The quantity of powder equivalent to100 mg of Metformin and Simvastatin was dissolved in 100ml volumetric flask containing 6.8 phosphate buffers. This solution was filtered through 0.45µm membrane filter. 1ml of above solution was diluted 100ml 6.8 phosphate buffer. The absorbances were measured at 233.2nm and 247.6nm using UV visible spectrophotometer.

6. *In-Vitro* Drug Release Study

The release of bilayer tablets was determined using USP Type II (Paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 37˚c± 0.5°c for 2 hour. Then dissolution media remove added phosphate buffer (6.8pH). The stirring speed was 50 rpm. Aliquot of the solution was collected at specific interval were replaced with fresh dissolution medium. The Metformin and Simvastatin were analyzed spectrophotometrically at 233.2 nm and 247.6 nm respectively using simultaneous equation method (**Figure 1** and **2**).

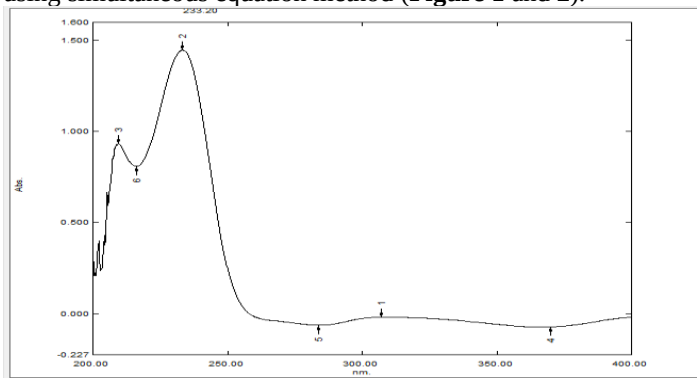

Fig 1: λmax 247.6 at Metformin

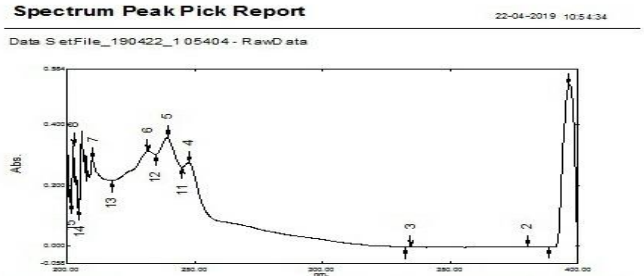

Fig 2: λmax at 233.20 nm for Simvastatin

RESULT AND DISCUSSION

Preformulation Study

Compatibility Study (FTIR)

FTIR spectrum of metformin, simvastatin and that of drug + excipients were shown in **Figure 3, 4, and 5**.

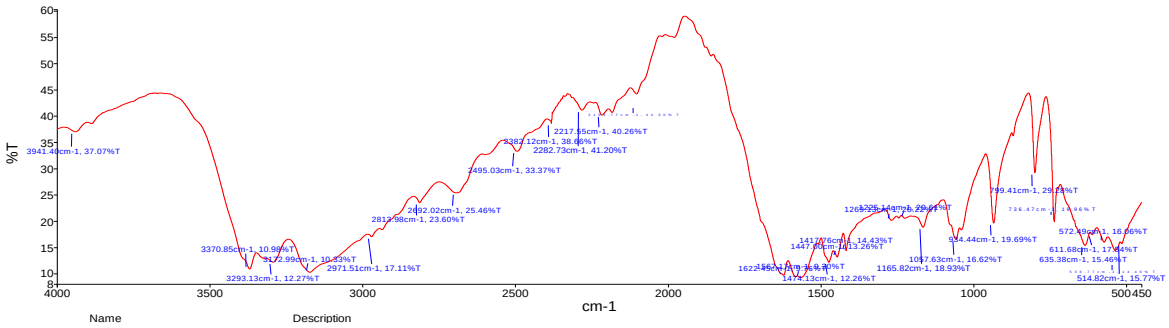

Fig 3: FTIR spectrum of Metformin

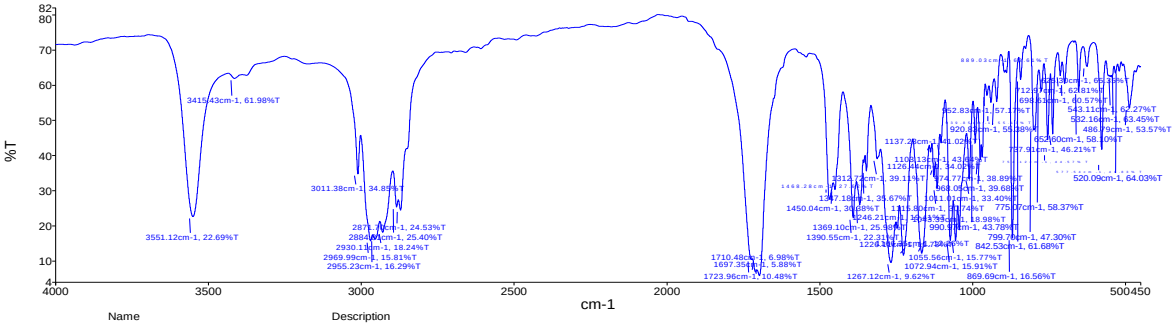

Fig 4: FTIR Spectrum of Simvastatin

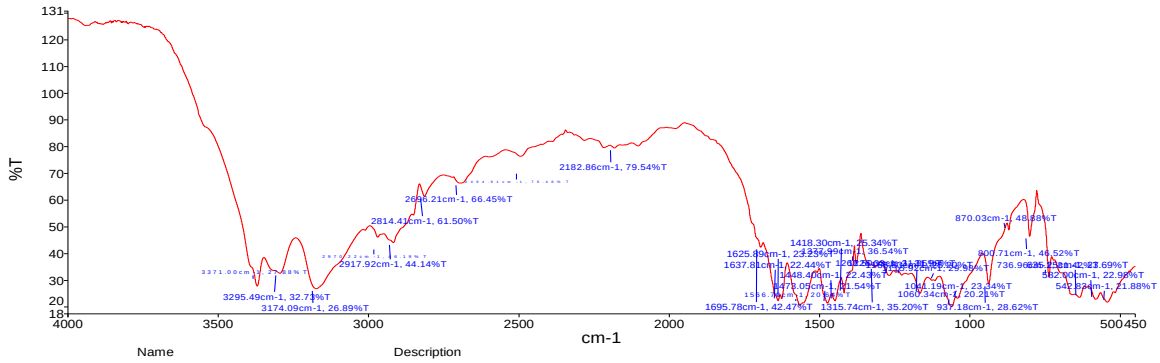

Fig 5: FTIR Spectrum of Drug + Excipients

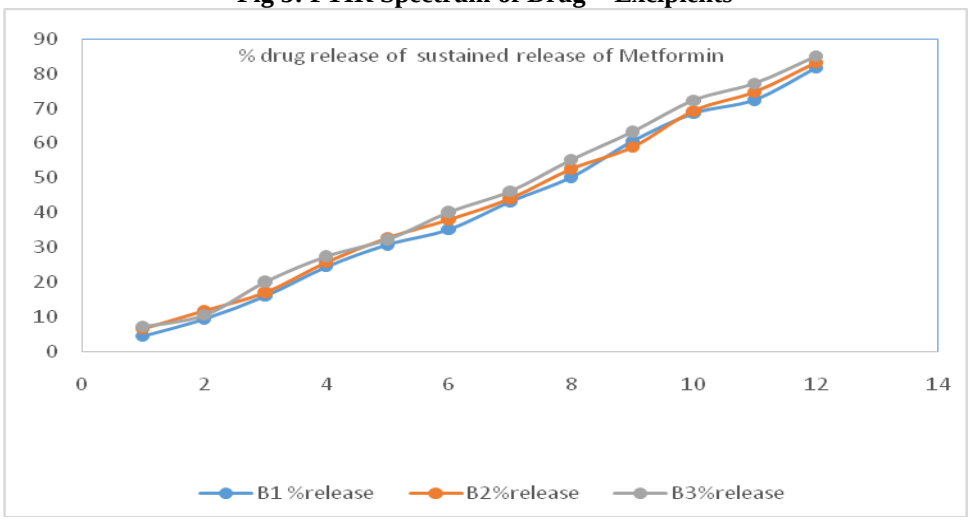

Fig 6: % Drug Release of Sustained Release of Metformin

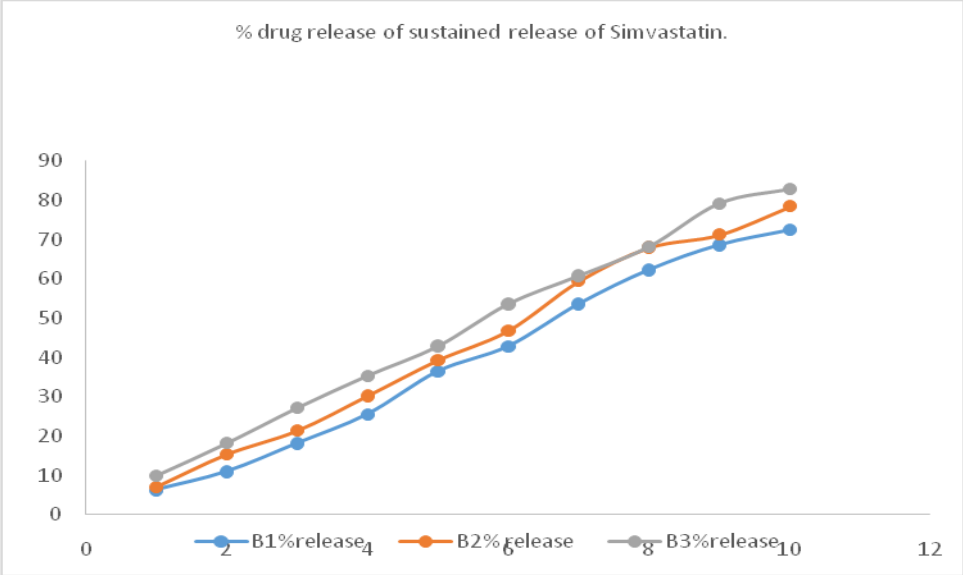

Fig 7: % Drug Release of Sustained Release of Simvastatin

Table 4: Precompression Evaluation of tablet

Sr. No	Parameter	B1	B2	B3
1	Bulk density(g/ml)	0.5263	0.588	0.55
2	Tapped density(g/ml)	0.71	0.74	0.66
3	Compressibility index (%)	26.76	21.62	16.66
4	Hausner's ratio	1.36	1.25	1.20
5	Angle of repose(degree)	36.86	38.65	37.59

Table 5: Post-Compression Evaluation

Sr. No	Parameter	B1	B2	B3
1	Uniformity weight(mg)	999.5	998.5	998
2	Thickness(mm)	4.42	4.49	4.5
3	Hardness(kg/cm(kg/cm$^{2)}$	7.39	7.10	7.55
4	Friability (%)	0.5	0.3	0.2
5	Drug content of Metformin (%)	87.56	86.58	93.56
6	Drug content of Simvastatin (%)	94.50	89.36	95.23

Table 6: % Drug Release Data of Metformin Hydrochloride Sustained-Release

Time(Hrs)	B1	B2	B3
1	4.58	6.6	7.36
2	9.51	11.8	10.65
3	16.14	17.1	20.25
4	24.51	25.82	27.56
5	30.22	32.82	32.4
6	35.22	38.03	40.23
7	43.22	44.13	46.23
8	50.25	52.66	55.27
9	60.58	58.96	63.32
10	68.56	69.42	72.36
11	72.47	74.85	77.25
12	81.63	83.29	85

Table 7: % Drug Release Data of Simvastatin Sustained Release

Time (hrs)	B1	B2	B3
1	6.34	7.07	9.92
2	10.99	15.36	18.16
3	18.16	21.38	27.16
4	25.55	30.23	35.36
5	36.43	39.30	42.89
6	42.82	46.82	53.63
7	53.56	59.36	60.80
8	62.25	67.96	68.23
9	68.58	71.19	79.25
10	72.35	78.35	82.90
11	78.71	85.52	88.36
12	88.2	91.46	93.46

Pre-compression Evaluation

Pre-compression parameters like angle of repose, bulk density, tapped density, Hausner ratio of all batches was represented **Table 4**. Flow properties also found to be passable flow properties for all batches.

Post-Compression Evaluation of Tablet

The prepared tablets were evaluated for weight variation, dissolution test (**Figure 6 and 7**), thickness, hardness uniformity of dosage units and friability. The weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. The hardness of 6 tablets was determined. The Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated. The drug content determined. The test values are including in **Table 5, 6 &7**.

CONCLUSION

The prepared tablets showed satisfactory results for various evaluation tests such as tablet hardness, friability, weight uniformity, drug content and *In-vitro* dissolution study. The optimized formulation based on all the parameter B3 batch useful for the patient in disease of diabetes and hypercholesterolemia.

ACKNOWLEDGEMENT

Authors are thankful to flamingo pharmaceuticals and Vishal Institute Pharmaceutical Education and Research, Ale for providing the raw materials to carry out this research work successfully.

DATA AVAILABILITY

Not declared

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

CONFLICTS OF INTEREST

The authors have no known conflict of interest.

FUNDING INFORMATION

Not declared.

AUTHORS' CONTRIBUTION

All the authors were contributed for manuscript preparation, conducting of the experiments, data collection, interpretation and analysis of the result.

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