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ESTIMATION OF HMG-COA REDUCTASE INHIBITOR HAS CHRONOPHARMACEUTICAL DELIVERY SYSTEM *VIA* NOVEL COATING METHOD

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Keywords:

MCC, SSG, Polymer, Compressed coated method

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ABSTRACT: Introduction: The aim of the present study is to formulate and evaluate the simvastatin chronopharmaceutical delivery system using a novel coating method to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 6 h. **Observation:** Simvastatin is a hyperlipidemia drug that inhibit the synthesis of cholesterol by inhibiting the HMG-COA reductase enzyme. **Experiment:** The basic design of the system consists of a rapid release core and a controlled release coat. The powder blend was evaluated for the angle of repose, Carr's index, Hausner ratio, and compressibility index. The core tablet was evaluated for *in-vitro* release. The coated tablet was evaluated for weight variation, hardness, thickness, friability, disintegration, *in-vitro* dissolution, *in-vitro* comparative study, acid uptake test, rupture test, swelling studies, SEM, stability studies and FTIR, *etc*. **Results and Discussion:** The preformulation studies were revealed compatible results, and the rupture time, swelling time, acid uptake study showed satisfactory results by which it indicates the core molecule will be released at a prominent time period so that the availability of the drug entity has been greater base on the chronological behavior of the disease. In this study among the seven formulations, the formulations F7 shows a better drug release of 98.8% at the end of 10 h. **Conclusion:** From the above results, it concluded the release of drugs was based on disease condition, so the release and bioavailability of a drug entity will be better and constant throughout the disease condition in order to increase the level of therapy.

INTRODUCTION: Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of the oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained-release), thereby ensuring sustained therapeutic action [1]. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand the release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration.

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Such a release pattern is known as pulsatile release [2]. There are many conditions that demand pulsatile release like,

1. Many body functions follow a circadian rhythm, *e.g.,* Secretion of hormones, acid secretion in stomach, and gastric emptying.
2. Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.
3. The lag time is essential for the drugs that undergo degradation in gastric acidic medium (*e.g.,* peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
4. The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady-state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible [3].

A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independently of environmental factors like pH, enzymes, gastro-intestinal motility, *etc.* [4] These time-controlled systems can be classified as a single unit (*e.g.,* tablet or capsule) or multiple units (*e.g.,* pellets) systems. These systems are designed according to the circadian rhythm of the body [5]. The multiple unit systems like pellets or Mini-tablets are preferred for drug dosage forms because the coating of the medicated units can be formulated to trigger the release in order to comply with the release profile of a pulsatile design. Simvastatin, a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor (statin) is an antihyperlipidemic agent. Simvastatin lowers the lipid level in blood and thereby prevent cardiovascular disease [6]. It is used in the treatment of hypercholesterolemia, as it reduces levels of low-density lipoproteins and triglycerides and raises high-density lipoprotein levels. Simvastatin is a BCS class-II drug. It is very sensitive to oxidization and having a very short half-life of about 2 to 3 h.

MATERIALS: Simvastatin and ethylcellulose were procured as a gift sample from Fourrts India Pvt. limited, Chennai. Eudragit L100 and RS100 were procured as a gift sample from Madras Pharmaceuticals, Chennai. Isopropyl alcohol and Di butyl phthalate purchased from Chandan and co chemical.

METHODS:

Formulation of Core Tablets by Direct Compression: Tablets of simvastatin were made by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15 min by trituration using glass mortar and pestle. Microcrystalline cellulose was used as direct compressing agent. Sodium starch glycollate were used as disintegrating agents [7]. Magnesium stearate and Talc were used as lubricants. Tablets were compressed in minipress tablet compression machine using 6 mm round concave punches.

TABLE 1: COMPOSITION OF CORE TABLET

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Drug	30	30	30	30	30	30	30
Microcrystalline cellulose	50	50	50	50	50	100	100
Sodium starch glycollate	2	2	2	2	2	2	2
Lactose	80	45	10	60	50	10	10
Magnesium stearate	4	4	4	4	4	4	4
Talc	34	19	4	54	14	4	4

Coating of the Core Tablet:

Compression Method: Coating was made by using different pH-sensitive polymers like Eudragit S-100, L-100, ethyl cellulose. It's a novel approach to producing a coating layer over the core tablet [8]. For this accurate quantity of pH depended polymer was taken. Half the quantity of weighted polymer was placed in the die cavity. Then the core tablet was polymer was poured. Then at optimum speed, the tablet was compressed using 9 mm punch**.**

TABLE 2: POLYMER RATIO (COATING)

Polymer	F1	F2	F3	F4	F5	F6	F7
Ethyl cellulose	50	50	50	50	50	50	50
Eudragit L-100	50	100	150	-	-	-	50
Eudragit RS-100	-	-	-	50	100	150	50
Total wt	300	300	300	300	300	300	300

Evaluation:

Saturation Solubility Studies: Saturation solubility was determined by the shake-flask method. Plain simvastatin in excess quantity was placed in glass-stoppered flasks containing 10 ml of distilled water, pH 1.2, pH 6.8, pH 7.4, respectively [9]. The samples were placed in a mechanical shaker (technico, thirumudivakam) at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatman no. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 238 nm. The results were shown in **Table 7** and **Fig. 1**.

Drug-Excipient Compatibility Studies: The compatibility between drug and polymers was evaluated using Infrared spectroscopy (IR). Physical mixtures were prepared to study the effect of sample manipulation. In addition, the samples of the physical mixture were heated at 55 °C for three weeks to obtain more reliable conclusions [10]. The IR shows that all peaks are present in simvastatin spectra are present in the physical mixture. The result was shown in **Fig. 2, 3,** and **4**.

Pre-Compression Parameters:

Bulk Density: Apparent bulk density was determined by placing prepared pellets into a graduated cylinder and measuring the volume and weight as it is. That was calculated by formula

$$Db = W/Vb$$

Where, W = Weight of powder taken, Vb = bulk volume.

Tapped Density: The accurately weighed blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum. That was calculated by formula

$$Dt = W/Vt$$

Where, W = Weight of powder taken, Vt = tapped volume.

Compressibility Index: The compressibility index is a measure of the propensity of a powder to be compressed. The compressibility index is calculated using measured values for bulk density (D_b) and tapped density (D_t) as follows:

Carr's index = (Tapped density – Bulk density / Tapped density) × 100

Hausner's Ratio: Hausner's ratio was calculated by the following equation

$$\text{Hausner's ratio} = Do/Dt$$

Where, Dt = tapped density, Do = bulk density

Angle of Repose: Angle of repose was determined by using the funnel method. The accurately weighed blend was poured from the funnel that can be raised vertically until a maximum cone height h was obtained, and diameter heap d was measured. The repose angle Φ was calculated by formula.

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

Where, h = height of tip of funnel from horizontal ground surface and, r = the radius of the base of conical pile. The results were shown in **Table 8**.

Post-Compression Studies:

Friability Testing: 20 tablets were taken, it is weighed, and initial weight was noted, then it was placed into the Roche friabilator [11,] and test was performed for 4 min by using 25 rpm after that tablet were weighed and friability was calculated by using the following formula.

Percentage loss = Initial weight of tablet – final weight of tablet × 100 / Initial weight of the tablet

Weight Variation: Individually, tablets were selected randomly, and the average weight was calculated, not more than 2 tablets from this average weight should not deviate. The test was performed According to the Indian Pharmacopoeia 2010; Weight variation was calculated by using the following formula.

Percentage weight variation = Weight of single tablet – average tablet × 100 / Average weight of the tablet

Hardness Testing: The crushing strength kg/cm^2 of prepared tablets was determined for tablets by using Monsanto hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, is recorded. Average of three readings was taken and results were tabulated.

Thickness of Core Tablet: The thickness of the core tablet was measured by using Vernier calliper.

Disintegration Test for Simvastatin Coated Tablet: Disintegration test on the coated tablet of simvastatin was performed by using phosphate buffer pH.7.4, the tablets of simvastatin were taken and placed in 6 respective tubes of disintegration apparatus and disintegration time of the tablet was measured.

Drug Content: The tablet were tested for their drug content; Randomly 10 tablets were weighed and powdered. The powder equivalent to 100mg was weighed accurately and transferred to 100ml of volumetric flask, then dissolved with 5ml of methanol, then the flask is sonicated for 5 min [12]. The Volume then made up to 100ml with phosphate buffer pH 7.4. The above solution was filtered through Whatman paper, and absorbance was measured at 238nm. The results were shown in **Table 9**.

***In-vitro* Dissolution Studies of Core Tablet:** The *in-vitro* release pattern of core tablets was studied visually by taking images of the core tablets in a petridish containing dissolution medium (Phosphate buffer pH 7.4) [13] at the specific time intervals of 10 min up to 1 h. The result was shown in **Fig. 6**

***In-vitro* Dissolution Studies of Coated Tablet:** Study was performed by using pH 1.2, 6.8 and 7.4 phosphate buffers for 10 h initially 2 h in pH 1.2 (HCl) followed by 3 h in 6.8 pH and 5 h in 7.4pH, the Dissolution study was carried out at 37 °C and 50 rpm by using USP type II apparatus. 1ml sample were removed from the dissolution medium at every 1 h and diluted to 10 ml with respective pH buffer, and its absorbance was checked by using UV spectroscopy at 238 nm [14]. The results were shown in **Table 10** and **Fig. 7** and **8**.

Kinetic Studies:

Zero Order Kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$W_0 - W_t = K_0 t$$

First Order Kinetics: This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model.

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Higuchi Model:

$$Q_t = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and K_H = the Higuchi release rate

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus concentration indicates that the drug release follows strict Fickian diffusion.

For purpose of data treatment, the above equation is usually reduced to:

$$Q = Kt^{1/2}$$

Korsmeyer Peppas Model:

Korsmeyer developed a simple semi-empirical model, relating the drug release exponentially to the elapsed time (t).

$$Q_t/Q_\alpha = K_k t^n$$

The result was shown in **Table 11**.

***In-vitro* Comparative Study:**

Dissolution Studies for Innovator-1 and F7 Formulation: The dissolution study (F-7, SIMCOR) was carried out for 10 hours using USP paddle-type 2 dissolution apparatus in 0.1N HCl (pH 1.2) (900 ml) was placed in dissolution flask and allowed to obtain temperature at 37 ± 0.5 °C and 50 rpm for first 2 h followed by 3 h in 6.8 pH and 7.4 pH phosphate buffer. A 1 ml sample was collected from each vessel at every 1hr up to 10 h

and diluted to 10 ml with respective pH medium [15]. The absorbance was measured by using UV spectroscopy at 238 nm. The withdrawn sample was immediately replaced by an equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time. The results were shown in **Table 12** and **Fig. 9**.

Dissolution Studies for Innovator-2 (ZOCOR) Tablet: The dissolution test of the immediate-release tablet of simvastatin was performed by using pH 1.2 (0.1N HCl) for 1 h. The Dissolution study was carried out at 37 °C and 50 rpm by using USP type II apparatus. 1ml sample was withdrawn from the dissolution medium at the interval of 15, 30, and 60 min. then diluted to 10ml with respective pH medium [16], the absorbance was measured at 238 nm. The withdrawn sample was immediately replaced by an equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time. The results were shown in **Table 12** and **Fig. 9**.

Acid Uptake Studies: Six coated tablets were weighed individually and place in the disintegration tubes. The disintegration basket was filled with 0.1N HCl, and the test was performed up to 2 hrs in acidic medium. The tablets were removed from the disintegration basket, then dehydrated with tissue paper and take weight again. The percentage of weight gain was reported as percentage acid uptake [17]. Though during this test, the tablet was fully disintegrated; hence, it counted as 100% acid uptake. If the values <5% it suggests that the tablets would readily pass the acid phase of the delayed-release dissolution testing. The results were shown in **Table 13** and **Fig. 10**.

The % acid uptake by the tablet was calculated by the formula

$$FA = (TF\text{-}TI/TI) \times 100$$

Where; FA = Percentage of acid uptake, TF = Final weight of the coated tablet, TI = Initial weight of the coated tablet.

Rupture Test: The Rupture test on coated tablets was carried out using the USP paddle 2 apparatus. Here all other parameters were the same as *in-vitro* dissolution method [18]. The rupture time was carried out in pH- 1.2, 6.8, and 7.4. The time at which the outer coating layer starts to rupture is called lag time. This was determined by the Rupture test. The result was shown in **Fig. 11**.

Swelling Studies: The percentage swelling capacity of tablets was determined in the containers filled with 10 ml of pH 1.2 and pH 7.4 phosphate buffers [19]. Tablets were removed from containers at predetermined regular intervals, blotted with tissue paper, weighed and again placed in medium till the outer coating of the tablet started to rupture. The % swelling was calculated using the formula. The result was shown in **Table 15** and **Fig. 12** and **13**.

$$\% \text{ swelling} = ((Wt - Wo) / Wo) \times 100$$

Where Wt is the weight of the wet tablet at a time, Wo is the weight of the dry tablet.

Surface Morphology Study: The external surface morphology was evaluated by using the SEM (Sem-jeol Jsm-840, nanotechnology lab, SRM University, Katankulathur). The tablet was mounted directly on the SEM sample stub using the double-sided sticking tape and coated with gold film (thickness 200 nm) under the pressure low vacuum [20]. The voltage was used is 20KV, and the width was 3.5 mm. The result was shown in **Fig. 14**.

Accelerated Stability Studies: Accelerated stability studies were performed as per the ICH guidelines [21]. Selected formulations of simvastatin compressed coated tablets were sealed in aluminum foil cover and stored at (40 ± 2 °C / 75 ± 5 % R.H) for a period of 3 months and evaluated for physical appearance, hardness, and drug content. The result was shown in **Table 16**.

RESULTS AND DISCUSSION:

Solubility Study: Solubility studies were studied with distilled water, pH 1.2, 6.8, and 7.4. The pure drug simvastatin shows partial solubility in distilled water and shows the highest amount of solubility in pH 7.4. The results were shown in **Table 3** and **Fig. 1**.

TABLE 3: SOLUBILITY STUDY FOR PURE DRUG

Pure drug	Solubility (µg/ml)
Distilled water	1.29
pH 1.2	14.8
pH 6.8	19.6
pH 7.4	26.4

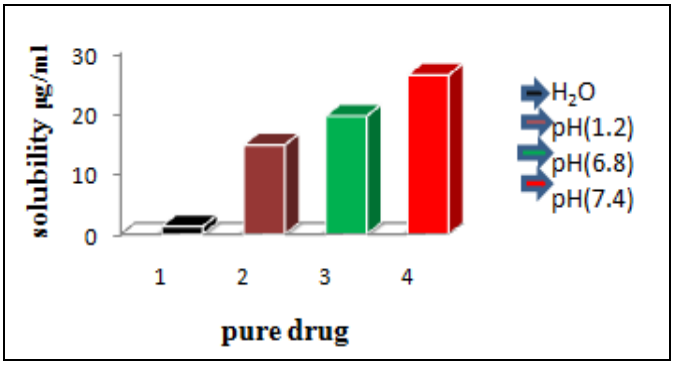


FIG. 1: SOLUBILITY STUDIES OF SIMVASTATIN IN DIFFERENT pH

Drug Excipient Compatability Study: FTIR spectroscopy was used to study the possible interactions between Simvastatin and the polymer. There is no significant difference in the FTIR spectra of pure drug and physical mixture of drug and polymer, All major peaks of Simvastatin were observed at wavenumbers 3550.31 cm^{-1} (free O–H stretching vibrations); 2960 and 2877 cm^{-1} (C–H stretching vibrations); and 17047 cm^{-1} (stretching vibration of ester and lactone carbonyl functional groups); 1267, 1166 and 1064 cm^{-1} (C-O stretching of esters and anhydrides) were retained in physical mixtures with simvastatin, which clearly indicate that no interaction exists between pure drug and polymer, it was observed that there were no changes in the main peaks in IR spectra of a mixture of drug and polymers, This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers. The results were shown in **Fig. 2, 3,** and **4**.

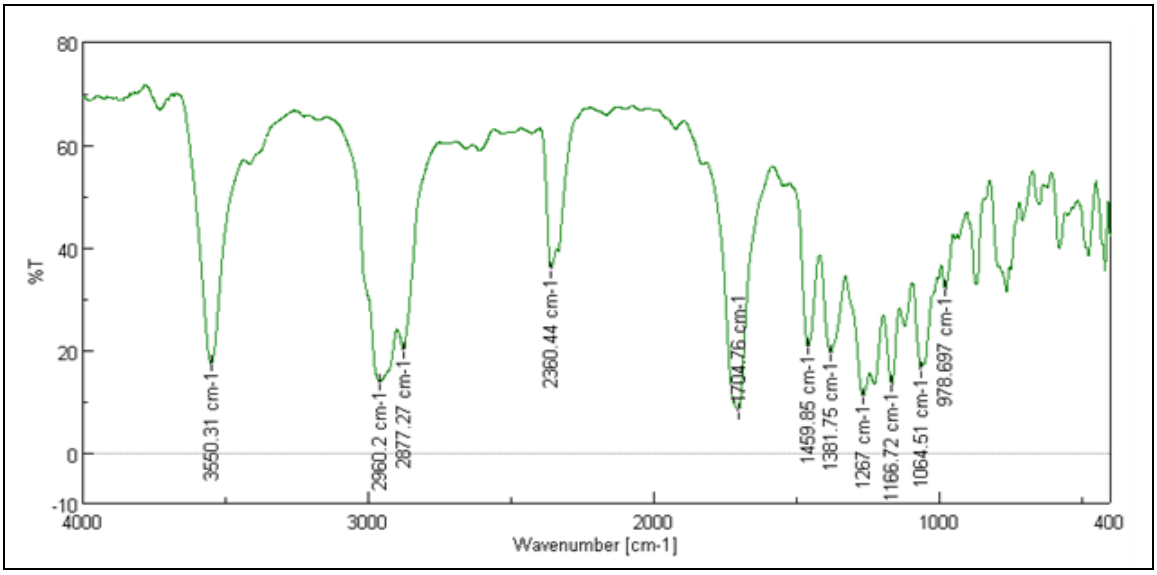


FIG 2: FTIR FOR PURE DRUG

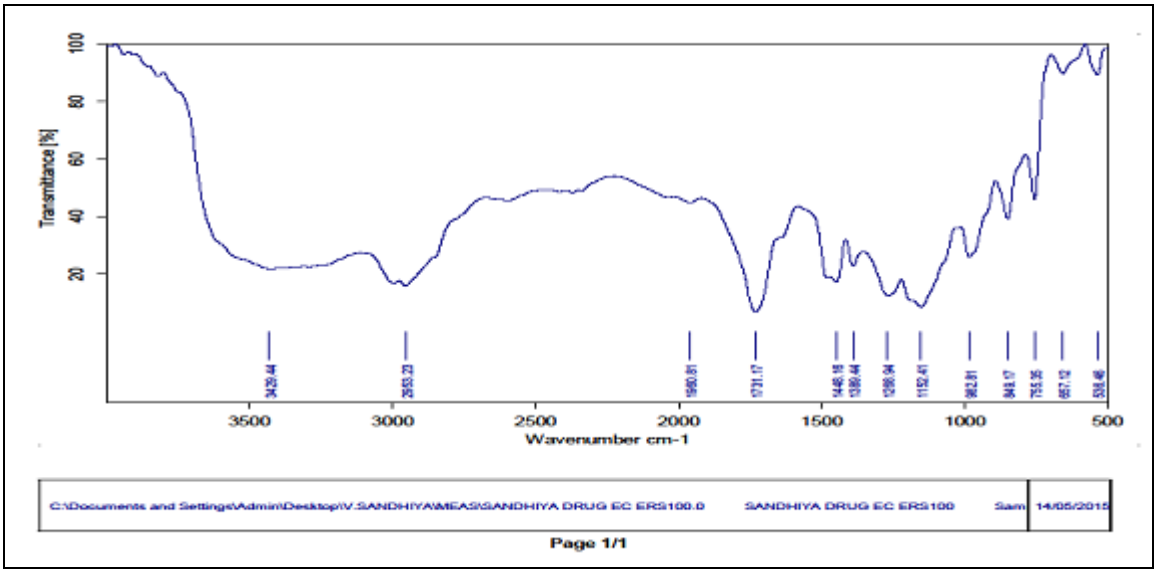


FIG. 3: FTIR FOR DRUG, EC, EUDRAGIT S 100

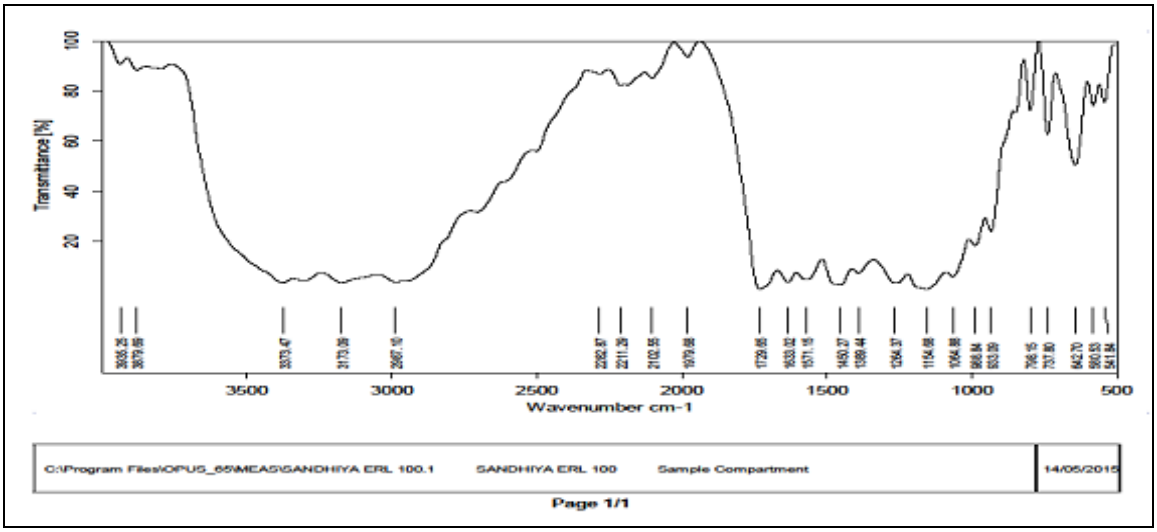


FIG. 4: FTIR FOR DRUG, EC, EUDRAGIT L-100

Pre-Compression Parameters: The blend for all the formulations F1-F7 was evaluated for bulk density, Hauser ratio, Carr's index, tapped density, and angle of repose. The value of bulk density and tapped density was within a limit from 0.2-0.3 gm/ml. The value of the Hauser ratio was found to be in the range of 1.034-1.094. The value of Carr's index was found to be 5.62 to 10.2%, and the angle of repose for all the formulations was found to be in the range of 24.23°-28.31°, which ensure good flow property. The results were shown in **Table 4**.

TABLE 4: PRECOMPRESSION PARAMETERS

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hauser's ratio	Carr's index	Angle of Repose (θ)	Formulation code	Bulk density (gm/ml)
F1	0.287±0.038	0.330±0.028	1.12±0.020	8.28± 2.16	25.92±0.4	F1	0.287±0.038
F2	0.323±0.017	0.378±0.005	1.18±0.054	14.26±1.78	24.95±0.1	F2	0.323±0.017
F3	0.292±0.010	0.330±0.015	1.16±0.040	13.79±2.37	24.56±0.10	F3	0.292±0.010
F4	0.298±0.022	0.348±0.098	1.16±0.01	13.12±1.16	23.89±0.3	F4	0.298±0.022
F5	0.301±0.014	0.367±1.018	1.18±0.020	15.21±3.42	25.17±0.1	F5	0.301±0.014

Post-Compression Parameters: All the formulation F1-F7 was evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, disintegration, *in-vitro* dissolution, swelling studies, rupture studies, acid uptake studies *etc*. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets for all the formulations was ranged between 4.93 to 5.87 kg/cm^2. The % friability for all the formulations was found to be 0.48-0.71%. The values of drug content were found to be 99.22-100.6. The values of disintegration were found to be 11.48-23.12. The results were shown in **Table 5**.

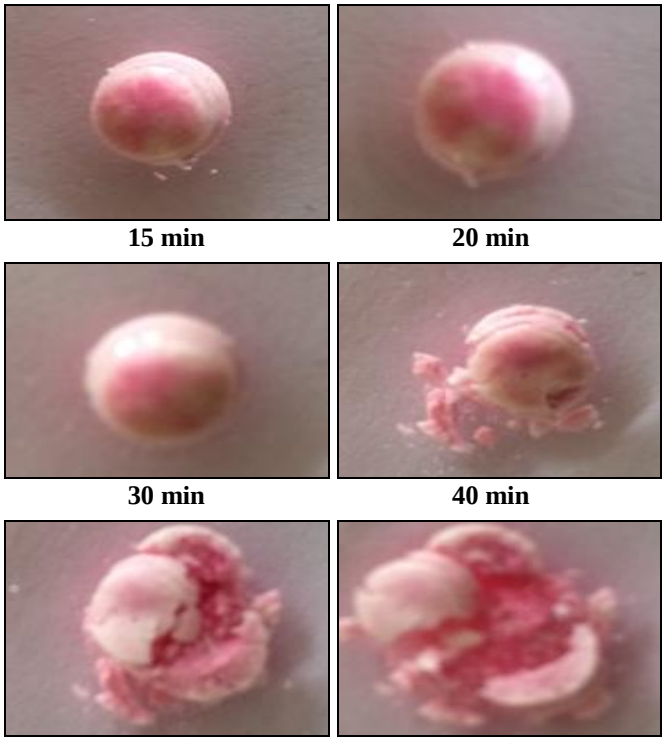
TABLE 5: POST-COMPRESSION PARAMETERS

Formulation code	Thickness (mm)	Weight variation (mg)	Hardness (Kg/cm²)	Friability (%)	% Drug content	Disintegration Time (min)
F1	4.39±0.12	299± 0.12	5.80±0.12	0.69±0.015	99.2±0.12	15.6± 0.12
F2	4.36±0.08	298±0.1	5.56±0.24	0.51±0.017	100.2±0.1	18.26± 0.1
F3	4.33±0.2	301±0.14	5.63±0.08	0.48±0.014	100.6.8±0.7	14.38± 0.2
F4	4.29±0.1	299±0.1	4.93±0.15	0.64±0.015	99.4±0.32	11.48± 0.15
F5	4.35±0.3	299±0.2	5.73±0.25	0.71±0.016	99.6±0.2	19.32± 0.1
F6	4.38±0.13	302±0.18	5.66±0.17	0.54 ± 0.02	99.7±0.16	20.54± 0.2
F7	4.38±0.11	297±0.17	5.6 ± 0.24	0.49 ± 0.2	100.5±0.18	23.12± 0.1

***In-vitro* Release of Core Tablet:** All the seven formulations of the prepared core tablet of simvastatin were subjected to *in-vitro* studies. These studies were carried out using a petri dish containing dissolution medium up to 1 h. The result was shown in **Fig. 6**.

Core tablet Coated tablet

FIG. 5: SCHEMATIC VIEW OF CORE AND COATED TABLET



15 min 20 min

30 min 40 min

50 min 60 min

FIG. 6: *IN-VITRO* RELEASE OF CORE TABLET UPTO 1 h

***In-vitro* Dissolution of Coated Tablet:** All the formulations (F1- F7) of prepared coated tablets of simvastatin were subjected to *in-vitro* release studies. These studies were carried out using USP dissolution apparatus type-II in different pH medium 1.2 for 2 h, 6.8 for 3 h, and 7.4 for 5 h.

The formulations F1, F2, and F3 were formulated with different ratios (1:1, 1:2, 1:3) of pH-sensitive polymers (Ethylcellulose, Eudragit L 100). Formulation F4, F5, and F6 were formulated with different ratios of pH-sensitive polymers (Ethyl-cellulose, Eudragit S100). F7 was formulated with a combination of Ethylcellulose, Eudragit L 100, Eudragit S100. Formulation F1 to F7 was remaining intact in pH 1.2 for 2 h. The release of drug was negligible.

Formulations F1, F2, F3 were found to be 90.5, 81.2, and 69.7% of drug release at the end of 6 to 8 hrs. For all three formulations, the lag time was found to be between 3 to 4 h; it is in the range of pH 6.8. This may be based on the solubility nature of the polymer and the concentration of the polymer used in the formulation.

The drug release for the formulations F4, F5, was found to be 81.2, 78.5% at the end of 10 h. The lag time of these formulations was found to be between 5.5-6.5 h, as the concentration of polymer increasing the lag time also increases, thereby decrease in the drug release. Though the required lag time of 6 h was obtained in F5 formulation, but the drug release was low. So, to in order to increase the release of drugs, the formulation F6 was formulated with the same ratio for formulation F5 with an increase in the concentration of microcrystalline cellulose. The drug release was found to be 89.7% at the end of 10 h.

For further increase of drug release formulation F7 was formulated with different ratio of (ethyl-cellulose, eudragit L 100, eudragit S100) the combination of these polymer shows good sustaining efficacy compared to other formulation, the % of drug release was based on the chrono-pharmacological behavior of the disease, shows 98.9% of release at the end of 10 h compared to other formulation. Which indicate the concentration of drug was more for the site of action compared to other formulation the result was shown in **Table 6** and **Fig. 7** and **8**.

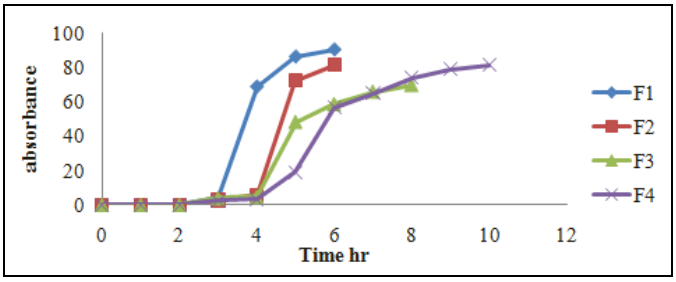


FIG. 7: *IN-VITRO* RELEASE OF F1, F2, F3, F4

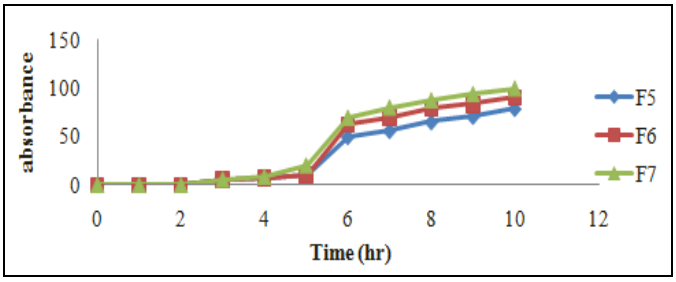


FIG. 8: *IN-VITRO* RELEASE OF F5, F6 AND F7

TABLE 6: *IN-VITRO* RELEASE OF COATED TABLET

Time (hr)	F1	F2	F3	F4	F5	F6	F7
With pH-1.2							
0	0	0	0	0	0	0	0
1	0.003±0.1	0.002±0.2	0.004±0.1	0.003±0.1	0.005±0.1	0.003±0.01	0.004±0.02
2	0.004±0.1	0.003±0.14	0.006±0.2	0.005±0.11	0.007±0.12	0.006±0.03	0.005±0.01
With pH-6.8							
3	3.92±0.2	2.67±0.1	3.74±0.13	2.28±0.13	4.9±0.11	5.3±0.1	5.63±0.14
4	68.9±0.13	5.82±0.1	4.63±0.11	3.21±0.12	7.2±0.1	7.3±0.9	8.42±0.12
5	86.4±0.2	72.4±0.2	48.2±0.1	18.8±0.1	9.6±0.2	10.2±0.06	20.1±0.11
With pH-7.4							
6	90.5±0.11	81.2±0.01	54.6±0.2	56.4±0.2	49.5±0.1	62±0.12	68.9±0.22
7	-	-	65.8±0.1	62.6±0.1	55.6±0.13	69.3±0.18	79.4±0.31
8	-	-	69.7±0.13	74.1±0.2	64.7±0.12	78.5±0.13	86.9±0.02
9	-	-	-	78.9±0.12	70.4±0.1	82.7±0.02	93.2±0.06
10	-	-	-	81.2±0.11	78.5±0.1	89.7±0.10	98.9±0.08

Kinetic Release: Drug release data of formulation F7 was best explained by the Higuchi equation, as the plot showed the highest linearity (r^2 = 0.9694), followed by zero-order equation (r^2 = 0.9111). As the drug release was best fitted in Higuchi kinetics, indicating that the rate of drug release is diffusion. The result was shown in **Table 7**.

TABLE 7: R^2 VALUE FOR FORMULATION F7

Kinetic parameter	R^2	n-value
Zero-order plot	0.9111	-
First-order plot	0.8335	-
Higuchi plot	0.9694	-
Korsmeyer Peppas plot	0.875	0.72

Further, the mechanism of drug release was found by the Korsmeyer-Peppas equation; the diffusion exponent "n" was between 0.5-1.0, which appears to indicate the mechanism is non-Fickian diffusion. And indicates that the drug release was controlled by more than one process both diffusion and dissolution.

TABLE 8: *IN-VITRO* COMPARATIVE STUDIES

Time (min)	Innovator-1	Innovator-2	F7
0	0	0	0
15	0	53.6	0
30	0	72.4	0
60	16.9	91.6	0.004
120	22.2		0.005
180	29.5		5.63
240	39.4		7.2
300	48.4		10.4
360	57.3		68.9
420	61.1		79.4
480	66.9		86.9
540	73.2		93.2
600	78.6		98.9

***In-vitro* Comparative Dissolution Studies:** The comparative study was done for best formulation (F7 and DF7) and marketed product SIMCOR, and ZOCOR. At the end of 10 h study, the formulation F7 shows 98.9% of drug release, and the formulation DF7 shows 95.2% of drug release. The marketed product SIMCOR shows 78.9% of drug release at the end of 10 h, and the marketed product ZOCOR shows 91.9% of drug release at the end of 60 min. the result was shown in **Table 8** and **Fig. 9**.

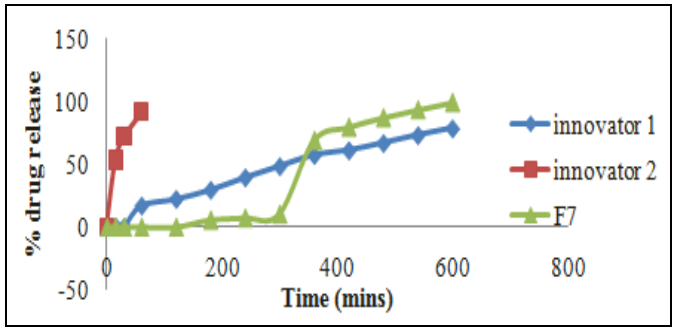


FIG. 9: *IN-VITRO* RELEASE OF INNOVATORS AND FORMULATION F7

Acid Uptake Studies: The optimized formulation of Simvastatin coated tablets (F7) with Ethylcellulose Eudragit L100-S100 were studied for acid uptake studies, to evaluate the efficiency of ethylcellulose and Eudragit L100, S100 as coating polymer to protect the acid liable simvastatin in 1.2 pH.

The results of all coated tablet formulations showed acid uptake values in the range of 0.013% which are less than 5% indicating significant protection of the drug from the acidic environment, if the values more than 5% it indicated there was 100% of water uptake, thereby ethylcellulose, Eudragit L100 and S 100 were used as coating materials. The results were shown in **Table 9** and **Fig. 10**.

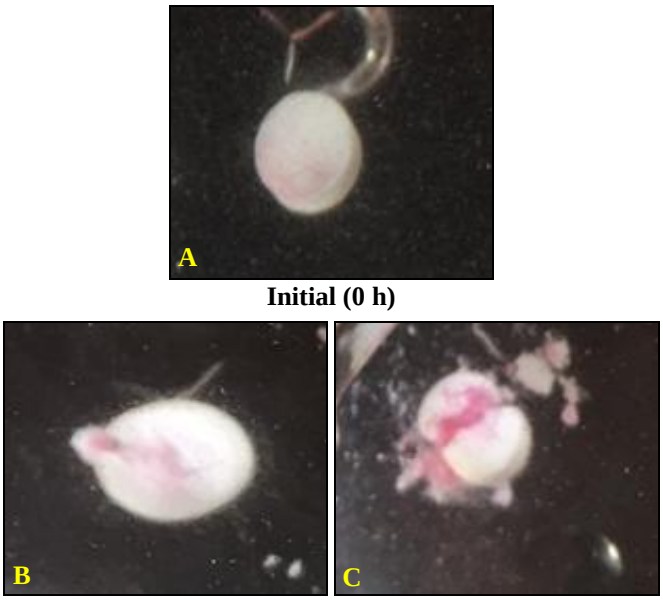
TABLE 9: ACID UPTAKE STUDY FOR OPTIMIZED FORMULA

Formulation code	Initial weight	Final weight	Percentage of acid uptake
F7	0.301	0.305	0.013

Initial (0 h) After 2 h

FIG. 10: ACID UPTAKE STUDIES

Rupture Studies: The optimized formulation F7 are subjected to rupture test, the rupture test was carried out using USP paddle 2 apparatus at 37 °C, the time at which the outer polymer coating starts to rupture is called as rupture time. The rupture time of optimized formulation F7 was found to be in a range between 4.40 to 6.14 h. It ensures there was no rupture in 1.2 pH. The result was shown in **Fig. 11**.



Initial (0 h)

4.40 h 6.14 h

FIG. 11: RUPTURE TEST FOR OPTIMIZED FORMULATION F7 IN DIFFERENT PH A) pH 1.2 B) pH 6.8 C) pH 7.4

Swelling Studies: Formulations F7 of prepared coated tablets of simvastatin were subjected to swelling studies. These studies were carried out using the watch glass. The swelling studies of the pulsatile tablet during 5 h studies were found to have very good sustaining efficacy. The percentage swelling at the end of the 5th h of formulation F7 was found to be 3.3% to 16.6% in pH 1.2 and 3.3% to 36.6% in pH 7.4. In F7 Ethylcellulose, Eudragit L 100 and S 100 in the ratio of 1:1:1 is showing sufficient swelling in 5 h. So an increase in the concentration of polymer will decrease the % water uptake capacity and increase the Lag-time. The results were shown in **Fig. 12** and **13**.

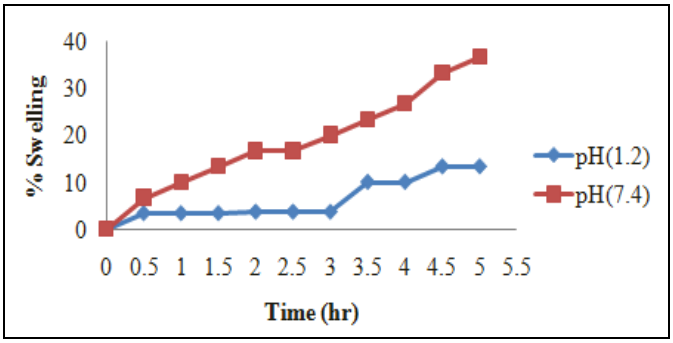


FIG. 12: PERCENTAGE SWELLING OF F7 IN DIFFERENT pH

Formulation code (F7)

After 5 h (pH-1.2) After 5 h (pH-7.4)

FIG. 13: SWELLING STUDIES IN DIFFERENT pH

Surface Morphology: The surface morphology of an optimized formulation F7 shows uniform swelling of the polymer in pH 7.4. The results were shown in **Fig. 14**.

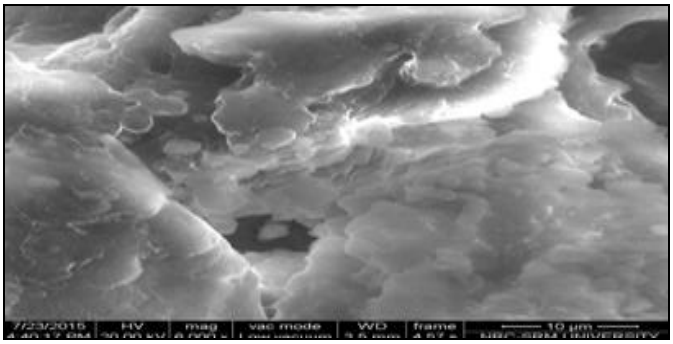


FIG. 14: SURFACE MORPHOLOGY OF F7 FORMULATION

Stability: Stability studies were carried out of the most satisfactory formulation F-7 at 40 ± 2°C / 75 ± 5 % RH for three months as per ICH guidelines.

At various time intervals of 30 days, 60 days, and 90 days end, samples were evaluated for physical appearance, hardness, % drug content, and % drug release. There was no major change in the various evaluation parameters. The results were shown in **Table 10**.

TABLE 10: STABILITY STUDIES FOR FORMULATION (F7)

Evaluation parameter	After 30 days	After 60 days	After 90 days
	F7	F7	F7
Colour and appearance	No change	No change	No change
Hardness	5.60±0.16	5.58±0.15	5.58±0.14
% drug content	100.4±0.18	100.3±0.17	100.3±0.12
% drug release	98.9±0.06	98.6±0.02	98.4±0.01

CONCLUSION: HMG-CoA reductase inhibitors, statins, reduce cholesterol levels, increased expression of LDL receptors, and decrease triacylglycerol (TAG) rich lipoproteins. Chrono-therapy with HMG-CoA reductase inhibitors has suggested that evening dosing could be more effective than morning dosing.

Chronotherapeutic treatment with immediate-release dosage forms may be unfeasible if the symptoms of the disease are pronounced during the night or early morning. Therefore, therapy with modified-release dosage forms with controlled higher drug plasma levels during the time of disease attack or incidence could be more effective treatment than with immediate-release dosage forms. Pulsatile drug delivery systems are designed to release the drug as a pulsed manner after a pre-determined lag time.

To increase the drug release at the site of action of a disease according to circadian rhyme, at the right time, the right amount. Two novel coating techniques are used. This novel techniques increase the lag time and show burst release according to the need of the pathophysiology of the disease compared to conventional tablets, thereby increasing the bioavailability.

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