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Preparation and In Vivo Evaluation of Extended Release Trilayer Matrix Tablets Containing Simvastatin Solid Dispersions

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ABSTRACT

The solid dispersion method was originally used to improve the dissolution properties and the bioavailability of poorly water soluble drugs by dispersing them into water soluble carriers. In addition to the above, dissolution retardation through solid dispersion technique using water insoluble and water swellable polymer for the development of controlled release dosage forms has become a field of interest in recent years. The objective of this present investigation was to develop extended release (ER) trilayer matrix tablets containing simvastatin solid dispersion prepared by direct compression and consisted of middle active layer with different grades of hydroxypropylmethylcellulose (HPMC), guar gum, ethyl cellulose. Upper and lower layers are prepared with Carnauba wax, guar gum and carbopol 934P. The developed drug delivery system provided prolonged drug release rates over a period of 24 h. The release profile of the optimized formulation (HF14) was described by the Zero-order and Higuchi model. In-vivo bioavailability studies were carried out with the optimized formulation (HF14) and reference standard. A fair correlation between the dissolution profile and bioavailability for the optimized formulation was observed. The results indicate that the approach used could lead to a successful development of a trilayer extended release formulation up to 24h. These results also demonstrated that the Simvastatin solid dispersion incorporated trilayer tablets shown more bioavailability because of its conversion from crystalline to amorphous form.

Keywords: Simvastatin, release order kinetics, Geomatrix, In-vivo bioavailability studies

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INTRODUCTION

Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms[1]. A number of design options are available to control or modulate drug release from a drug delivery system. Most oral controlled release dosage forms fall in the category of matrix, reservoir or multi-layer systems. Lately, multi-layer matrix systems are gaining importance in the design of oral sustained drug delivery systems. A multi-layer system consists, usually, of a hydrophilic matrix core containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (barrier-layer) applied on one or both faces of the core during tabletting[2,3,4.] The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery[5].

The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate[6,7]. In the device, the coat layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length is counter balanced by the simultaneous increase of the area available for drug release[8,9]. The use of naturally occurring biocompatible gums has been the focus of recent research activity in the design of dosage forms for oral controlled release administration, and hydrophilic polymers matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[10].

There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix. The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release[11].

Simvastatin is designated as 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro -4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester. Simvastatin is widely used in the treatment of dyslipidemia as an adjunct to diet. It is practically water insoluble crystalline compound (BCS Class II drug) and the dissolution is the rate-limiting step that controls its oral absorption[10, 11]. Therefore, improvement in solubility and dissolution rate is essential to enhance drug bioavailability[12]. Its biological half life and bioavailability are 3 h and 5% indicating

extensive first pass metabolism in liver, respectively. It is well absorbed from GIT[13, 14]; therefore, it is vital to augment its aqueous solubility, dissolution rate and bioavailability from its oral solid formulations[15, 16, 17, 18].

The main aim of the present study was to incorporate simvastatin solid dispersions to enhance it's in trilayered controlled release matrix tablets with different hydrophobic and hydrophilic polymers to achieve zero-order drug release for controlled plasma concentration.

MATERIALS AND METHOD

Materials

Simvastatin pure drug was generous gift from MSN Laboratories Ltd., Hyderabad, India. Carbopol 934P, HPMC K 4 M & HPMC K 100 M was obtained from Rubicon labs, Mumbai. Guar gum, EC and carnauba wax was gifted from Granules India Ltd, Hyderabad, India. All other chemicals used were of analytical grade.

Methods

Formulation of controlled release Simvastatin trilayer matrix tablets

The trilayered matrix tablets of Simvastatin were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90%drug release during 12hours. This layer would then be sandwiched between barrier layers (Upper & Lower layers) so as to continue the drug release for 24hours.

Preparation of middle active layer

Fourteen formulations (F1-F14) for active layer were formulated using polymers like different grades of HPMC (HPMC K4M & HPMC K100M) and Guar gum. All the formulations were varied in concentration of release retardant polymers and simvastatin solid dispersions[13], talc (1.5mg) & magnesium stearate (1.5mg) constituted in all the formulations. These materials were screened through ≠60 and mixed together in motor by using pestle. Final mixtures were compressed by using 12mm diameter flat punches on a sixteen station rotary tablet press where only one station was operative and other station were nullified Formulation F1-F14 containing drug and other polymers prepared under condition as showed in table.

Table 1: Formulation trails for active layer (F1-F7)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Simvastatin (SD equivalent to 40mg)	160	160	160	160	160	160	160
HPMC K 4 M	20	25	30	32	35	40	45
HPMC K 100M	---	---	---	----	---	----	----
Ethyl cellulose	25	23	22	21	21	20	18
Guar gum	15	15	10	12	12	09	09

Carbopol 934P	12	11	11	9	10	09	08
Dibasic calcium phosphate	15	13	14	13	09	09	07
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 2: Formulation trails for active layer (F8-F14)

Ingredients (mg)	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**
Simvastatin (SD equivalent to 40mg)	160	160	160	160	160	160	160
HPMC K 4 M	---	----	----	----	----	----	----
HPMC K 100M	35	37	35	40	40	30	47
Ethyl cellulose	10	13	12	12	14	15	11
Guar gum	16	11	09	15	9	12	9
Carbopol 934P	13	12	13	11	11	15	10
Dibasic calcium phosphate	13	14	16	09	13	15	10
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Preparation of barrier layers

The barrier layers (Upper & Lower layers) was formulated employing hydrophobic polymers Carnauba wax and Guar gum, which include water soluble DCP & EC. Composition of barrier layers was depicted in Table 3.

The procedure tried to make the compacts was via direct compressions. For the first procedure the carnauba wax, Guar gum and other polymers are mixed in mortar and lubricated with magnesium stearate. The mix is then compressed using rotary press having 12mm flat tooling.

Table 3: Composition for barrier layer of simvastatin trilayer tablets

Ingredients (mg)	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Carnauba wax	5	10	15	20	25	30	35	40
Guar gum	20	16	20	17	18	10	12	12
Ethyl cellulose	22	24	22	18	20	22	20	20
Dibasic calcium Phosphate	50	47	40	42	34	35	30	25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Formulation of Simvastatin tryilayer tablets:

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortar and pestle for about 20 minutes. Initially, the volume of die cavity (12mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (450mg). Then the pre weighed amount of powder equivalent to bottom layer (100mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and 250mg of the drug containing middle active layer optimized formulation (F14) was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre weighed (100mg) amount of powder equivalent to top layer and

compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Eight formulations were made, tri-layered matrix tablets of each composition were compressed and tested for their friability (n=6), Hardness (n=3), thickness (n=3), drug content(n=3) and drug release characteristics (n=3).

Table 4: Composition of Simvastatin trilayer matrix tablets

Ingredients (mg)	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14
Middle Layer (F14)								
Simvastatin	160	160	160	160	160	160	160	160
HPMC K 100M	50	50	50	50	50	50	50	50
Ethyl cellulose	08	08	08	08	08	08	08	08
Guar gum	10	10	10	10	10	10	10	10
Sodium CMC	10	10	10	10	10	10	10	10
Dibasic calcium phosphate	09	09	09	09	09	09	09	09
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Barrier Layer (on each side)								
Carnauba wax	5	10	15	20	25	30	35	40
Guar gum	20	16	20	17	18	10	12	12
Ethyl cellulose	22	24	22	18	20	22	20	20
Dibasic calcium Phosphate	50	47	40	42	34	35	30	25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of Simvastatin trilayer matrix tablets

Weight variation, hardness, thickness, ffriability were evaluated.

Drug content / Assay

20 tablets were accurately weighed and powdered.10mg equivalent powder was dissolved in 50ml distilled water and sonicated for 15 minutes. It was filtered and washed with distilled water. Filtrate and washings were combined. Final volume was made up to 100ml with distilled water. Absorbance of this solution was determined in a UV spectrophotometer at 247nm. Amount of Simvastatin in tablets was calculated by using regression equation.

***In-vitro* drug release profile**

In vitro drug release studies for developed Simvastatin trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900ml Phosphate buffer pH 6.8 at 37± 0.5^0C temperature. The amount of drug release was determined by UV visible spectrophotometer (Shimadzu UV 1800) at 247nm.

Drug release kinetics

To describe the kinetics of the drug release from matrix tablet, mathematical models such as Zero-order, First order and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Drug-excipient compatibility studies:

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

Ppharmacokinetic studies of Simvastatin

Animal Preparation

Male rabbits were (weighing 2-3kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25^0C, Relative Humidity 45% and 12h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and waterad libitum. The protocol of animal study was approved by the institutional animal ethics committee of CMR College of Pharmacy, Medchel. (**IAEC NO: CPCSEA/1657/IAEC/CMRCP/Ph.D-15/48**).

***In vivo* study design**

The rabbits were randomly divided into two groups each group contains six animals. The group A was received prepared Simvastatin (40mg), standard conventional tablets (40mg) was administered group B with equivalent dose of animal body weight. Blood samples (approximately 0.5ml) were obtained with syringes by marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24h post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000rpm in cooling centrifuge for 5min to 10min and stored frozen at −20°C until analysis.

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000rpm for 10min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature.

HPLC Method:

Shimadzu HPLC (Model LC-20AT contain C18 column coated with 5 micron particles), Mobile phase consists of Acetonitrile:Water:Ortho phosphoric acid at 65:35:0.1% v/v (adjusted to pH 2.8 with Ortho phosphoric acid), Flow rate - 1mL/min, Volume of injection - 20µL, Retention Time (minutes)- Simvastatin - 3.88min, Carbamazepine (internal standard) - 5.91mins. Before using the mobile phase, it was degassed by passing it through a 0.45µm filter. The mobile phase was pumped at an isocratic flow rate of 1.0mL/min at room temperature. The UV detection wavelength was set at 235nm[19].

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain C_{max}i.e., T_{max} and t ½ values, area under plasma concentration–time curve from zero to the last sampling time (AUC_{0-t}), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). $AUC_{0-t}$was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$

RESULTS AND DISCUSSION

Preparation of simvastatin active layer

The matrix tablets of Simvastatin were prepared without the barrier layers by direct compression method. All the formulation trails were subjected to *in vitro* dissolution to determine the drug release profile.

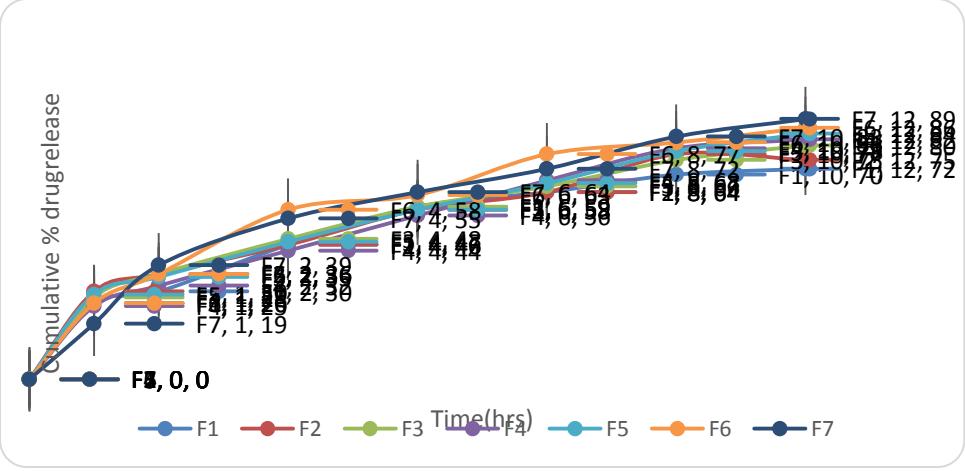

Figure 1: In vitro Dissolution profile of F1-F7 Simvastatin active layer formulations

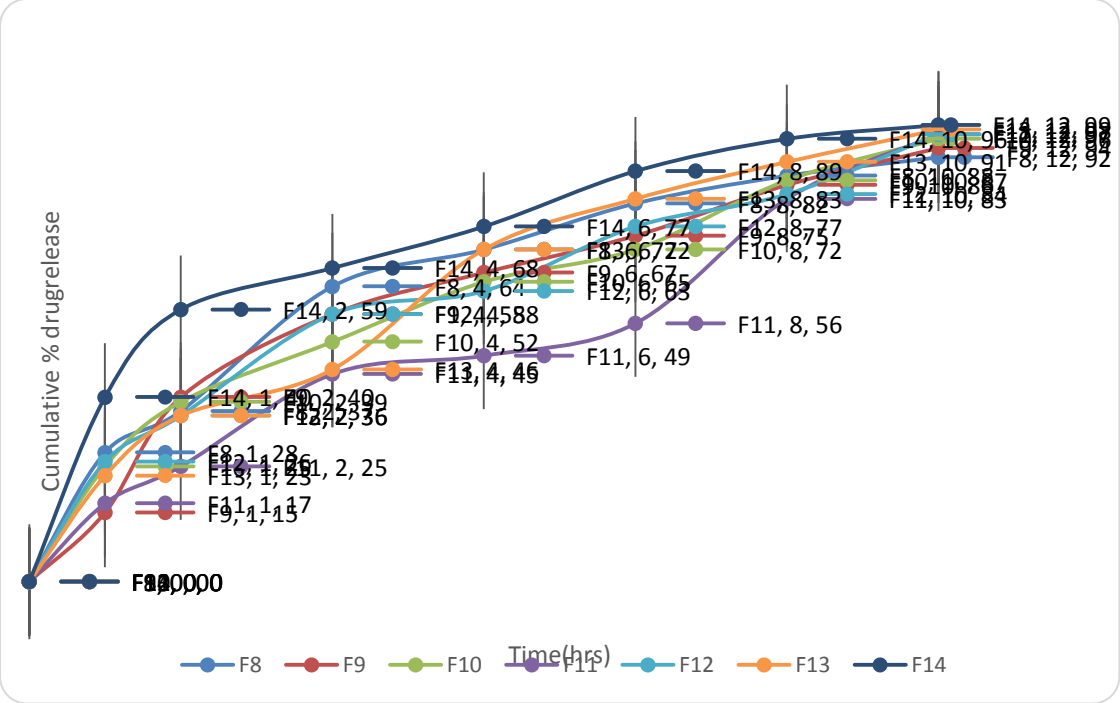

Figure 2: In vitro Dissolution profile of F8-F14 Simvastatin active layer formulations

From the above results, the formulation F14 was decided as optimized formulation based on the highest drug release i.e. 99.7±0.21 upto 12 h when compare with other formulations as active layer of the trilayer tablets.

Physical evaluation of simvastatin trilayer tablets:

The evaluation parameters of all the tablets are within the I.P limits. Hence all the tablets were subjected to in vitro dissolution test to determine the release profiles.

Table 5: In-vitro dissolution studies of Simvastatin trilayer tablets

Time(h)	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14	Marketed product
1	12.34±0.01	14.16±0.01	16.21±0.04	18.22±0.04	19.22±0.04	20.85±0.04	20.47±0.05	21.02±0.04	95.01±0.08
2	22.11±0.02	24.28±0.02	22.23±0.05	23.21±0.05	25.32±0.02	21.25±0.05	24.54±0.05	26.99±0.09	
4	32.15±0.13	33.38±0.34	34.28±0.05	36.32±0.04	36.35±0.03	37.23±0.45	38.43±0.05	39.23±0.03	
6	41.25±0.05	42.45±0.03	43.79±0.05	44.15±0.14	45.62±0.04	46.54±0.05	48.25±0.04	49.99±0.05	
8	51.16±0.19	52.98±0.094	53.23±0.05	55.42±0.08	56.32±0.05	57.15±0.04	58.45±0.02	59.99±0.07	
12	60.34±0.05	62.99±0.05	53.75±0.06	64.12±0.05	66.46±0.05	66.99±0.05	68.74±0.03	69.97±0.05	
16	69.75±0.43	72.55±0.11	73.68±0.26	75.24±0.24	76.53±0.14	78.32±0.01	78.65±0.03	79.99±0.05	
20	80.24±0.05	81.20±0.05	82.95±0.07	84.21±0.05	85.15±0.06	88.22±0.05	86.85±0.02	89.55±0.06	
24	86.12±0.04	90.24±0.03	93.45±0.01	91.22±0.02	93.55±0.04	94.24±0.04	95.25±0.02	99.06±0.29	

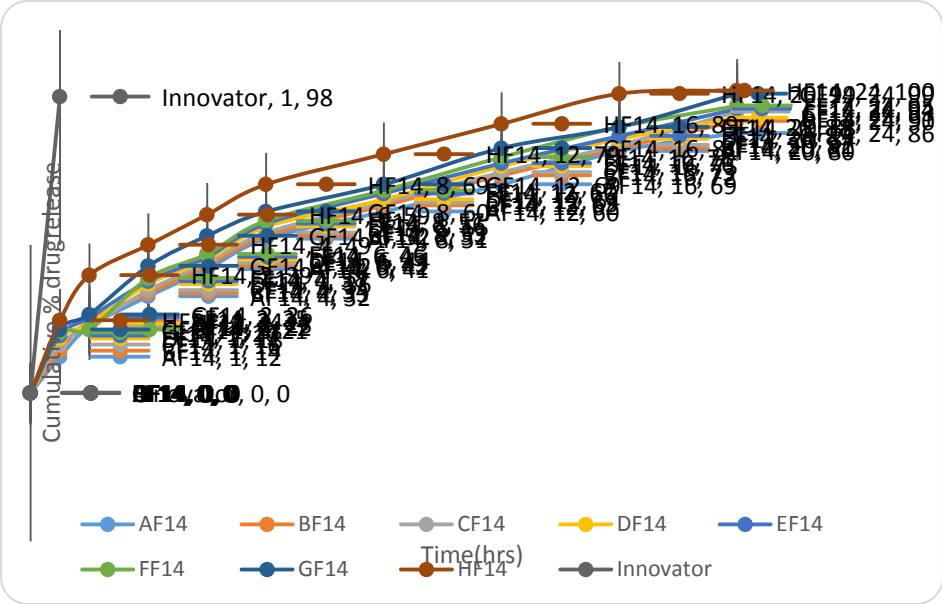

Figure 3: Comparison of Cumulative percentage drug release of Simvastatin trilayered matrix tablets and reference standard

The *In vitro* drug profile of Simvastatin from different formulations was carried and the results are depicted in Table 5 & Figure 3. The trilayer tablets extended the drug release upto 24hrs. The highest drug release was found in the formulation HF14 i.e 99.06±0.29% within 24hrs. HF14 was found to be optimized formulation based on the dissolution and other evaluation parameters. The in vitro drug release profile from reference standard conventional tablet was found to be 95.01±0.08% within 60min.

Release order kinetics of Simvastatin trilayer matrix tablets with reference standard

In the present study drug release mechanism of simvastatin trilayer matrix tablets are best fitting to zero order and Higuchi model because regression coefficient was seen closest to 1 in these models which conforms diffusion assisted mechanism of release. The reference standard release was explained by first order kinetics as the plot showed highest linearity as the drug release was best fitted in first order kinetics. The results are summarized in **Table 6.**

Table 6: Release order kinetics of Simvastatin trilayer matrix tablets with reference standard

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer Peppas R^2	Korsmeyer Peppas n value
AF14	0.972	0.864	0.942	0.975	0.558
BF14	0.980	0.863	0.947	0.976	0.604
CF14	0.984	0.867	0.951	0.981	0.573
DF14	0.982	0.865	0.949	0.979	0.634
EF14	0.985	0.868	0.952	0.982	0.598
FF14	0.987	0.869	0.954	0.983	0.721
GF14	0.989	0.870	0.955	0.985	0.719

HF14	0.993	0.870	0.957	0.987	0.695
Marketed Product	0.914	0.977	0.928	0.905	0.665

Pharmacokinetic studies:

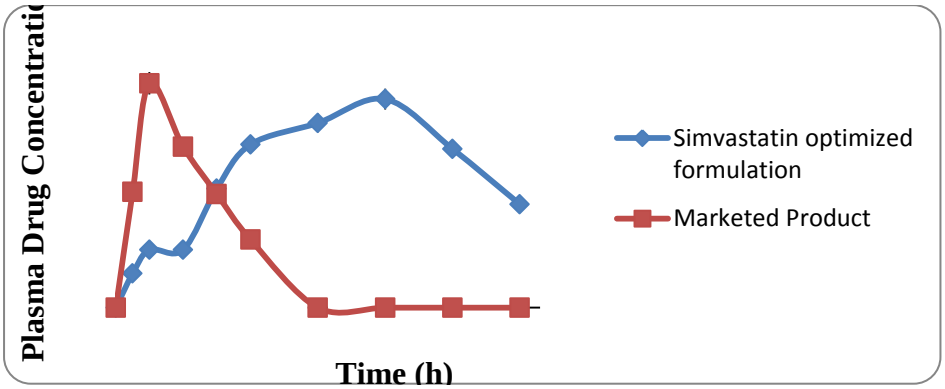

Figure 4: Plasma Concentrations of Simvastatin Optimized formulation and Innovator at different time intervals

Table 7: Comparison of pharmacokinetic parameters of Simvastatin Optimized formulation and Innovator

Parameters	Simvastatin Optimized formulation	Innovator
C_{max} (ng/ml)	144.13±0.01	178.14±0.01
AUC $_{0-t}$ (ng h/ml)	3135.65±0.12	923.25±0.02
$AUC_{0-\infty}$ (ng h/ml)	7217.75±0.14	2394.14±0.02
T_{max} (h)	8.02±0.14	1.15±0.12
$t_{1/2}$ (h)	10.5±0.014	2.50±0.05

Bioavailability Parameters

Mean plasma concentration profiles of prepared Simvastatin optimized formulation and marketed product are presented in Figure 4. Simvastatin optimized formulation exhibited as sustained release in vivo when compared with marketed tablet. All the pharmacokinetics parameters displayed in Table 7. In this study the prolonged drug absorption was achieved with the test formulation. The average peak concentration of the reference formulation was higher than that of the test (178.14±0.01ng/ml for the test formulation versus 144.13±0.01ng/ml for the reference). AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. AUC_{0-inf} for optimized formulation was higher (7217.75±0.14 ng h/ml) than the innovator 2394.14±0.02ng h/ml. Statistically, AUC_{0-t} of the optimized preparation was significantly higher ($p<0.05$) as compared to innovator. Higher amount of drug concentration in blood indicated better systemic absorption of Simvastatin from optimized formulation as compared to the innovator product.

CONCLUSION

Solid dispersion systems have been utilized during the past four decades to increase dissolution rate and bioavailability of poorly soluble drugs. In recent years in addition to dissolution rate and bioavailability enhancement great attention has been paid to use solid dispersion for the development of controlled release dosage forms. The solid dispersions have tremendous potential in the area of controlled release dosage form design because of the wide availability of a variety of carriers those are either poorly soluble or swellable in aqueous medium. All formulations displayed sustained release with the simvastatin incorporated solid dispersion trilayer matrix tablets, however three-layer tablet formulations demonstrated lower drug release compared to matrix tablets. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF14 was found to be optimized formulation. The drug release from HF14 was found to fit Zero order and best fitted to Higuchi's model confirming to be diffusion assisted mechanism. FTIR studies revealed that, there was no interaction between the drug and polymers used in the formulations. In vivo bioavailability studies were conducted for optimized formulation HF14 and reference standard. The optimized formulation of simvastatin trilayer matrix tablet was shown significant plasma concentration with controlled release and maintained for 24 hrs

REFERENCES

1. Reddy K.R, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS PharmSciTech 2003; 4(4): 1–9.
2. Conte U, Maggi L. Multi-layer tablets as drug delivery devices. Pharm Techn. 1998; 2: 18–25.
3. Chidambram N, Porter W, Flood K, Qiu Y. Formulation and characterization of new layered diffusional matrices for zero-order sustained release. J. Control. Release. 1998; 52: 149–158.
4. Efentakis M, Politis S. Comparative evaluation of various structures in polymer controlled drug delivery systems and the effect of their morphology and characteristics on drug release. Eur. Polym. J. 2006; 42:1183–1195.
5. Vishwakarma A. G , Mogal R. T, Pawar A. Y, Bi-Layer Tablet - A New Ways in Oral Drug Delivery System, International Journal of PharmTech Research 2014; 6(5), 1416-1428.
6. Conte U, Maggi L, Colombo P, La Manna A. Multi-layered hydrophilic matrices as constant release devices. J Control Rel 1993; 26: 39-47.
7. Yihong Qui, Chidambaram N, Kolette F. Design and evaluation of layered diffusional matrices for zero order sustained-release tablets. J Control Rel 1998; 51: 123-130.
8. Conte U, Maggi L. Modulation from Geomatrix multi-layer matrix tablets containing drugs

of different solubility. Biomaterials 1996; 17(9): 889-896.

9. Yihong Q, Kolette F. Design of sustained release matrix system for a highly water soluble compound ABT-089. Int J Pharm 1997; 157: 46-52.
10. Tobyn MJ, Stani forth JN, Baichwal AR, Mc Call TW. Prediction of physical properties of a novel polysaccharide controlled release system. Int J Pharm 1996; 128: 113-22.
11. Praveen Kumar T, Pallavi Y, Deepthi K, Narayana Raju P. Formulation and evaluation of Entacapone sustained release matrix tablets. The Pharma Innovation 2014; 3(8): 80-88.
12. Abhijith S, Amrish C. Formulation and Evaluation of Pulsatile Tablet in Capsule Device. IJPPS 2013; 5(2): 125-129.
13. Balakrishnaiah M, Rama Mohan Gupta V. Enhancement of solubility and dissolution rate of Simvastatin by solvent evaporation technique. Der Pharmacia Lettre 2016; 8 (7): 94-104.
14. Jyothirmai B, Satyadev T, Santosh T, Syama Sundar B. Development and Validation of an RP-HPLC Method for the Determination of Simvastatin in Human Plasma. IJRPC 2014; 4(2): 457-466.
15. Kang B. K, Lee J. S, Chon S. K, Jeong S. Y, Yuk S. H, Khang G, Lee B. H, Cho S. H. Development of self micro emulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of Simvastatin in beagle dogs. Int. J. Pharm 2004; 274 (1–2): 65–73.
16. Ambike, A. A, Mahadik, K. R, Paradkar A. Spray-Dried Amorphous Solid Dispersions of Simvastatin, a Low Tg Drug; In Vitro and In Vivo Evaluations. Pharm. Res. 2005; *22* (6): 990–998.
17. Prasad Tandale, Dipti Joshi, Gaud RS. Formulation and Evaluation of Extended Release Solid Dispersions Conatining Simvastatin. Asian J Biom Pharma Sci 2011; 1(3): 13-19.
18. Uekama K, Hirayama F, Irie T. Cyclodextrin Drug Carrier Systems Chem. Rev 1998; 2045.
19. Venkateshwarlu E, Satish Kumar P, Sainath Reddy K, Sharvana Bhava Bandaru S, Suresh Reddy G. Determination of Simvastatin and Diltiazem in Rat's Plasma by HPLC and Pharmacokinetic Studies, Int. J. Pharm. Sci. Rev. Res 2013; 21(1): 53-56