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FORMULATION AND IN-VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF SIMVASTATIN USING TAMARIND SEED POLYSACCHARIDE AS RELEASE MODIFIER

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ABSTRACT

The present study was aimed to develop sustained release matrix tablets of Simvastatin using tamarind seed polysaccharide as a matrix forming hydrophilic polymer. Simvastatin is an anti-hyperlipedaemic drug with short half life (t1/2) of 3hrs and usually oral dosage regimen (5-40mg) taken to 4 times a day. To reduce the frequency of administration and also to improve the patient compliance, sustained release formulation of Simvastatin is desirable. The Simvastatin matrix tablets were prepared by wet granulation method using tamarind seed polysaccharide as release retardant. Six formulations of different drug: polymer concentrations were formulated. First three formulations contain drug with tamarind seed polysaccharide and other three formulations contains drug with polymer combination of TSP: HPMC K100M -F1 (1:1), F2 (1:2), F3 (1:3) F4 (1:1), F5 (1:2) and F6 (1:3).

Simvastatin sustained release matrix tablets are evaluated for pre-compression parameters and post-compression parameters; all the parameters were found to be within the limits. The dissolution studies were performed using USP apparatus type-II in 0.1NHCl (2 hours) and pH 6.8 phosphate buffer (10 hours) as dissolution medium for 12 hours. These studies showed that formulation F3 consisting of drug: polymer in the ratio of 1:3 was found to sustain the release of Simvastatin over a period of 12hrs.The optimized formulation was subjected to different kinetic models including zero order, first order, Higuchi model and Korsmeyer peppas model. The final optimized formulation F3 was subjected to Stability studies for 3 months according to ICH guidelines.

KEYWORDS: Simvastatin, Sustained release, Tamarind seed polysaccharide.

INTRODUCTION

Oral drug delivery system has been known for decades as it is the most widely utilized route of administration explored for the systemic delivery of drugs. The traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug that may lead to the risk of dose fluctuation, this arises the need of a formulation that control the drug release and maintain a near-constant or uniform blood plasma level.

Sustained release drug delivery systems are designed to achieve prolong therapeutic effect by continuously releasing medicament over an extended period of time after administration of single dose.[4] Natural polymers are much safer than synthetic, they provide many applications in the formulation development of a sustained release dosage form such as binder, release modifier, and because of the ease availability at an affordable price, high safety margin and higher productivity can be used in the formulation development of sustained release dosage form.

Hydrophilic polymer matrix systems are widely used in sustained release drug delivery systems because of their flexibility to obtain a desirable drug release. Hence, the present study is to enhance the use of natural polymer as release modifier to develop Simvastatin sustained release matrix tablets. Simvastatin is an anti-hyperlipedaemic drug with short half life (t1/2) and usually oral dosage regimen (5-40 mg) to be taken 4 times a day. To reduce the frequency of administration and also to improve the patient compliance, sustained release formulation of Simvastatin is desirable.

The main aim of the work is to evaluate the prolonged drug dissolution profiles by changing the concentration of polymer matrix systems in order to reduce the frequency of administration and to improve patient compliance.

MATERIALS AND METHODS

Materials

Simvastatin was obtained as a gift sample from Hetero drugs Pvt.Ltd, Hyderabad. Tamarind seed polysaccharide was extracted from tamarind seeds (*Tamarindus indica).*HPMCK100M, microcrystalline cellulose, magnesium stearate and talc from Finar chemicals (LR).

METHODS

Drug-Excipient compatibility studies

The compatibility studies were performed using Fourier transform-Infra Red Spectrophotometer (Bruker-Alpha). The spectrums of drug and drug-Excipients were taken with the accumulation of 24 scans and a resolution of 4cm^{-1} over the range of 400-4000 cm^{-1}.

UV Spectrophotometric method for Simvastatin

Simvastatin was analyzed by SCHIMADZU UV-1800 Spectrophotometer having double beam detector configuration. Calibration curve (standard graph) of Simvastatin was plotted in 0.1N HCl and Phosphate buffer pH 6.8.

Formulation development

Preparation of Simvastatin matrix tablets

All the matrix tablets each containing 40mg of Simvastatin were prepared by wet granulation method.

METHOD[1]

Accurately weighed quantity of Simvastatin, Tamarind seed polysaccharide and Micro crystalline cellulose were taken in mortar and were mixed geometrically. Sufficient quantity of distilled water was added to prepare wet mass and was passed through a # 22 mesh sieve. Then the granules were dried at 40°c and dried granules were again screened using (14-20# screens). Granules were lubricated with talc (1%) and magnesium stearate (1%) and compressed into tablets on a rotary punching machine.

Formulations

Table1: Formulation Series of Simvastatin Sustained Release Matrix Tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6
Simvastatin	40	40	40	40	40	40
Tamarind seed polysaccharide	40	80	120	20	40	60
HPMC K 100M	-	-	-	20	40	60
Micro crystalline cellulose	165	125	85	165	125	85
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Distilled water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	250	250	250	250	250	250

Evaluation of tablet

1. Pre-compression evaluation (evaluation of granules)
2. Post-compression evaluation (evaluation of compressed tablets).

Pre compression evaluation (evaluation of granules)

Bulk Density

The bulk density was determined by transferring the accurately weighed sample of powder to the graduated measuring cylinder. The initial volume and weight was noted. Ratio of weight of the sample to volume was calculated by using the following formula.

Bulk density = Mass/initial Volume

Tapped Density

Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (100). The final volume after 100 tapings was noted. The tapped density was determined by the following formula.

Tapped density = Mass/Tapped Volume

Percentage Compressibility (or) Carr's index (%)

It is directly related to flow rate, cohesiveness and particle size. Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

Hausner's Ratio

It indicates the flow properties of powder and is measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density/Bulk density.

Angle of Repose [6]

It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal. Angle of repose was determined by the fixed funnel and free standing cone method .The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of powder. The obtained granules were allowed to flow through the funnel freely onto the surface.

Angle of repose (Θ) = $\tan^{-1}$ (h/r)

Where, h = height and r = radius.

Evaluation of tablets

Official and unofficial tests

Official Tests: Weight variation, disintegration, dissolution, drug content.

Non-Official Tests: Hardness, Friability and Thickness**.**

Non –official tests

Thickness

It can be dimensionally described & controlled. Tablet thickness can be measured by using digital Vernier caliper. Tablet thickness should be controlled within a range of ±5% variation of standard value.

Hardness [7]

Tablet hardness can be defined as the force required breaking a tablet in a diametric compression. In this test the tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Generally used Hardness testers are: Monsanto Tester, Strong-Cobb Tester, Pfizer Tester, Erweka Tester, and Schleuniger Tester.

Friability [7]

The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. This consist of a plastic chamber that revolves at 25rpm, dropping the tablets through a Distance of six inches in the friabilator, which is then operate for 100 revolutions. The tablets are reweighed.

$$\text{Friability (\% loss)} = \frac{(W1 - W2)}{W1} * 100$$

Where,

W1 = Initial weight of the 20 tablets.

W2 = Final weight of the 20 tablets after testing.

Official Tests

Weight Variation test

Take 20 tablets and weigh individually. Calculate average weight and compare the individual tablet weight to the average weight. According to IP 1996, out of twenty tablets ±5 % variation can be allowed for not more than two tablets. According to USP 2004, ±5% weight variation can be allowed for not more than two tablets out of twenty tablets. Percent weight variation was calculated as follows. Average weights of the tablets were calculated.

Percentage deviation = $[(W_{avg}) – (W_{Initial}) / (W_{avg})] \times 100$

Where,

W_{avg} = Average weight of tablets,

$W_{Initial}$ = Individual weight of tablet.

Table 5: Weight Variation Limits

Average Tablet Weight	Percentage Deviation
Up to 80 mg	±10%
More than 80mg, Less than 250mg.	±7.5%
250mg or more	±5%

Content Uniformity Test

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10^{th} tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

In vitro Dissolution Studies[2, 3]

In vitro dissolution studies were performed using USP- II (paddle) dissolution apparatus at 50 rpm. The dissolution study was carried out for 12 hours. 900 ml of 0.1NHCl was used as dissolution medium for 2hours and then the rest of the 10 hours the dissolution was performed in phosphate buffer pH 6.8 maintained at 37±0.5ºC. An aliquot (5ml) was withdrawn at specific time intervals and was replaced by the buffers and drug content was determined by UV-visible spectrometer at 238.50 and 238.8nm.

Kinetic studies[2, 3]

In order to analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate equation describes the systems where the drug release rate is independent of its concentration. The first order equation describes the release from system where release rate is concentration dependent. Higuchi model describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.Korsmeyer Peppas model is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

The following plots were made from the in-vitro drug release data

1. Cumulative %drug release vs. time (zero order kinetic model);

2. Log Cumulative %drug remaining vs. time (First order kinetic model);

3. Cumulative %drug release vs. Square root of time (Higuchi model);

4. Log cumulative of %drug release vs.log time (Korsmeyer peppas).

Stability studies

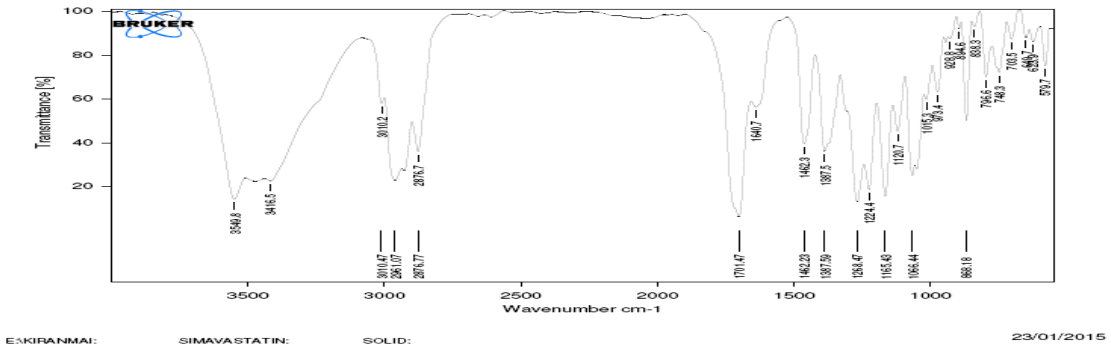
The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). Stability studies of optimized formula of sustained release matrix tablets were carried out by storing the formulation at 40 ^{o}C and 75%RH for 3 months in stability chamber.

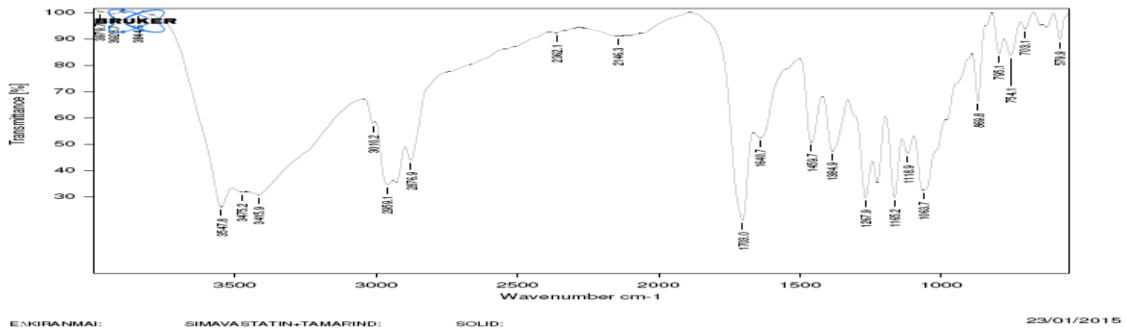
RESULTS AND DISCUSSIONS

Fourier Transformation Infra-red (FTIR) analysis

Table 6: FTIR spectrum analysis

S.No.	Frequency, cm-1	bond	Functional group	Pure drug (Simvastatin)	Drug+ TSP	Optimized formula(F3)
1	3100-3000	=CH-stretch	Alkenes	3010.2	3010.7	3012.0
2	1710-1665	C=O stretch	α,βunsaturated aldehyde	1701.4	1703.0	1694
3	900-675	C-H	Aromatics	868.10	869.3	868
4	1470-1450	C-H bend	Alkanes	1462.5	1461.5	1464.9
5	1320-1000	C-O stretch	Alcohols, ester, ethers.	1268.47	1268.2	1268.7





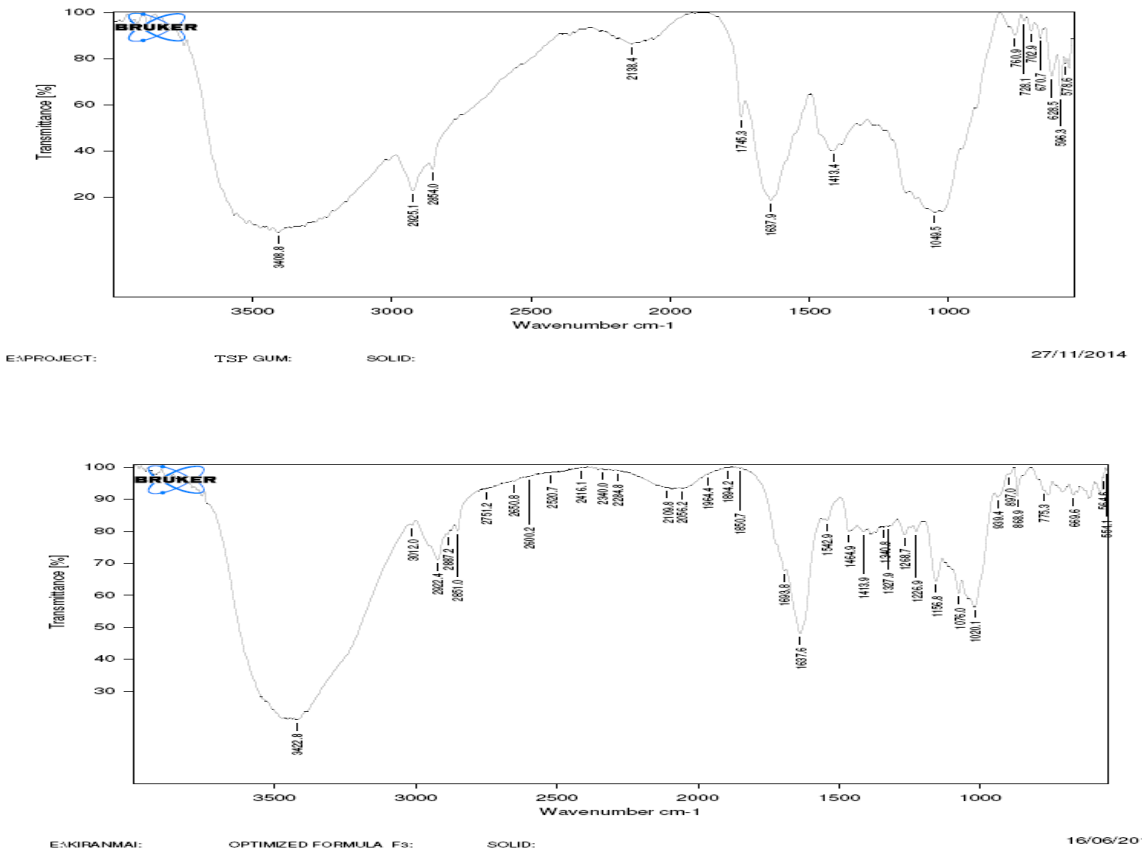


Figure-1: FT-IR spectrum of A- Pure drug; B- Drug+tamarind seed Polysaccharide; C- Tamarind seed polysaccharide; D- Optimized formula.

The FT-IR spectrum of pure drugs Simvastatin and FTIR spectra of drug with the optimized formulation showed that there is a negligible difference in the position of characteristics of absorption bands of the functional groups of the drug and the drug has remained in its normal form even when the formulation was prepared, without undergoing any chemical interaction with the polymers and other excipients used. Thus, it is clear from FT-IR study that there is no interaction of the drug with the polymer.

Ultraviolet Visible (UV-visible) spectroscopy

Preparation of calibration curve in 0.1N HCl:

Table 7: Concentration and Absorbance Values for Simvastatin in 0.1N HCl

Concentration	Absorbance
2ppm	0.138
4ppm	0.257
6ppm	0.376
8ppm	0.487
10ppm	0.618

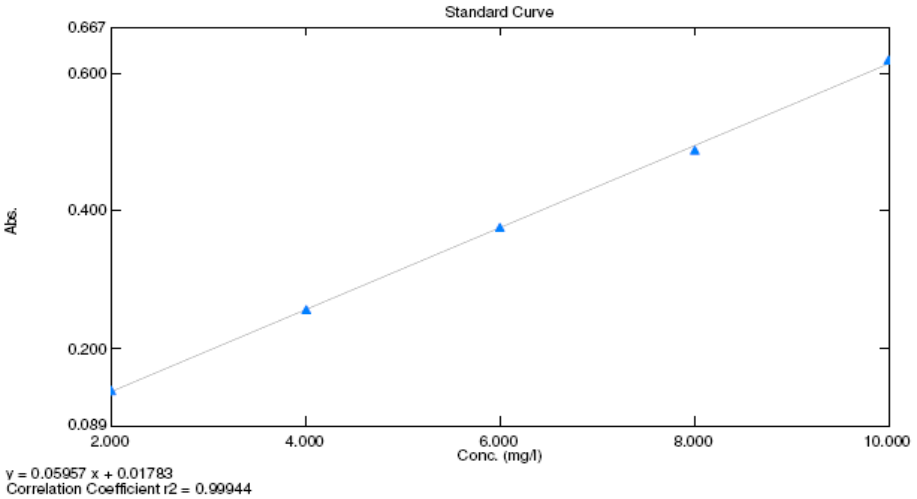


Figure-2: Standard graph of Simvastatin in 0.1 N HCl

Calibration curve of Simvastatin in pH 6.8 phosphate buffer

Table8: Concentration and Absorbance values of Simvastatin in pH 6.8 phosphate Buffer

Concentration (ppm)	Absorbance
2	0.117
4	0.164
6	0.218
8	0.263
10	0.310

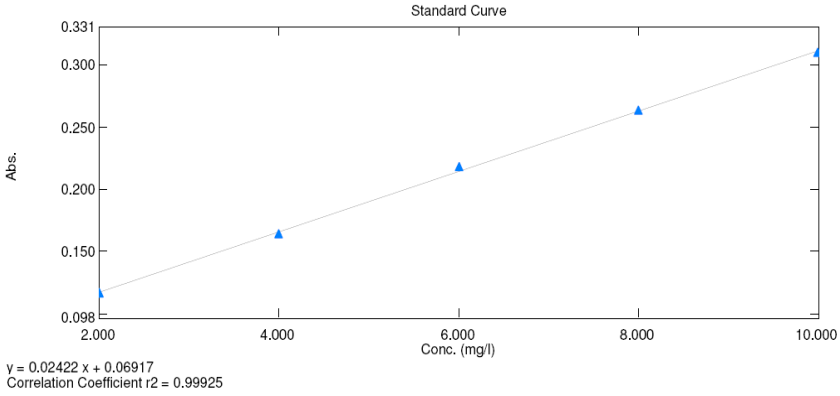


Figure-3: Standard graph of Simvastatin in pH 6.8 Phosphate Buffer

Standard curve of Simvastatin in 0.1 N HCl was plotted as shown in Table7 & Figure 2.Wavelength of maximum absorption was found to be 238.50nm. The drug sample obeyed the Lambert-Beer's law in concentration range of 2-10µg/ml with R^2 value 0.999.Standard curve of Simvastatin in Phosphate Buffer (pH 6.8) was also plotted as shown in Table 8 &

Figure 3. Wavelength of maximum absorption was found to be 238.80nm. The drug sample obeyed the Lambert-Beer's law in concentration range of 2-10µg/ml with R^2 value 0.999.

Evaluation of Pre-compression Blend

Table 9: Flow properties of Pre-compression Blend

Formulation (F)	Angle of repose(Ɵ)	Bulk density (gm / cm3)	Tapped density (gm / cm3)	Hausner's ratio	Compressibility index(%)
F-1	25°20´±0.43	0.35	0.42±0.004	1.2±0.011	16.4±0.8
F-2	22°65´±0.29	0.36±0.003	0.42±0.004	1.14±0.001	12.7±0.1
F-3	23°71´±0.24	0.35±0.003	0.44±0.004	1.2±0.011	18.1±0.74
F-4	23°64´±0.31	0.44±0.008	0.47±0.009	1.08±0.001	7.7±0.13
F-5	25°40´±0.38	0.33±0.002	0.36±0.006	1.1±0.01	8.8±0.8
F-6	23°65´±0.13	0.33±0.002	0.39±0.003	1.2±0.002	16.8±0.12

Mean ± SD, n = 6

The pre-compression blend for matrix tablets were characterized with respect to angle of repose, Hausner's ratio, compressibility index and all parameters were within the limits indicating good flow property for all batches.

Evaluation of Simvastatin Sustained Release Matrix Tablets

Table10: Evaluation parameters of Simvastatin Matrix Tablets

Formulation (F)	Hardness (kg/cm2)	Thickness (mm)	Friability (% w/w)	Content uniformity (%)	Weight variation	
					Average weight(mg)	Percentage deviation (%)
F-1	3.9±0.13	4.01±0.07	0.78±0.02	97.95±0.5	250.3±1.2	0.13±0.54
F-2	4±0.06	4.09±0.09	0.64±0.04	100±0.44	249±0.9	-0.40±0.4
F-3	4.01±0.11	4.07±0.12	0.54±0.01	99.34±0.51	250.6±0.6	0.24±0.25
F-4	3.7±0.19	3.99±0.09	0.81±0.03	98.18±0.28	250.3±1.7	0.13±0.74
F-5	3.86±0.10	4.09±0.09	0.75±0.03	99.5±0.44	249.6±1.9	-0.14±0.83
F-6	3.9±0.08	4.07±0.14	0.80±0.01	99.05±0.43	250.3±1.2	0.13±0.54

Mean ± SD, n = 6

All the tablets of six batches complied with official requirements of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.5-4.5 kg/cm² and the friability values were less than 1% indicating that the tablets were compact.

The thickness of the tablets ranged from 3.5-4.5mm.All the formulations showed the content of drug ranged from 90-100% of Simvastatin and good uniformity of drug content was observed. Hence, all the quality control parameters of the Simvastatin sustained release matrix tablets were found to be within limits.

In vitro drug release study

Table 11: Percentage drug release of Six Formulations in 12 Hours

Time	F-1	F-2	F-3	F-4	F-5	F-6
0	0	0	0	0	0	0
1	5.17±2.08	3.15±0.13	1.35±0.13	5.51±0.35	4.27±0.37	2.02±0.39
2	5.51±1.65	3.37±0.27	1.8±0.15	6.75±0.37	4.83±0.2	2.58±0.46
3	24.75±2.27	22.05±1.17	14.06±1.5	30.93±2.32	29.02±0.95	21.37±0.30
4	42.41±2.35	30.93±3.12	27.22±2.1	56.25±3.94	44.88±3.83	29.81±3.00
5	60.75±2.9	52.31±3.61	33.63±2.5	82.35±3.55	55.12±2.47	44.55±2.41
6	73.35±2.51	60.75±3.05	40.38±3.2	93.48±3.65	57.82±2.25	50.96±2.41
7	77.4±4.29	68.17±3.21	54.67±3.6	-	67.83±1.18	62.55±3.57
8	88.98±1.91	81.9±3.55	63.22±3.00	-	80.43±1.19	74.13±4.10
9	97.87±1.58	89.88±0.61	73.46±2.61	-	88.87±1.01	81.33±2.5
10	-	96.07±1.30	81.9±2.00	-	99±0.89	89.88±1.5
11	-	-	89.88±2.71	-	-	95.62±2.75
12	-	-	97.31±1.5	-	-	-

Mean ±SD, n=6

Comparative In-Vitro Dissolution Profiles of Formulations (F1-F6)

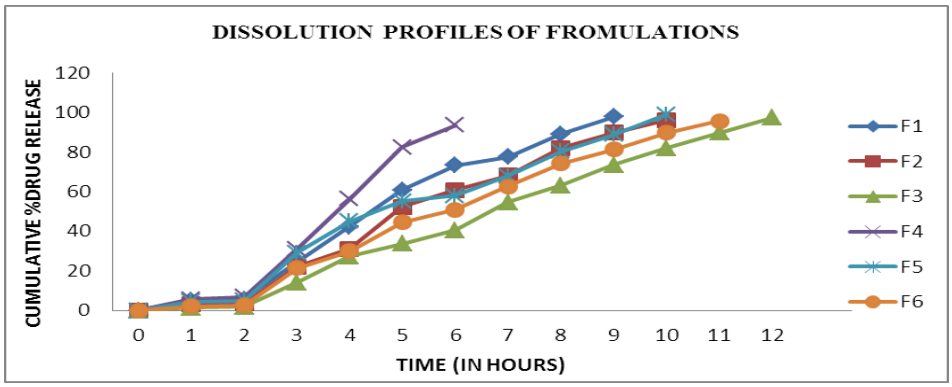


Figure-4: Dissolution Profiles of Formulations F1, F2, F3, F4, F5 and F6

After performing the dissolution studies for F1-F6 formulations, F3 formulation showed 97.3% drug release after 12 hours. Among all the formulations F3 shows the better release pattern compared to other formulations.

Kinetic models for an optimized formulation

Table 12-Drug Release Kinetic Parameters

S.No	Kinetic model	R^2	n(slope)
1	Zero order	0.925	6.923
2	First order	0.810	-0.107
3	Higuchi plot	0.925	6.923
4	Korsmeyer-peppas plot	0.818	0.169

R^2=Correlation coefficient

To know the drug release kinetics from these formulations, the dissolution data were subjected to different kinetic model such as Zero order, First order and Higuchi model and Korsmeyer-Peppas model. The line of equations and regression coefficient of kinetic study for optimized formulation are shown in table 29. The regression coefficient was considered as main parameter to interpret release kinetics. From the results obtained it is clear that the optimized formula follows zero order and Higuchi model.

Stability studies

Table 13: Stability studies of optimized formulation (F3)

S.No	Parameters	Initial	After one month	After three months
1	Thickness(mm)	4.15±0.02	4.13±0.01	4.12±0.01
2	Hardness(kg/cm^2)	04±0.2	04±0.13	04±0.15
3	Friability(%W/V)	0.52±0.015	0.53±0.02	0.51±0.01
4	Weight variation(mg)	249.8±0.6	249.9±0.5	249.57±0.7
5	Content uniformity (%)	99.02±0.57	99.03±0.45	99.04±0.54
6	Percentage drug release (%)	97.31±1.5	97.1±1.2	97.4±1.25

After conducting Stability studies for formulation F3 at 40°C and 75%RH for 3 months, no much variation were found in evaluation parameters of the optimized formula (F3).Hence, the formulation was found to be stable.

CONCLUSION

It was concluded that the sustained release matrix tablets of Simvastatin were successfully developed in order to sustain the drug release rate by using tamarind seed polysaccharide as release retardant. Six formulations are prepared using different polymer percentages and various evaluation parameters like Angle of repose, Bulk density, Tapped density, Hausner's ratio, hardness, friability, weight variation, drug content and drug release of the formulations were found to be satisfactory. Among all the formulations F3 shows the better release pattern compared to other formulations evident from dissolution studies. Formulation F3 releases 3.37% of drug in the first one hour IN 0.1N HCl and after 2 hours in acid buffer prolongs the release of remaining drug up to 12 hours in phosphate buffer pH 6.8,whereas other formulations do not prolong the release up to 12 hours. Hence considering the dissolution studies and all other evaluation parameters formulation F3 was considered as an optimized formulation and the optimized drug release after 12 hours was found to be 97.31%. After performing the kinetic models for the optimized formula (F3) it was found that the formulation follows zero order and Higuchi model i.e. drug release from the matrix device is by diffusion process and shows zero order drug release. The stability studies were carried out

for period of 3 months as per ICH guidelines, and no change was found in the evaluation parameters after 3 months hence the formulation passes stability testing.

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