



[Research article]

## Design and evaluation of Bilayered tablets of Simvastatin

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### ABSTRACT

The Objective of this study was to formulate bilayer tablets comprising of Simvastatin in both Extended Release layer and immediate release layer and to carry out *in vitro* dissolution studies for the formulated tablets as per official specifications. Bilayer tablets comprised two layers, i.e. immediate release and extended release layer. Simvastatin is an orally active anti hypertensive agent. For immediate release drug and polymer ratio (Simvastatin: croscarmellose sodium in the formulations I1 to I3 was prepared in the ratio (1:1, 1:2, 1:3). Whereas for extended release, drug and polymer ratio (Simvastatin: HPMC K4M) were formulated as 1:0.5, 1:1, 1:1.5, 1:2 and 1:2.5 in Formulations C1 to C5. The immediate release layer comprised sodium starch glycolate and croscarmellose sodium as super disintegrant and sustained release layer comprised ethyl cellulose and HPMC K4M as release retardant polymers. Direct compression method was used for formulation of bilayer tablets. Accelerated stability studies were carried out in accordance with ICH guidelines. Ethyl cellulose and HPMC K4M retarded the release of Simvastatin from the controlled release layer for 12 hrs. After stability tests, degradation of both drugs were found but the drugs, contents were found to be within the range. Drug release mechanism release exponent (n) were determined for all formulations (0.689-0.789). The immediate release layer of Simvastatin was found to follow a first order release model and the extended release layer of Simvastatin was found to follow zero order release model.

**Key Words:** Simvastatin, Bilayer tablets, Extended Release, Immediate release, Croscarmellose sodium and *In-Vitro* drug release.

### INTRODUCTION

Oral drug delivery is the most important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. Oral medication is generally considered as one of the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration and cost-effective manufacturing

process<sup>1,2</sup>. An immediate release system allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. Many dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. For example, a tablet containing a pain killer should disintegrate quickly in the gastrointestinal tract to

allow a fast uptake into the body<sup>2</sup>. Modified-release solid oral dosage forms include delayed, extended-release and targeted release drug products. Extended-release systems allow for the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained- or controlled-release dosage forms<sup>3,4</sup>.

Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bilayer tablets are preferred when the release profiles of the drugs are different from one another<sup>5,6</sup>. Simvastatin inhibit cholesterol synthesis by competing effectively to inhibit the HMG CoA reductase the rate limiting step in the cholesterol synthesis thus depleting the intracellular supply of cholesterol. This depletion leads to increased activity and number of LDL receptors which increase the clearance of LDL and causing secondary reduction in LDL synthesis. As a result Statins reduces LDL by up to 60% reduce TG up to 40% and increase HDL up to 10%. The therapeutic benefits also include plaque stabilization. Therefore the objective of the present study was to develop new directly compressed, double-layer tablets (DLTs) of Simvastatin, a highly potent a lipid lowering drug with short half-life, that are characterized by initial burst drug release in the stomach and comply with the release requirements of sustained-release products<sup>7,8</sup>.

## EXPERIMENTAL METHODS

### Materials

#### Pre-formulation studies

Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It is the first step in rational development of drug dosage forms of a drug substance. It provides the information required to

define the nature of the drug and a framework for the drug combination with pharmaceutical excipients in dosage form. Hence, pre-formulation studies were performed on the obtained sample of drug for identification and compatibility studies<sup>9,10</sup>.

#### FTIR Studies

The FT-IR spectrum of the obtained drug sample was compared with the standard FT-IR spectra of the pure drug. Compatibility Studies of Drug & Polymers: Prior to the development of the dosage forms the pre-formulation study was carried out. Hence infrared spectra of pure drug and the physical mixture of drug and polymers were taken.

#### Formulation Development

The pharmaceutical development studies have to be carried out with the purpose of selecting right dosage form and a stable formulation. These studies give detailed description of all the steps involved in the process of formulation development. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled in order to give reliable and reproducible quality product<sup>12,13</sup>.

#### Formulation of Bilayer Matrix Tablet

The bilayer tablet was prepared by direct compression method. Development of bilayer tablet of Simvastatin was carried out in three stages. Two layers (Immediate release layer and controlled release layer) were formulated separately using different concentration of polymers in different ratios. After optimization of individual layers by in-vitro studies and statistical methods bilayer tablet was prepared using optimized formulae. Bilayer tablet was prepared on rotary tablet compression machine. First the extended release layer was precompressed on compression machine manually and the immediate release layer was loaded on top of precompressed layer and punched with 6 mm punch on compression machine automatically<sup>14,15,16</sup>. Composition of immediate release and extended release layers are shown in Table 2 and Table 3.

**Table 2: Composition of immediate release layer**

S. No	Formulation Code Composition (mg)	I <sub>1</sub>	I <sub>2</sub>	I <sub>3</sub>
1	Simvastatin	20	20	20
2	Croscarmellose sodium	20	40	60
3	Sodium starch glycolate	50	40	30
4	Microcrystalline cellulose	50	40	30
5	Talc	5	5	5
6	Magnesium stearate	5	5	5
7	Total weight	150	150	150

**Table 3: Composition of extended release layer**

S. No	Formulation Code Composition (mg)	C <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>	C <sub>5</sub>
1	Simvastatin	20	20	20	20	20
2	Ethyl cellulose	50	40	30	20	10
3	HPMC K4M	10	20	30	40	50
4	Microcrystalline cellulose	20	20	20	20	20
5	Talc	5	5	5	5	5
6	Magnesium stearate	5	5	5	5	5
7	Total weight	150	150	150	150	150

## EVALUATION PARAMETERS

### Angle of repose

This is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the loose powder can be measured by angle of repose. The rougher & more irregular the surface of particles the greater will be angle of repose. The blend was passed through a funnel fixed to a burette stand at a height of 4cm. a graph paper was placed below the funnel on the table<sup>17,18</sup>. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula

$$\theta = \tan^{-1}(h/r)$$

Where,  $\theta$  = angle of repose, H = Height of the pile, R=Radius of the pile

### Bulk density

The bulk density is used as a measure to describe packing materials or granules. Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount (25gms) of powder sample to the graduated cylinder with the aid of a funnel<sup>19,20</sup>. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

$$\text{Bulk density} = W/V_0 \text{ g/ml}$$

Where, W= Mass of the blend,  $V_0$ =Untapped volume

### Compressibility index

It is the propensity of a powder to be compressed. It is measured by tapped apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula<sup>19,20</sup>.

$$\text{Compressibility index} = [(V_o - V_f) / V_o] \times 100$$

$$\% \text{ Compressibility} = [(Tapped \text{ density} - \text{Bulk density}) / Tapped \text{ density}] \times 100$$

$$\text{Hausner's ratio} = Tapped \text{ density} / \text{Bulk density}$$

The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

### Loss on drying

The loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (1g) was determined by using electronic LOD (helium lamp) apparatus at 105 °C.

## Drug Content Analysis

### Drug content for Simvastatin

Twenty tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 20 mg of Simvastatin was taken into 100 ml volumetric flask. The amount of drug present in a 2 mg equivalent amount of powder was determined by, dissolving the powder mixture in HCl buffer pH 2.0 containing 0.5 % w/v of SLS and suitably diluted. Further 1ml of the above solution was diluted to 10ml with HCl buffer pH 2.0 containing 0.5 % w/v of SLS. Drug concentration was determined from Simultaneous equation<sup>21,22</sup>.

### Drug content for Simvastatin in pH 6.8 Phosphate buffer

Twenty tablets of each formulation of extended release layers were weighed and powdered. A quantity of powder equivalent to 20 mg of Simvastatin was taken into 100 ml volumetric flask. The amount of drug present in a 20 mg equivalent amount of powder was determined by dissolving the powder mixture in Phosphate buffer pH 6.8 and suitably diluted with Phosphate buffer pH 6.8. Further 1ml of the above solution was diluted to 10ml with Phosphate buffer pH 6.8. UV absorbance was measured at 239 nm. Drug concentration was determined from standard calibration curve<sup>23,24</sup>.

### In vitro drug release studies

The release of drug from different batches of prepared tablets was studied by using USP dissolution apparatus type II (paddle type). The dissolution medium used was 900 ml of HCl buffer of pH 2.0 for 2 h and phosphate buffer of pH 6.8 for 10hrs. The temperature was maintained at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  with continuous stirring at a rate of 50

rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV

Spectrophotometer at 279 nm for immediate release layer Simvastatin and Simvastatin at 238 nm for sustained release layer against a blank<sup>25,26</sup>.

### Drug release kinetics<sup>27,28,29,30,31</sup>

To study the release kinetics, data obtained from in vitro drug release study was tested with the Zero order equation, first order equation, Higuchi square root law and Korsmeyer-Peppas equation. Zero order equation assumes that the cumulative amount of drug release is directly related to time.

The equation may be as follows:

$$C = k_0 t$$

Where,  $K_0$  is the zero order rate constant expressed in unit concentration/time and  $t$  is the time in hour. A graph of concentration vs time would yield a straight line with a slope equal to  $K_0$  and intercept the origin of the axes. The release behaviour of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows.

### Evaluation of pre-compressed blends

The bulk density and tapped density for all the formulations of immediate release layer the bulk density and tapped density varied from 0.454 to 0.491 and 0.498 to 0.545 respectively. The values obtained were within the acceptable range and there was no large difference noticed. The percentage compressibility of powder was determined using Carr's compressibility index. Compressibility index lies within the acceptable range of 8.84 to 10.17. All formulations showed good compressibility. The values were found to be in the range of 27.91 to 28.64. All the formulations showed angle of repose below  $30^{\circ}$  which indicates a good flow property of the blends. The values were found to be in the range of 1.10-1.11. All the formulations showed Hausner's ratio below 1.11% which indicates an excellent flow property of blends (**Table 4**).

**Table 4: Pre compression parameters of immediate release layer**

Formulation code	Angle of Repose $\pm$ S.D	Bulk density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
I <sub>1</sub>	27.95 $\pm$ 0.72	0.454	0.498	8.84	1.10
I <sub>2</sub>	27.91 $\pm$ 0.63	0.468	0.521	10.17	1.11
I <sub>3</sub>	28.64 $\pm$ 0.81	0.491	0.545	9.91	1.11

### Evaluation of Precompression parameters of Extended release layer

For all the extended release layer formulations bulk density and tapped density was found to be varied calculate the % compressibility and Hausner's ratio.

The percentage compressibility of powder was 11.74. All formulations showed good compressibility. The values of angle of repose were found to be in the range of 27.97 to 29.18. All the formulations showed angle of repose below 30° which indicates a good flow property of the blends.

from 0.465 to 0.606 and 0.518 to 0.673 respectively. The values obtained were within the acceptable range with no large difference. The result can be used to

determined using Carr's compressibility index. The values obtained were within the range of 8.71 to 10.23. The values of Hausner's Ratio were found to be in the range of 1.10-1.13. All the formulations showed hausner's ratio below 1.18% which indicates a good flow property of blends.

Formulation code	Angle of Repose $\pm$ S.D	Bulk density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
C <sub>1</sub>	28.13 $\pm$ 0.43	0.465	0.518	10.23	1.11
C <sub>2</sub>	28.33 $\pm$ 0.95	0.454	0.597	8.71	1.10
C <sub>3</sub>	29.18 $\pm$ 0.64	0.606	0.665	8.87	1.10
C <sub>4</sub>	27.97 $\pm$ 0.53	0.594	0.673	11.74	1.13
C <sub>5</sub>	53 $\pm$ 0.77	0.486	0.541	10.17	1.11

**Table 4: Pre compression parameters of extended release layer**

### Physical evaluation of tablets

Twenty tablets were randomly selected from each formulation and evaluated for uniformity of weight. The values are almost uniform and were within the USP specifications. The weights of tablets ranged from 101 $\pm$ 0.75 mg to 101.9 $\pm$ 0.64 mg. Thus all the formulations passed the test for weight variation. The thickness of tablets was determined using a calibrated dial calliper. Mean thickness (n=3) is almost uniform in all the formulations and the values obtained are from 2.49 $\pm$ 0.01 to 2.84 $\pm$ 0.02 mm. The standard deviation values indicated that all the formulations were within the range with uniform thickness. The values of hardness for

tablets are ranged from 3.78 $\pm$ 0.18 to 5.17 $\pm$ 0.17. The lower values of standard deviation indicate that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. The friability values ranged from 0.40 to 0.69. All the values are below 1% indicating that the tablets of all formulations are having good friability property. The disintegration test was performed for immediate release layer of all formulations. The disintegration time recorded for I<sub>1</sub>, I<sub>2</sub> and I<sub>3</sub> formulations was 36, 30 and 75 min respectively.

**Table 5: Physico chemical characteristics of bilayer matrix tablets**

Formulation batch code	Average weight(g) $\pm$ S.D	Hardness(kg/cm <sup>2</sup> ) $\pm$ S.D	Thickness $\pm$ S.D	Friability(%)	Disintegration time for layer (sec)
I <sub>1</sub> C <sub>1</sub>	101.4 $\pm$ 0.86	3.78 $\pm$ 0.18	2.75 $\pm$ 0.01	0.58	36 $\pm$ 1.53
I <sub>1</sub> C <sub>2</sub>	101.4 $\pm$ 1.07	4.28 $\pm$ 0.17	2.84 $\pm$ 0.02	0.69	36 $\pm$ 1.53
I <sub>1</sub> C <sub>3</sub>	101.7 $\pm$ 0.98	4.23 $\pm$ 0.18	2.49 $\pm$ 0.01	0.62	36 $\pm$ 1
I <sub>1</sub> C <sub>4</sub>	101.9 $\pm$ 0.64	5.17 $\pm$ 0.17	2.72 $\pm$ 0.01	0.54	36 $\pm$ 1.53
I <sub>1</sub> C <sub>5</sub>	101.5 $\pm$ 0.8	3.82 $\pm$ 0.12	2.61 $\pm$ 0.01	0.4	36 $\pm$ 1

### In vitro drug release study

The in-vitro study was carried out by using USP dissolution apparatus II (Paddle type). From the dissolution profile of all the extended release

formulations i.e., (C<sub>1</sub>-C<sub>5</sub>), it was found that the formulation C<sub>2</sub>, C<sub>3</sub>, C<sub>5</sub> showed drug release up to 12 hrs. In these three formulations C<sub>2</sub> showed best release profile when compared to the other

two formulations. The formulation C<sub>1</sub> and C<sub>4</sub> showed their release profile up to 11 h only. It is because of the presence of more amount of hydrophilic matrix in C<sub>1</sub> formulation. Faster release of drug from the hydrophilic matrix was probably due to gel effect, erosion effect. C<sub>4</sub> formulation released drug up to 11 hrs higher release rate because of higher fraction of ethyl cellulose is in comparison to HPMC. Due to the insufficient amount of HPMC, the gaps formed in the matrix system were not filled properly and the drug diffuses out through the cracks/pores. Formulation C<sub>2</sub> containing Ethyl cellulose (2%) and HPMC (4%) showed maximum delayed release. Possibly swelled gel of HPMC might have packed sufficiently the aforementioned cracks. The drug release of C<sub>2</sub> formulation in 2 and 12 hrs was 19.36% and 84.26% respectively. From the dissolution profile of all immediate release formulations i.e., (I<sub>1</sub>-I<sub>3</sub>), it was found that I<sub>2</sub> formulation showed faster release. It has 1% croscarmellose sodium and 4% sodium starch glycolate used in the allowable range. The drug released was 89.52% within 60 min. I<sub>1</sub> formulation showed 85.31% drug release within 60 min because of presence of less percentage of croscarmellose sodium. I<sub>3</sub> formulation showed 81.91% drug release within 60 min because of excess superdisintegrants. Comparative *in vitro* drug release pattern of immediate release layers of Simvastatin was shown in Fig 15. The extended release formulation C<sub>2</sub> and immediate release formulation I<sub>2</sub> showed best release. Hence I<sub>2</sub>C<sub>2</sub> was selected as the Optimized formulation for further studies.

### Release Kinetics

The release profiles of extended release layer of Simvastatin of all formulations were compared with zero order, first order, The data were processed for regression analysis using MS-Excel statistical functions. The data was evaluated for zero order, first order, Higuchi plot and Korsmeyer-Peppas model, the R<sup>2</sup> values obtained. The data suggested that release kinetics of Simvastatin from C<sub>1</sub> to C<sub>5</sub> follow Zero order drug

release, because the values of regression coefficient obtained for zero order release profiles are higher as compared to first order and Higuchi plot. The mechanism involved in the release of drug from polymer matrix traced by comparing the n values of formulations which obtained from Korsmeyer-Peppas model. The n values were in between the range of 0.5 to 1. The release profiles of immediate release layer of Simvastatin of all formulations were compared to zero order and first order. The data was processed for regression analysis using MS-Excel statistical functions. The data was evaluated for first order and zero order. The data suggested that release kinetics of Simvastatin from I<sub>1</sub> to I<sub>3</sub> seem to follow first order drug release because the values of regression coefficient obtained for first order release profiles are higher as compared to zero order.

### Stability Studies

The accelerated stability studies were carried out according to ICH guidelines. Optimized formulation I<sub>2</sub>C<sub>2</sub> was packed in strips of aluminum foil laminated with PVC by strip packing and this packed formulation was stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40°C and 75% RH (zone III conditions as per ICH Q<sub>1</sub> guidelines) for 3 months. The tablets were evaluated before and after one month of stabilization for the drug content, Friability, hardness, disintegration and *in vitro* release. After a period of 3 months, the samples were observed for any change in appearance of tablet and no change in the appearance of tablet was noted. The drug content of Simvastatin and Simvastatin in the formulation was found to be 94.18±0.93, 95.32±0.64 and 94.76±0.75 which showed slight decrease in drug content but statistically insignificant. The formulation I<sub>2</sub>C<sub>2</sub> was found to be stable in terms of drug content and slight decrease in hardness and increase in friability. The *In vitro* release profiles of I<sub>2</sub>C<sub>2</sub> formulation initially and after 3 months was almost comparable and there was no much difference observed. Thus the developed formulation was found to be stable at given storage conditions (Table 6).

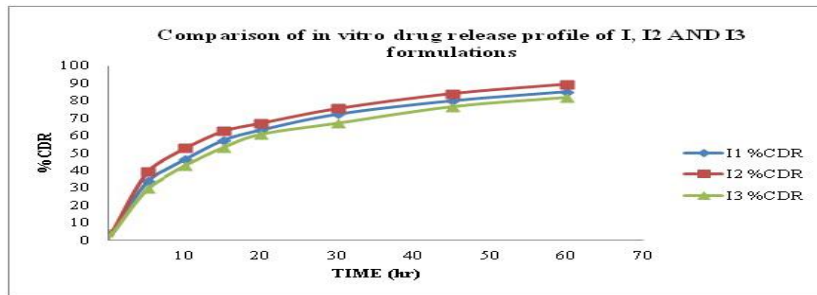


Fig. 1: Comparative In vitro drug release of immediate release layers of Simvastatin (immediate release)

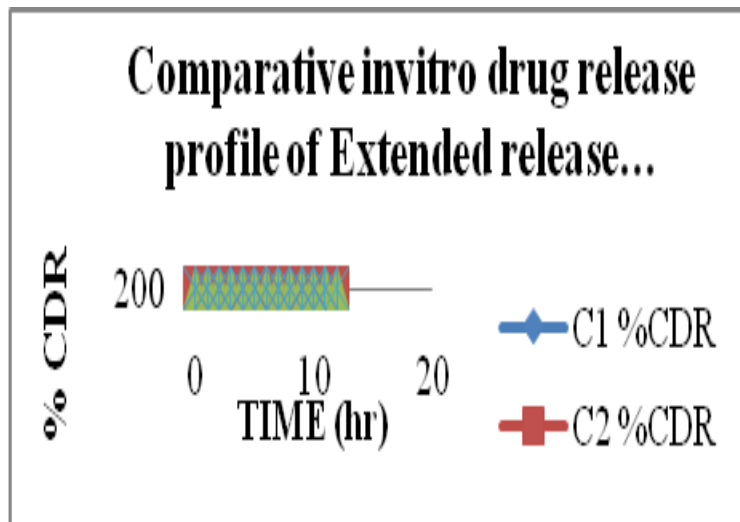


Fig. 2: Comparative In vitro drug release profile of extended release layers of Simvastatin

In- Vitro drug release profile of formulation  $C_1I_2$ ,  $C_2I_2$ ,  $C_3I_2$ ,  $C_4I_2$  and  $C_5I_2$  of stored at  $40 \pm 2^\circ\text{C}/75 \pm 5\%$  was carried out for the final formulation for the period of 12 hours. The observation showed that the formulation  $C_3I_2$  giving maximum release of drug at  $58.450 \pm 0.97$  at the end of 1 hour indicates release of drug from the immediate release layer and at the end of 12 hours the cumulated percentage of drug release observed maximum was  $96.52 \pm 1.23\%$  for the same formulation. The release of drug after 1 hour indicates release from the extended release layer.

## CONCLUSION

The data suggested that release kinetics of Simvastatin from  $C_1$  to  $C_5$  follow Zero order drug release, because the values of regression coefficient obtained for zero order release profiles are higher as compared to first order and Higuchi plot. The accelerated stability studies showed that drug content of Simvastatin and Simvastatin in the

formulation was found to be  $94.18 \pm 0.93$ ,  $95.32 \pm 0.64$  and  $94.76 \pm 0.75$  which showed slight decrease in drug content but statistically insignificant. The formulation  $I_2C_2$  was found to be stable in terms of drug content and slight decrease in hardness and increase in friability were observed. The observation showed that the formulation  $C_3I_2$  giving maximum release of drug at  $58.45 \pm 0.97$  at the end of 1 hour indicates release of drug from the immediate release layer and at the end of 12 hours the cumulated percentage of drug release observed maximum was  $96.52 \pm 1.23\%$  for the same formulation. The release of drug after 1 hour indicates release from the extended release layer. Therefore, in the present study an attempt has been made to formulate bilayer matrix tablets of sustained release Simvastatin and immediate Simvastatin layer, which can be expected to ensure patient compliance, sustained release of drug, more uniform plasma levels and less dose related side effects.

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