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Formulation, Optimization and Evaluation of Bilayer Tablet of Metformin HCl & Rosuvastatin

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Abstract The aim of present study is to formulate and evaluate the bilayered tablets containing Rosuvastatin as immediate release (IR) portion and Metformin Hydrochloride as sustained release (SR) portion in order to produce a single tablet containing two different classes of drugs as widely prescribed by doctors and to have better patient compliance. The sustained release layer of Metformin HCl was prepared by using different grades of swellable polymer HPMCK4M and HPMC E3 LV, Ethyl Cellulose by wet granulation method. The Immediate release tablets of Rosuvastatin by wet granulation method using various concentration of sodium starchglycolate as super disintegrant. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The drug release study of Rosuvastatin and Metformin Hydrochloride were evaluated using Type II (Basket) dissolution apparatus under sink condition. The release studies of Rosuvastatin were carried out for 30 minutes by using 900ml of pH 7.4 phosphate buffer was used as dissolution medium at a temperature of 37ºC ±0.5ºC. The paddle was stirred at a speed of 100 rpm by using UV- Visible spectrophotometer measured at 354 nm. And for Metformin hydrochloride the release studies were carried out for 10 hours in 900ml of 0.1N HCl was used as dissolution medium for first 2 hours followed by pH 6.8 phosphate buffer solution for next 8 hours maintained at a temperature of 37ºC ±0.5ºC. The paddle was stirred at a speed of 100 rpm by using UV-Visible spectrophotometer measured at 233 nm. The release rates of Rosuvastatin from all the formulations were more than 99.74% at the end of 30 minutes. In case of HPMC K4M and HPMC E3 LV, ETHYL CELLULOSE based tablets with the increasing of polymer content the release mechanism moved to super case. Total four trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation, the stability studies of the products also comply with ICH guidelines.

Keywords Bilayer tablets, Rosuvastatin, Metformin Hydrochloride, HPMC, Sustained release, Immediate release

Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated [4].

Type and Classes of Tablets[4,6]

Oral tablets for ingestion

Compressed tablets
Multiple compressed tablets
Layered tablets
Compression-coated tablets
Repeat-action tablets
Delayed-action and enteric-coated tablets
Sugar and chocolate –coated tablets
Film coated tablets
Chewable tablets

Tablets Used in the Oral Cavity

Buccal tablets
Sublingual tablets
Troches and lozenges
Dental cones

Tablets administered by other routes

Implantation tablets
Vaginal tablets

Tablets used to prepare solutions

Effervescent tablets
Dispensing tablets
Hypodermic tablets
Tablet triturates

Bilayered Tablet[18,27]

Bilayer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed.

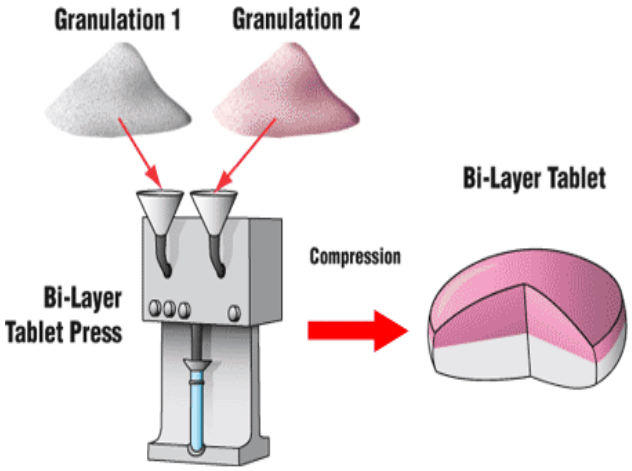


Figure 1: General Concept of Bilayer Tablets

Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug, later, either as second dose or in an extended release manner.

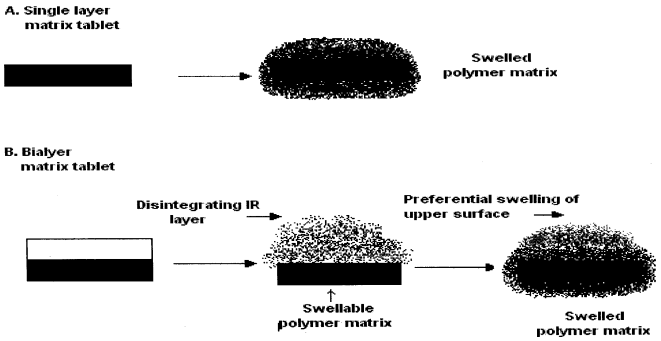


Figure 2: Release pattern of Tablets (A) Single Layered (B) Bilayered

Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. More are possible but the design becomes very special. Figure 3 represents compression cycle of bi-layer tablet.

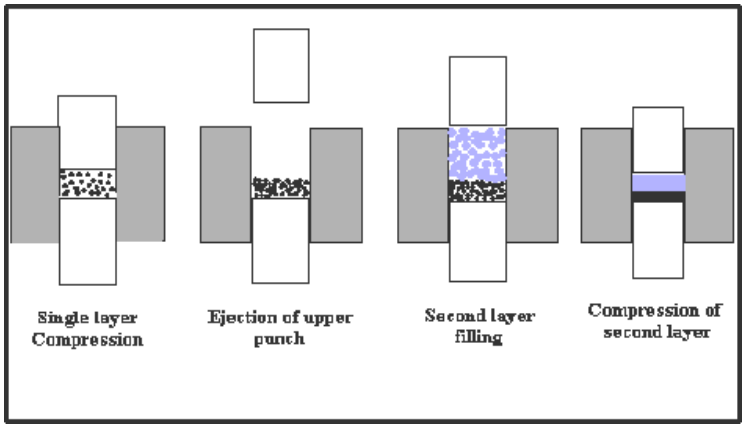


Figure 3: Compression cycle of bi-layer tablet.

Material & Method

Materials used in the present Investigation

Table 1: Materials used in the present Investigation

Sr. No.	Materials	Supplier/Manufacturer
1.	Metformin Hydrochloride	Cadila Healthcare ltd, Ankleshvar, India.
2.	Rosuvastatin Ca^{+2}	Cadila Healthcare ltd, Ankleshvar, India.
3.	HPMC K 100M/4M	Signet chemicals, India.
4.	DCP Granular	Signet chemicals corporation Pvt. Ltd. India.
5.	Cross Povidone XL	ISP Technologies, USA.
6.	Microcrystalline Cellulose pH101	FMC Biopolymer,
7.	Sodium Starch Glycolate	Signet chemicals, India.
8.	Colloidal silicon dioxide	Cabot sanmar Ltd., Chennai, India.
9.	Magnesium Stearate	Amishi drugs & Chemicals, Ahmedabad,India.
10.	Talc	Dow Chemicals, India.
11.	Ferric Oxide Red	Rona Dychem Pvt. Ltd.

List of Equipment

The following equipments were utilized during the product development of bilayertablet of antidiabetic drug.

Table 2

Sr. No.	Equipments/ Machine	Supplier/Manufacturer
1.	Electronic weighing balance (PG 403-S)	Mettler Toledo, Denver Instrument, India.
2.	Cage Blender	Cadmach machinery Co., Pvt. Ltd., Ahmedabad, India.
3.	Bulk Density measurement apparatus (ETD-1020)	Electro lab, India.
4.	"D" Tooling 8 Station Tablet compression machine	Cadmach machinery Co., Pvt. Ltd.,Ahmedabad, India
5.	Tablet Hardness Tester (VK 200)	Benchsavertm Series,(VANKEL). India.
6.	Friability test apparatus (EF-1W, EF-2)	Electro lab, India
7.	Vernier caliper	Omega Instruments Ltd., India.
8.	Dissolution Test Apparatus(TDT-06T)	Electrolab, Mumbai, India.
9.	UV SpectrophotometerUV-1700 Double beam Spectrophotometer	Shimadzu (Kyoto, Japan.).
10.	HPLC (LC- 2010 CHT)	Shimadzu (Kyoto, Japan.).
11.	Quadro Co-mill	Quadro engineering, Waterloo, Canada

Pre formulation Study

Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Solubility Study

Solubility of drug and polymer are important to design dissolution medium for dosage form. If 1 gm of drug dissolves in less than 1 ml of solvent then it is a very soluble. If 1 gm of drug dissolves in 10 ml of solvent then it is a freely soluble. If 10 gm of drug dissolve in to 30 ml of solvent then it is a soluble. If 30 gm of drug dissolve in 100 ml of solvent then it is a sparingly soluble. If 100 gm of drug dissolve in 1000 ml of solvent then it is a slightly soluble. If 1000 gm of drug dissolve in 10,000 ml of solvent then it is a very slightly soluble. If 10,000 gm of drug dissolve in more than that of solvent then it is a practically insoluble or insoluble.

Bulk Density: Loose Bulk Density: Weigh accurately 25 g of drug (M), which was previously passed through 20 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the following formula

Bulk Density+ Weight of powder/ Bulk volume '

Tapped Density = Weight of power / Tapped volume

Carr's Index The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD)*100]/TD

TD = Tapped Density
BD= Bulk Density

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder orgranular material.
Hausner's Rtio = TD/BD

Table 3: Effect of Carr's Index and Hausner's Ratio on flow property

Carr's Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Angle of Repose The angle of repose of API powder was determined by the fix funnel method. The accurately weight powder were taken in the funnel. Adjust the funnel clam so that the gap between the bottom of the funnel stem and peak of the powder pile is about 3 cm. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone and height were measured and angle of repose was calculated using the following equation. $\tan\theta = h/r$

Where, h and r are the height and radius of the powder cone respectively.

Table 4: Angle of repose (ϕ) value and Flow property

Angle of Repose (Φ)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

Drug – Excipients compatible study

Metformin Hydrochloride:

Rosuvastatin Ca+2:

Compatibility between drug and excipients were studied by HPLC method. Rosuvastatin(500mg), Compatibility between drug and excipients ratio were studied by HPLC method. Metformin Hydrochloride(500mg), Metformin Hydrochloride:PVP K 90(1:0.5), Metformin Hydrochloride:MCC(1:0.5), Metformin Hydrochloride:HPMC K 4M(1:1), Metformin Hydrochloride: HPMC K 100M(1:1), Metformin Hydrochloride: Glyceryl behenate(1:0.25), Metformin Hydrochloride: Magnesium stearate(1:0.25) were mixed homogenously and passed through sieve number 40# then stored at 40ºC ± 5ºC and 75% ± 5% relative humidity in stability chamber (Remi Lab, Bombay). Samples were withdrawn after 1 month time intervals and analyzed for related substances by HPLC method.

Rosuvastatin:DCL 11(1:10), Rosuvastatin:DCP granular(1:8), Rosuvastatin:SSG(1:4), Rosuvastatin:Crospovidone XL(1:4), Rosuvastatin: Magnesium stearate(1:1), Rosuvastatin:Avicel PH102(1:5), Rosuvastatin:Arosil(1:2) were mixed homogenously and pass through sieve number 40#, Rosuvastatin:Ferric Oxide Red(1:0.25) was mixed homogenously and passed through sieve number 100# then stored at 40ºC ± 5ºC and 75% ± 5% relative humidity in stability chamber (Remi Lab, Bombay). Samples were withdrawn after 1 month time intervals and analyzed for related substances by HPLC method.

Analytical method development for Metformin Hydrochloride[104]

Determination of λ_{max} (peak) of Metformin HCL

Accurately 10 mg of Metformin Hydrochloride was dissolved in Phosphate buffer pH 6.8 and volume was made up to 100 ml in 100 ml volumetric flask to make 100µg/ml.From this solution withdraw 10 ml and was further diluted up to 100 ml to make 10 µg/ml. From this solution aliquots of 2, 4, 6 and 8 µg/ml were prepared by withdrawing 2, 4, 6, 8 ml of solution respectively by diluting it up to 10 ml with phosphate buffer and the spectra were scanned between 200-400nm. λ_{max} for above solution was found to be 233nm. Absorbance of each solution was measured at 233nm using Shimadzu UV-1601 UV/Visible double beam spectrophotometer and phosphate buffer pH 6.8 as reference standard. This process was repeated 3 times in 3 different days.

Table 5: Absorbance of different concentration of Metformin HCL

Concentration (µg/ml)	Absorbance Mean ±SD
2	0.192±0.00115
4	0.335±0.00057
6	0.509±0.00057
8	0.713±0.0010

Assay of Metformin Hydrochloride

Assay of Metformin HCl was carried out by using USP-2007 method by HPLC method as following

Mobile phase: Dissolve about 1.2 g of sodium chloride in 900 ml of Milli Q water,add 0.87 g of pentane sulphonic acid sodium salt and 1 ml of triethylamine. Dilute up to the 1000 ml with Milli Q water. Adjust the pH to 3.5 with 1% solution of orthophosphoric acid.

Diluent: Use water as diluents.

Standard preparation: Transfer an accurately weighed quantity of about 50 mg of Metformin hydrochloride working standard to a 100 ml volumetric flask. Add about 50 ml of diluents and sonicate to dissolve. Make volume up to the mark with diluents and mix. Dilute 5.0 ml of this solution to 50.0 ml with diluents and mix. Prepare two independent sample preparations.

Sample preparation: Transfer an accurately weighed quantity of powder blend equivalent to about 250 mg of Metformin hydrochloride to a 500 ml volumetric flask. Add about 150 ml of diluents and sonicate for 15 minutes. Make volume up to the mark with diluents and mix. Filter the solution through 0.45 µm Millipore HVLP filter,collect the filtrate by discarding first few ml of the filtrate. Dilute 5.0 ml of the filtrate to 50.0 ml with diluents and mix.

Chromatographic system:

Column : Bondapack C18, (30cm × 3.9 mm), 10 µm

Detector : 233 nm

Flow rate : 1.5 ml/minInjection volume : 10 µl

System suitability: Chromatogragh the standard preparation and record the peak responses a directed under procedure. The relative standard deviation for five replicate standard injections is not more than 2.0%.

Procedure: Separately inject mobile phase, diluents, standard preparation and sample preparation into the chromatograph. Record the chromatograms and measure the peak responses for the analyte peaks.

Preparation of Metformin hydrochloride Tablet[104]

Granulation

Metformin hydrochloride, MCC 102, HPMC K100M were sifted through Seive no. #40. Then the above sifted materials were mixed in Rapid Mixer Granulator for 5 min (RPM of Impeller- 150). PVP K-90 was dissolved in mixture of IPA and water. (20gm + 32 gm) (20gm = 27 ml of IPA and 32gm= 32 ml of water. Total binder solution was 118 ml.) Then above mixture with binder PVP K-90 solution wasgranulated at Impeller RPM 150 and kneading for 2 min(Impeller RPM 150 and chopper RPM 1500). The granules were dried in tray dryer at 65°C (LOD 1.5 to2.5 % w/w). The granules were passed through mesh no.# 20 in oscillating granulator and then mix with 40# passed HPMC for 5 min. in Cage blender. Finally mixture was lubricated with Glyceryl behenate for 2 min in Cage blender. In Batch F1 to F3, HPMC K4M was used as a polymer instead of HPMC K100M with increasing concentration. And Batch F4 to F8, HPMC K100M was used as a Polymer replace with HPMC K4M. In Batch F1 to F6, Magnesium Stearate was used as a Lubricating agent instead of Glyceryl behenate with increasing concentration. And Batch F7 and F8, Glyceryl behenate was used as a Lubricant replace with Magnesium Stearate.

Table 6: Composition of Metformin Hydrochloride Tablet

Sr No.	**Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
		Qty(mg)/tab							
1	Metformin Hydrochloride	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00
2	MCC (Ran Q 102)	142.00	142.00	95.00	133.00	95.00	57.00	57.00	57.00
3	Methocel K 4 M (HPMC)	76.00	76.00	114.00	0.00	0.00	0.00	0.00	0.00
4	Methocel K100 M (HPMC)	0.00	0.00	0.00	76.00	114.00	152.00	152.00	152.00
5	PVP K 90	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
6	Isopropyl Alcohol	-	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
7	Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
8	Magnesium Stearate	12.00	12.00	21.00	21.00	21.00	21.00	0.00	0.00
9	Glyceryl Behenate	0.00	0.00	0.00	0.00	0.00	0.00	0.00	21.00
	TOTAL WEIGHT	**750.00**	**750.00**	**750.00**	**750.00**	**750.00**	**750.00**	**750.00**	**750.00**

Preparation of tablet of Metformin Hydrochloride layer

Granules of Metformin hydrochloride are compressed using 18×9 mm, capsule shape,having plane surface on lower punch and break line on upper punch using "D" Tooling 8 Station Tablet compression machine.

Evaluation of Metformin Hydrochloride Tablets layer

Table 7: Weight variation

Average Weight of Tablets (mg)	Maximum Percentage Difference Allowed
130 or less	10
130-324	7.5
More than 324	5

Friability

The friability of the Tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W0) or a sample of 10 Tablets are dedusted in adrum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

$$\%\text{Friability} = \frac{Wo - W}{Wo} \times 100$$

Hardness

The hardness of the tablets was determined by diametral compression using an schedunger type tester (Dr. Schedunger Scientific ind.). A tablet hardness of about 5- 10 kp is considered adequate for mechanical stability.

Drug Content

Drug content of Metformin hydrochloride was determined by HPLC method by above procedure as described in Section 5.1.2

In-vitro Dissolution study[ref]

In-vitro Dissolution study was carried out by USP method by using followingparameters

Dissolution parameters:

Medium : 900 ml ; Phosphate Buffer pH 6.8
Apparatus : Paddle
RPM : 100
Temperature : 37˚ C ± 0.5˚ C
Time : 1 hr, 2 hr, 6 hr and 10 hr

Preparation of Rosuvastatin Ca^{+2} Tablets

Rosuvastatin Ca^{+2} was mixed geometrically with Avicel in steel tube and passed through sieve no.#60. DCL 11 was passed through sieve no.#40 & Ferric Oxide Red was passed through sieve no.#100 and mixed in polybag. Then above both mixture were mixed in Polybag for 5 min. DCP- granular was passed through sieve no.40# and mixed in above mixture and shaked for 5 min. Sodium Starch Glycolate/Crospovidon XL is passed through sieve no #40 and Arosil is passedthrough #60then both are mixed with above mixture for 8 min in Cage blander. Finally the mixture was lubricated with 60# passed Magnesium Stearate for 3 min. in Cage blender. In Batch R1 to R3 Sodium Starch Glycolates was used and In Batch R4to R6 Crospovidone XL was used as a Disintegrating Agent.

Table 8: Composition of Rosuvastatin Ca^{+2} Tables

Sr No.	Ingredients	R1	R2	R3	R4	R5	R6
		Qty(mg)/Tab					
1	Rosuvastatin Ca^{+2}	10	10	10	10	10	10
2	DCL 11	127.6	127.6	127.6	127.6	127.6	127.6
3	Avicel ph 102	96	94	92	96	94	92
4	DCP- granular	52	52	52	52	52	52
5	Sodium Starch Glycolate	6	8	10	0	0	0
6	Crospovidone XL	0	0	0	6	8	10
7	Arosil	3.2	3.2	3.2	3.2	3.2	3.2
8	Ferric Oxide Red	0.4	0.4	0.4	0.4	0.4	0.4
9	Mg. Stearate	4	4	4	4	4	4
	TOTAL WEIGHT	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**

Compression of Rosuvastatin Ca^{+2} part of Tablets.

Free flowing part of Rosuvastatin was compressed using 18.5 × 8.7 mm, capsule shape, having plane surface on lower punch and break-line on upper punch using"D" Tooling 8 Station Tablet compression machine.

Evaluation Parameter of Rosuvastatin Tablet

Prepared tablets were evaluated for physical appearance, weight variation, friability, hardness, thickness, drug content uniformity and in-vitro dissolution studies

Weight Variation

The Weight Variation of Rosuvastatin tablets were determined by method which was already described in previous section.

Friability

The Friability of Rosuvastatin tablets were determined by method which was already described in previous section.

Hardness

The Hardness of Rosuvastatin tablets were determined by method which was already described in previous section.

Thickness

The Thickness of Rosuvastatin tablets were determined by method which was already described in previous section.

Drug content

Drug content of Rosuavastatin tablets were determine by HPLC method by above procedure.

Disintegration test

The disintegration time was measured by using USP disintegration test apparatus. Six tablets were placed in tubes and the basket was kept positioned in a 1-litre beaker of 6.8 pH phosphate buffer maintained at 37˚ C ± 0.5˚ C. The tablet remain 2.5 cm from the bottom of medium, a standard motor driven device move the basket containing tablet up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute.

Dissolution Test

Dissolution parameters:

Medium : 900 ml; Phosphate buffer pH 6.8
Apparatus : Paddle
RPM : 50 rpm
Temperature : 37˚ C ± 0.5˚ C

Time : 30 min.

Preparation of Bi-Layer Tablet of Metformin Hydrochloride and Rosuvastatin Ca^{+2}

Preparation of Bi-layer Tablet

Optimized batch of Metformin and Rosuvastatin was selected for formulation of bi- layer tablet. As previously reported procedure granules of Metformin layer and Rosuvastatin layer were prepared separately. One by one both layer were compressed in "D" Tooling 8 Station Tablet compression machine.

Dissolution Test

The in-vitro dissolution studies were carried out using USP apparatus type II at 50 rpm for Rosuvastatin immediate release layer in 900 ml ; Phosphate buffer pH 6.8 ,30 min .and at 100 rpm for Metformin extended release layer in 900 ml of Phosphate buffer pH 6.8 for 12 hours, maintained at 37 ± 0.5^0C using USP apparatus type I. The drug release at different time intervals was measured by HPLC method and UV- Visible method respectively. The release studies were conducted on using (6 tablets), and the mean values were plotted versus time.

Stability Study of Bi-Layer Tablet

The bi-layer tablets were stored at 40ºC ± 5ºC and 75% ± 5% relative humidity in stability chamber (Remi Lab, Bombay). Samples were withdrawn at 1 month time intervals and evaluated for drug content, in-vitro drug release study, weight variation, hardness, thickness and friability.

Result & Discussion

Result of Preformulation Studies:

Solubility of Drug

Solubility of Metformin Hydrochloride was determined by the method mentioned in section 5.1.1. Freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in acetone, chloroform, dichloromethane and ether.

Solubility of Rosuvastatin was determined by the method mentioned in section 5.1.1. Sparingly soluble in water and methanol, and slightly soluble in ethanol.

Bulk characterization of both the drugs:

Table 9: Bulk characterization of both the drugs

Sr. No	Drug	BD* (g/ml)	TD* (g/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (^{0})
1	**Metformin HCl**	0.34	0.67	47.65	1.95	43.68
2	**Rosuvastatin Ca^{+2}**	0.45	0.59	23.72	1.31	23.56

*BD- indicates Bulk density; TD- indicates Tapped density.

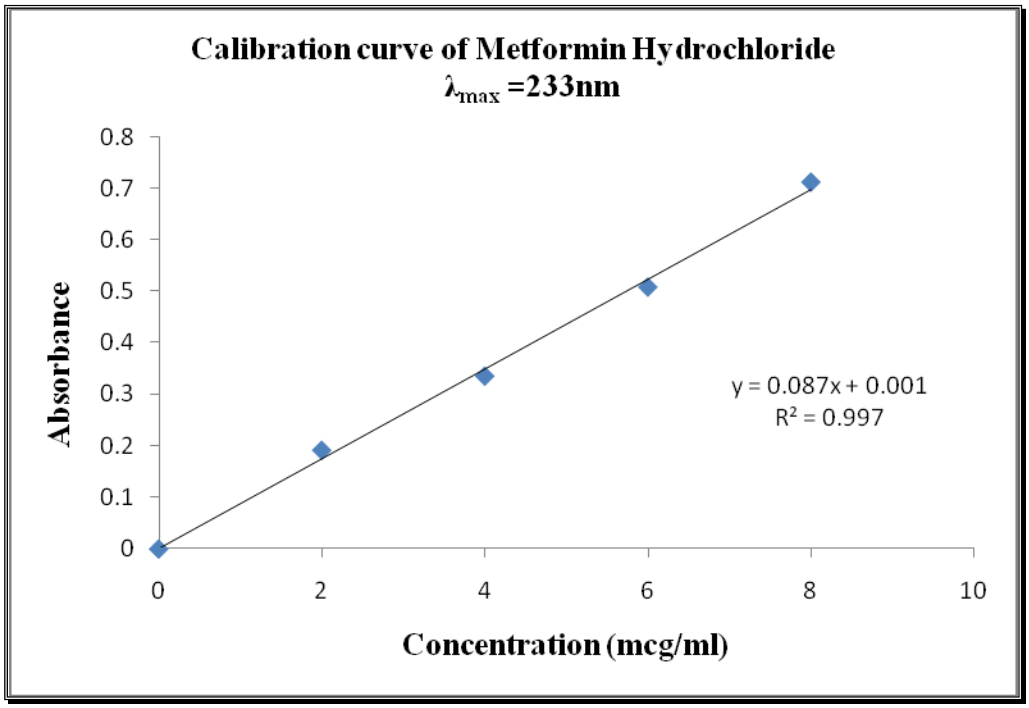
From the Results of Preformulation studies of the API, It was concluded that Metformin Hydrochloride has poor flow property and compressibility property while Rosuvastatin Ca^{+2} has passable flow and compressibility property. So, to improve the flow and compressibility property, it was beneficial to use the Lubricant in the formulation of tablet.

Development of Standard Calibration Curve for Metformin Hydrochloride

Table 10: Standard Calibration Curve for Metformin Hydrochloride

Sr. No.	Concentration (mcg/ ml)	Absorbance			Avg. Absorbance(± SEM)
		A1	A2	A3	
1	0	0	0	0	0
2	2	0.192	0.194	0.192	0.192 (± 0.001155)
3	4	0.336	0.335	0.335	0.335 (± 0.000577)
4	6	0.509	0.510	0.509	0.509 (± 0.000577)
5	8	0.713	0.712	0.714	0.713 (± 0.001)

Figure 4: Standard Calibration Curve for Metformin Hydrochloride



Drug – Excipients compatible study:

Drug-excipients interaction study by HPLC Method shown in Table No.6.3

Table 11: Drug – Excipients interaction study

Sr. No.	Ingredients	Initial Stage RS* (%w/w)	After 1 month RS* (%w/w)
1	Metformin Hydrochloride	0.09	0.10
2	Metformin Hydrochloride+PVP K 90	0.13	0.13
3	Metformin Hydrochloride + MCC	0.16	0.18
4	Metformin Hydrochloride + Methocel K 4 M	0.13	0.14
5	Metformin Hydrochloride + Methocel K 100 M	0.15	0.15
6	Metformin Hydrochloride + Glyceryl behenate	0.20	0.21

7	Metformin Hydrochloride + Magnesium stearate	0.19	0.19
8	Rosuvastatin	0.23	0.26
9	Rosuvastatin + DCL 11	0.12	0.13
10	Rosuvastatin + Avicel ph 102	0.29	0.31
11	Rosuvastatin + DCP- granular	0.12	0.15
12	Rosuvastatin + Sodium Starch Glycolate	0.15	0.16
13	Rosuvastatin + Cros-povidone XL	0.14	0.14
14	Rosuvastatin + Arosil	0.20	0.21
15	Rosuvastatin + Ferric Oxide Red	0.18	0.18
16	Rosuvastatin +Mg. Stearate	0.21	0.22

***** RS- Relative Substance

From the above study it was observed that there was no significance change in the RSvalue of drug-Excipients. So there was no interaction between drugs and Excipients.

Evaluation of Bilayered Tablets

The optimized Batch of Metformin Hydrochloride and Batch of Rosuvastatin Ca^{+2}were used for formulation of bi-layer tablet.

Extended Release Tablet of Metformin Hydrochloride

Compression Parameter

Average weight: - 750.00 mg

Hardness: - 5-6 kp

Thickness: - 4.40 - 4.42 mm

Immediate Release Tablet of Rosuvastatin Ca^{+2}

Compression Parameter

Average weight: - 300.00 mg

Thickness: - 2.0 - 2.10mm

Disintegration Time: - 3-4min.

Evaluation of Prepared Tablets

Eight batches of the bilayer tablets were evaluated for average weight, hardness,friability, disintegration time and drug content uniformity as shown in Table 6.4.

Table 12: Evaluation of Bilayered Tablets

Batch No.	Weight of tablets (mg) *	Hardness (kg/cm^2)	Friability	DT* (min) Rosuvastatin layer	Drug Content uniformity	
					Metformin	Rosuvastatin
F1+R1	1058	24	0.043%	3.8	96.8	98.7
F2+R2	1057	26	0.041%	3.5	98.3	99.2
F3+R3	1059	26	0.036%	3.9	95.9	102.3
F4+R4	1057	25	0.039%	3.1	98.7	98.6
F5+R5	1058	26	0.042%	3.6	97.5	99.4
F6+R6	1057	24	0.039%	3.9	101.2	98.8
F7+R6	1058	26	0.042%	3.7	98.4	96.7
F8+R6	1057	25	0.041%	3.8	98.7	99.4

*Average of 10 tablets, *DT-Disintegrating time

From table 12 it can be concluded that all the batches has acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content 105.1- 96.5 %, hardness 24-26 kg/cm^2, and friability 0.035% to 0.045% also disintegration time for Rosuvastatin Ca^{+2} 3-4 min.

In-Vitro Dissolution Test of Bi-Layer Tablet

Results of dissolution test for bi-layer tablet was represented in Table 6.4 and 6.6 for Metformin Hydrochloride and Rosuvastatin Ca^{+2} respectively. Results were represented as mean % drug release

Dissolution Test for Metformin Hydrochloride ER Tablet

Cumulative % drug release for Metformin Hydrochloride against Innovator is asshown in Table 6.5.

Table 13: Drug release for Metformin Hydrochloride (%)

Drug Dissolution Data of Metformin Hydrochloride (%)										
Time (hr)	**Ref.**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**As per USP**
0	0	-	0	0	0	0	0	0	0	0
1	32.3	-	51.2	38.7	45.1	42.1	37.2	21.3	31.2	20-40
2	43.2	-	71.8	61.2	64.8	58.6	54.8	47.5	43.9	35-55
6	75.9	-	92.1	87.3	88.2	85.2	81.1	69.1	72.2	65-85
10	98	-	99.8	94.2	96.9	89.1	87.2	91.2	97.8	more than 85

Table 14: Targeting specific Release Profile of Metformin Hydrochloride

Factor	F1	F2	F3	F4	F5	F6	F7	F8
F1 (Dissimilarity Factor)	-	83.47	88.56	24.92	3.80	38.97	30.20	11.11
F2 (Similarity Factor)	-	27.01	26.37	44.82	55.17	41.00	45.39	64.34

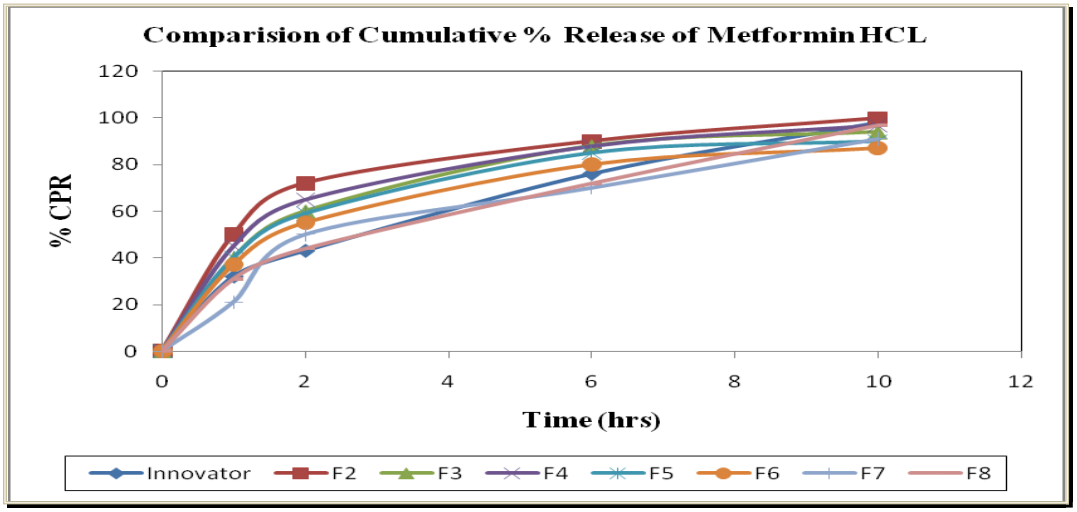


Figure 5: Dissolution profile of Metformin Hydrochloride

Dissolution Test for Rosuvastatin Ca^{+2} IR Tablet

Table 15: Drug release for Rosuvastatin (%)

Drug Dissolution Data of Rosuvastatin (%)							
Time (min)	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**Innovator**
0	0	0	0	0	0	0	0
5	37.2	31.9	33.4	35.2	37.6	41.2	41.3
10	67.3	59.2	60.1	62.3	57.2	67.1	66.7
20	96.1	83.8	79.3	80.7	87.6	86.3	86.1
30	99.2	97.6	94.1	92.6	96.4	99.8	99.8

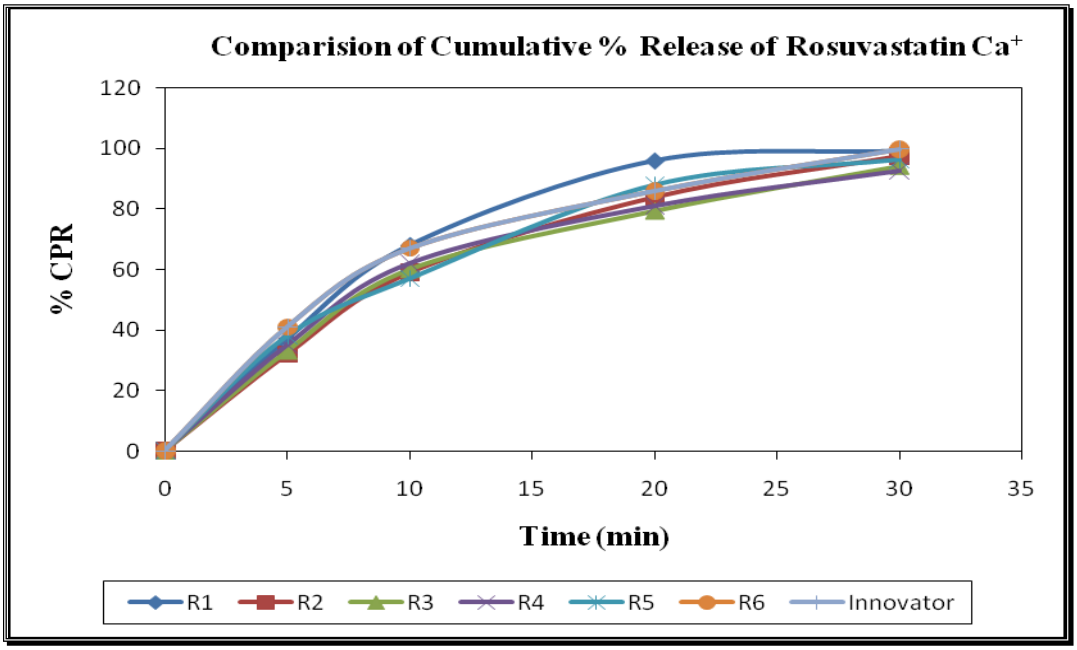


Figure 6: Dissolution profile of Rosuvasatin Ca^{+2}

Stability Study of Bi-Layer Tablet

Table 16: Stability study of Bi-layer tablet

Test	**Specification**	**Initial**	**After one month**
Description	White and Pink colored, capsule shape bilayered tablet, Break line on one side, plain	White and Pink colored, capsule shape bilayered tablet, Break line on one side, plain	White and Pink colored, capsule shape bilayered tablet, Break line on one side, plain
Dissolution: Medium=900ml Phosphate buffer pH6.8, USP	For Metformin Hydrochloride	1 Hr = 31% 2 Hr = 44% 6 Hr = 72% 10 Hr =97%	1 Hr = 30.65% 2 Hr = 43.75% 6 Hr = 72.60% 10 Hr =96.55%

Apparatus II, 100			
Dissolution: Medium=900ml, Phosphate buffer pH 6.8, USP Apparatus I, 50	For Rosuvastatin Ca^{+2}	In 30 min =99.9.00%	In 30 min = 98.85%
Assay	90 % to 110 % of stated amount of Metformin	Mean = 99.22%	Mean = 98.22%
	90 % to 110 % of stated amount of	Mean = 98.78%	Mean = 98.00%
Individual Impurity	0.37	0.42	0.40
Total Impurity	0.89	0.73	0.81
Thickness	---	6.80 – 6.93 mm	6.80 – 6.93 mm
Hardness	---	24-26kp	24-26kp
Friability	---	0.035%	0.045%

Summary & Conclusion

It was found that with the designing of bilayer tablet of Metformin Hydrochloride and Rosuvastatin Ca^{+2} in which Rosuvastatin Ca^{+2} in one-layer releases instantly due to the presence of CrosCarmelose sodium as superdisintergrating agent and Metformin Hydrochloride follow the release slowly by HPMC high molecular weigh matrix in the order to match with the innovator product. Finally, it was concluded that Bilayer tabletof Metformin Hydrochloride and Rosuvastatin Ca^{+2} can be prepared by using optimized level of high viscosity of HPMC in sustained release layer and cros carmelose sodium in instant release layer.

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