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ORIGINAL ARTICLE **OPEN ACCESS**

Design, Formulation and Evaluation of Osmotically Controlled Release Tablet of Simvastatin

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ABSTRACT
The objective of present investigation is to Formulate and development of controlled release Simvastatin Tablet based on Osmotically Controlled Release technology to increase the residence time of drug to improve the therapeutic effect by increasing the bioavailability. Simvastatin is the lipid lowering agent which is use to decrease the bad cholesterol level. It is potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme, [HMG-CoA] reductase which catalyzes the conversion of HMG-CoA to Mevalonate, an early rate determining step in cholesterol biosynthesis. For the preparation of osmotic controlled release tablet sodium chloride, mannitol is use as the osmotic agent. Sodium Lauryl Sulphate is use as wetting agent and pvpk30 as a binder. Isopropyle alcohol is use as the solvent for wet granulation. For the coating of the tablet various concentration of coating solution are use in which cellulose acetate PEG400 are use. Sorbitol is use as pore forming agent. Pre-formulation study, Micrometrics properties of granules was performed and there result was found to be limit. The prepared tablets were subjected to post- compression parameters and the percentage release found to be 83.8%. S2c2 batch are shows optimize batch. The dissolution data were subjected to various release kinetic model to recognize the mechanism of drug release. Finally it conclude that s2c2 formulation shows optimum result as osmotic controlled release tablet by attending zero order drug release for the effective treatment of hypercholestremia.
KEYWORDS: *Simvastatin, Osmotic release, controlled release, coating, semipermeable, tablet.*

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INTRODUCTION

Oral route is one of the convenient and efficient routes of drug administration. It is effective to achieve the local and systemic effect of drug. Conventional dosage form is usually
in the form of two or three daily doses, which can shows the large fluctuations in the drug plasma concentration and cause side effects on the human body. These problems overcome by to develop innovative methods for drug delivery via the oral route. Osmotically controlled drug delivery is the important approaches to achieve the controlled release of drug to obtained sufficient bioavailability. Osmotically controlled oral drug delivery system is the one which utilizes osmotic pressure for controlled delivery of active agent. In which core tablet is coated with rate controlling polymer which act as semi-permeable membrane with a micro-orifice drilled on the surface through which drug are release for longer period. [1-12]. Simvastatin is the lipid lowering agent which is use to decrease the bad cholesterol level. It is potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme, [HMG-CoA] reductase which catalyzes the conversion of HMG-CoA to Mevalonate, an early rate determining step in cholesterol biosynthesis. [2] The primary uses of Simvastatin are to treat dyslipidemia and to prevent atherosclerosis-related complications such as stroke and heart attacks in those who are at high risk. Simvastatin reduced overall mortality in people with existing cardiovascular disease and high LDL cholesterol by 30% and reduced cardiovascular mortality by 42%. The risks of heart attack, stroke, or needing a coronary revascularization procedure were reduced by 37%, 28%, and 37%, respectively. [3]
Absorption of Simvastatin is about 85% of an oral administration. However because of Simvastatin is undergo extensive first pass metabolism and hence bioavailability is low is about 5%. Both Simvastatin and its β-hydroxy acid metabolite are highly bound (approximately 95%) to human plasma proteins. Simvastatin can cross the blood-brain-barrier. Route of elimination of an oral dose of 14C-labeled Simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Peak plasma concentration

found to be 1.3-2.4 hours after administration. [4] So Osmotically controlled release drug delivery system is suitable for Simvastatin.

The objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of Simvastatin. [5]

MATERIAL AND METHODS

Materials:

Simvastatin is the gifted sample from (Flamingo pharmaceutical). Sodium Lauryl Sulphate sodium chloride, aerosil, magnesium stearate parches from (Thermosil fine chem.). Starch, PVP K30, cellulose acetate PEG400, Sorbitol is obtained from Hilab chemicals. [11, 12]

Method:

Formulation of Simvastatin core tablet:

Core tablet of Simvastatin were prepared by wet granulation technique with different concentration of osmotic agents. Drug and other excipients is passing though sieve no 40# without lubricants. The obtained powder mixture, PVP K30 was dissolved in isopropyl alcohol add this solution into it to produced coherent mass. Then the coherent mass was passed through sieve no 22 # to form granules. The wet granules dried at 50^0C for 30 min. the dried granules again pass through sieve no 22# to obtained uniform size granules. The lubricants were passed through 40 # sieve and mixed with dried granules. Finally lubricated granules compressed in to tablet compression machine to obtained core tablet. [1, 6]

Formulation Table:

TABLE .1 FORMULATION TABLE OF THE OSMOTICALLY CONTROLLED TABLET OF SIMVASTATIN.

Sr.No	Ingredients	S1	S2	S3
1	Simvastatin	40	40	40
2	Sodium Lauryl Sulphate	10	10	10
3	Sodium Chloride	15	20	25
4	Mannitol	50	50	50
5	Starch	70	65	60
6	Pvp K30	12	12	12
7	Magnesium Stearate	2	2	2
8	Aerosil	1	1	1
9	Isopropyl alcohol	q.s	q.s	q.s
	Total	200mg	200mg	200mg

Coating of Simvastatin Osmotic core tablet: [2]

Two coating solution are prepared by dissolving different concentration of polymer(cellulose acetate), pore forming agents (Sorbitol), plasticizer (PEG400), in sufficient quantity of ethanol and dichloromethane. Cellulose acetate is act as semi-permeable membrane coating. Coating of tablet was followed by stainless steel pan which having 200 mm diameter at 40 RPM rotation speed. Spraying of solution carried out through spray gun having nozzle which 1mm. drying temperature maintained by 40^0 c. After coating tablet were subjected in to tray drier for removing residual solvent.[1]

TABLE 2: FORMULATION TABLE FOR COATING SOLUTION.

Sr.No	Ingredients	C1	C2
1	Cellulose acetate	3.4 gm	3.1 gm
2	PEG400	0.6 gm	0.6gm
3	Sorbitol	0.3	0.6
4	Ethanol	15ml	15ml
5	Dichoromethane	85ml	85ml

Pre-formulation study: [7, 8, 9]

Identification test by U.V vis. Spectrophotometer:

25 mg of Simvastatin was weighed accurately and transferred it to 25 ml volumetric flask. Dissolved it in Phosphate buffer (6.8pH) and make the volume up to 25 ml with respective solvent. This was considered as stock solution (1000 mcg/ml). Further dilutions were made with this stock solution. I.e. 10 ml stock solution withdraws and dilute up to 100ml to form 100ppm. Then above solution was scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

Identification test by FTIR spectroscopy:

FTIR study of drug sample and identification studies was performed by potassium bromide (KBr) dispersion method (Perkin Elmer). Samples were prepared with KBr pellets (1 mg sample in 100 mg KBr) with a hydrostatic force of 100 PSI pressure for 1 minute. The scanning range was 400 to 4000 cm-1.

Melting point determination:

Melting point of drug sample was determined by using melting point apparatus. Small amount of drug sample was taken transferred in a thin walled capillary tube. The tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end. The capillary which contain sample was placed in melting point apparatus and heated and when drug sample was melted the melting point of sample powder was noted.

Determination of solubility:

Qualitative Solubility

Qualitative solubility analysis of drugs were done by dissolving 5 mg of drug in 5 ml different solvents such as distilled water, HCl (0.1N), phosphate buffer (pH 6.8), Phosphate buffer(pH 6.8), ethanol, methanol, acetone and chloroform were used to determine the solubility of drug.

FTIR Spectroscopy:

The drug-excipients interaction was studied by FTIR spectroscopy by KBr press pellet method. Sample for analysis and KBr were taken in 1:100 ratio and ground in motor for even distribution of sample in KBr. The pellet was prepared in the form of disk by applying pressure of 100 PSI for 1min using hydraulic press and subjected to FTIR. The pellet Scanned at 400 to 4000cm-1 IR range.

Pre-compression evaluation: [8, 9, 10]

Micromeritics properties of granules:

Bulk density:

Bulk density was determined by placing the granules into measuring cylinder and total volume was measured and also total powder weight was measured. The bulk density was calculated by using formula.

Bulk density (BD) = weight of powder /bulk volume.

Tapped density:

Tapped density of granules was determined by tapping the cylinder by using tapped density apparatus. Tapped the cylinder up to 100 times in tapped density apparatus and then measure the tapped volume and calculate the tapped density by using formula.

Tapped Density (TD) = weight of powder /tapped volume.

Hausner's ratio:

Hausner's ratio is the number that is correlated to the flowability of a powder or granules. It is calculated using formula,

Hausner's ratio = tapped density / bulk density.

Compressibility index:

Compressibility index was calculated by formula,

Carr's index (%) = Tapped density – bulk density/ tapped density* 100

Angle of repose:

The angle of repose of granules was determined by fix funnel method. The blend was poured through funnel separately until apex of pile so formed just touch the tip of the funnel. The angle of repose was calculated by using formula

$\theta = \tan^{-1} h/r$ H is height of pile; r is radius of pile.

Evaluation of coated tablet: [8, 9, 10]

Thickness:

The thickness of tablets was determined using Digital Vernier Caliper, (Mitutoyo, Japan). It is expressed in mm.

Weight variation:

20 tablets of each of formulation were weighed individually using an electronic balance. The average weight was calculated and individual tablet weight was compared with average value and the deviation was recorded.

TABLE 3: LIMITS FOR TABLET WEIGHT VARIATION TEST:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5%

Hardness:

Hardness is important parameter of evaluation of tablet. The resistance of the tablet to break under condition of handling, transportation and storage depend upon hardness. Hardness was determined by Monsanto hardness tester. It applies force to the tablet diametrically with the help of an in built spring. Triplicate determinations were done.

Friability:

Friability test is performed to assess the effect of abrasions and shock that may often cause tablet to chip, cap or break. Pre-weighed 10 tablets were placed in the plastic chamber of friabilator. Roche Friabilator was used for the purpose. This was then operated for 100 revolutions. Tablets dropping from a distance of six inches with each revolution, tablets was then dusted and reweighed. A maximum weight loss is not more than 1%. The percentage friability was determined by the formula.

% F= {Wo – W / Wo) ×100

Where,

% F= Friability in percentage

Wo= Initial weight of tablet

W= Final weight after revolution

Drug Content Uniformity:

In this test, 5 tablets were randomly selected and ground into morter to form powder. The powder sample equivalent to 40 mg was dissolved in 100ml of phosphate buffer pH 6.8, followed by stirring. The solution was filtered through a whattman filter paper, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 239 nm using phosphate buffer pH 6.8 as blank. Then absorbance of this solution was measured by using U.V-spectrophotometer (SHIMADZU; U.V1800).

***In vitro* drug release of osmotic controlled release tablet (Simvastatin)**

The In-vitro dissolution study for the Simvastatin osmotic controlled release tablets were carried out in USP type-II dissolution test apparatus (Paddle type) using 900 ml of phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed by measuring the absorbance at 239 nm using UV Visible spectrophotometer and calculate the percentage drug release.

RESULT AND DISSCUSSION:

Pre-formulation

The UV absorption of 10 µg/ ml in (6.8 pH) phosphate buffer found 247 nm at 200-400 nm rang exhibit maxima of Simvastatin. Solubility, melting point, compatibility study of Simvastatin was carried out and result is including in table 4.

TABLE.4 PREFORMULATION STUDY OF SIMVASTATIN.

Sr.No	Parameters	Observation
1	Identification by U.V visible spectrophotometer.	239 nm (ʎ max)
2	Melting Point	136^{0}c
3	Solubility	Very soluble in dichloromethane, soluble in phosphate buffer, freely soluble in ethanol, poorly soluble in water.
4	Compatibility study (FTIR)	Compatible.

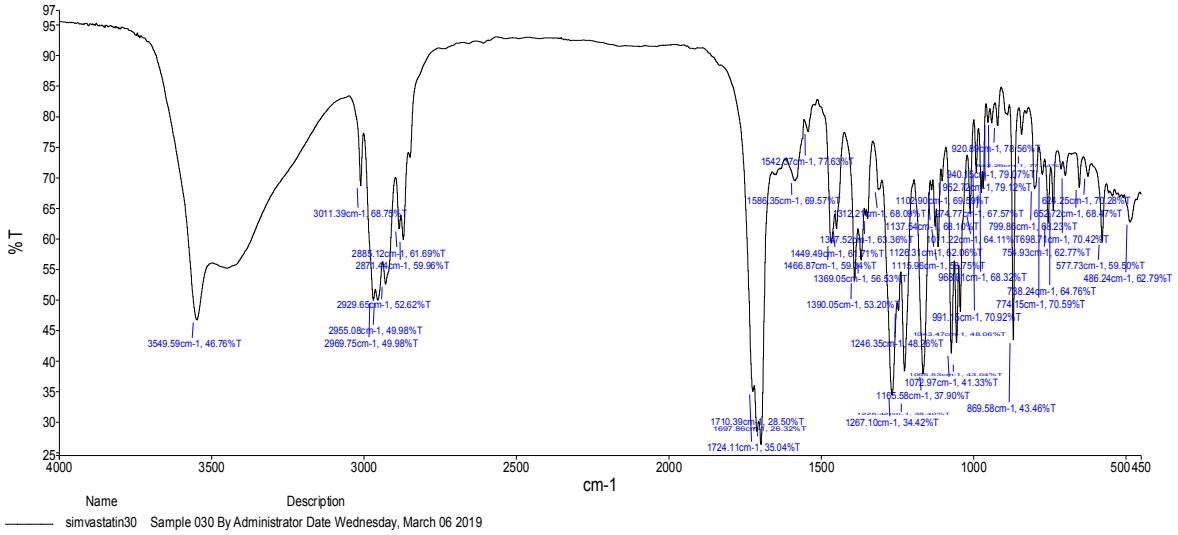

FIG 1. FTIR OF SIMVASTATIN

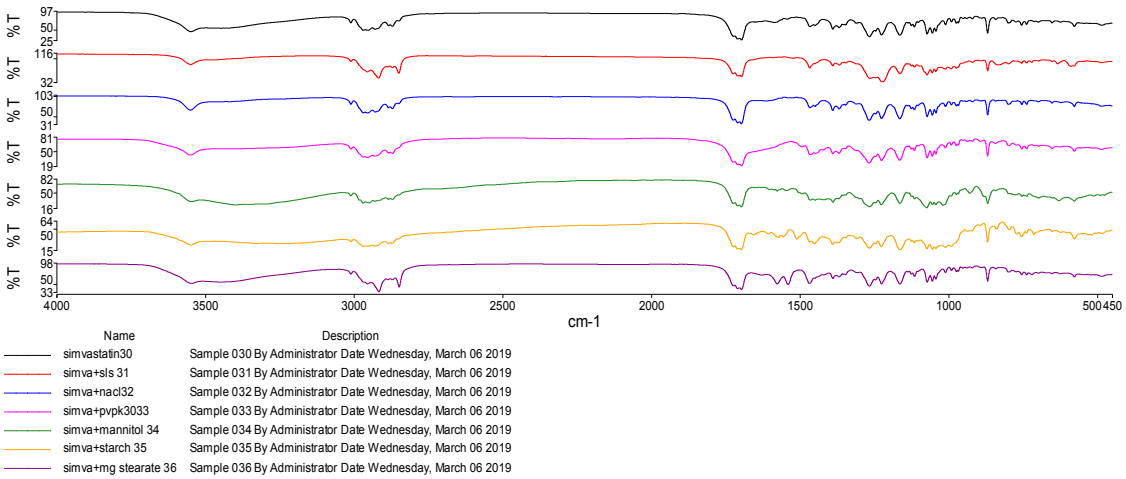

FIG 2. FTIR OF SIMVASTATIN AND EXCIPIENTS.

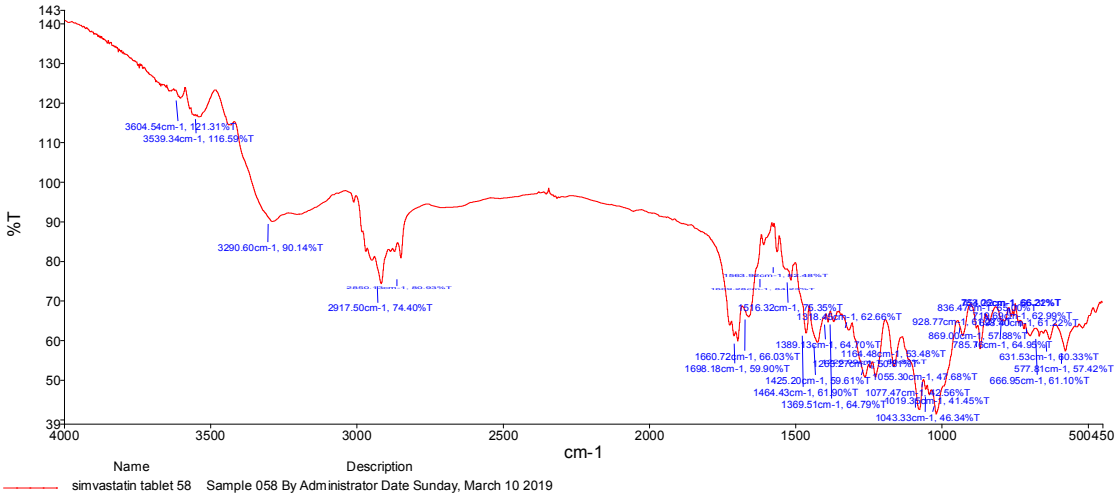

FIG 3. FTIR OF SIMVASTATIN TABLET.

Pre-compression evaluation of granules.

Micromeritics properties of granules such as bulk density, tapped density, compressibility index, hausner's ratio, angle of repose were studied and overall result include in table no 5. The compressibility index of the formulation 15 to 17% Indicating a good flow properties of powder which were further confirmed by determining the angle of repose, it is in the range of 11^0 to 15^0 which shows good flow properties.

TABLE .5 PRE-COMPRESSION EVALUATIONS OF GRANULES

Sr. No	Parameter	S1	S2	S3
1	Bulk density (g/ml)	0.65gm/ml	0.57gm/ml	0.66gm/ml
2	Tapped density (g/ml)	0.78gm/ml	0.66gm/ml	0.80gm/ml
3	Compressibility index (%)	16%	15%	17.5%
4	Hausner's ratio	1.2	1.15	1.21
5	Angle of repose (degree)	12.09^0	15.05^0	11.30^0

Post-compression Evaluation of Tablet:

The prepared tablets were evaluated for weight variation, thickness, hardness, dissolution test, uniformity of dosage units and friability. The weight variation test is done by weighing 20 coated tablets individually. Calculating the average weight and comparing the individual weights to the average. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. The hardness of 6 tablets was determined using.

The Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated.

The thickness of the each 10 tablets was measured with the Varnier Caliper. All test value is including in table 6. Drug content uniformity determined according to the USP requirements. Test value is including in table 6. In-vitro release study of osmotic controlled tablet of Simvastatin shown in table 7.

TABLE. 6 POST-COMPRESSION EVALUATION OF TABLET

Sr.No	Parameter	S1C1	S2C1	S3C1	S1C2	S2C2	S3C2
1	Uniformity weight(mg)	208mg	211mg	206mg	210mg	215mg	210mg
2	Thickness(mm)	3.2 mm	3.1 mm	3.2 mm	3 mm	3.1 mm	3 mm
3	Hardness(kg/cm^2)	5.2kg/cm^2	5kg/cm^2	5.2kg/cm^2	5kg/cm^2	6kg/cm^2	5kg/cm^2
4	Friability (%)	0.23	0.19	0.31	0.20	0.26	0.18
5	Drug content	97.2%	96.8%	98.2%	97.4%	98.5%	97.9%
6	% drug release	86.3%	88.6%	85.7%	84.1%	83.8%	88.3%

TABLE. 7 *IN-VITRO* DISSOLUTION OF SIMVASTATIN OSMOTIC TABLET.

time min	S1C1	S1C2	S1C3	S1C2	S2C2	S3C2
0	0	0	0	0	0	0
60	20.4	19.5	20	18.9	19.5	19
120	28.5	30.1	28.9	29.3	29.5	30.5
180	42.5	46.7	40	42.8	40.3	46.7
240	56.2	53.9	51.9	49.8	55.2	56.9
300	63.8	66.2	60.5	64.9	61	68.2
360	70.6	74.3	75	74.6	77.3	75.9
420	81.7	79.5	82.1	78.9	80.6	80.2
480	86.3	88.6	85.7	84.1	83.8	88.3

FIG 4: % DRUG RELEASE OF SIMVASTATIN OSMOTIC TABLET.

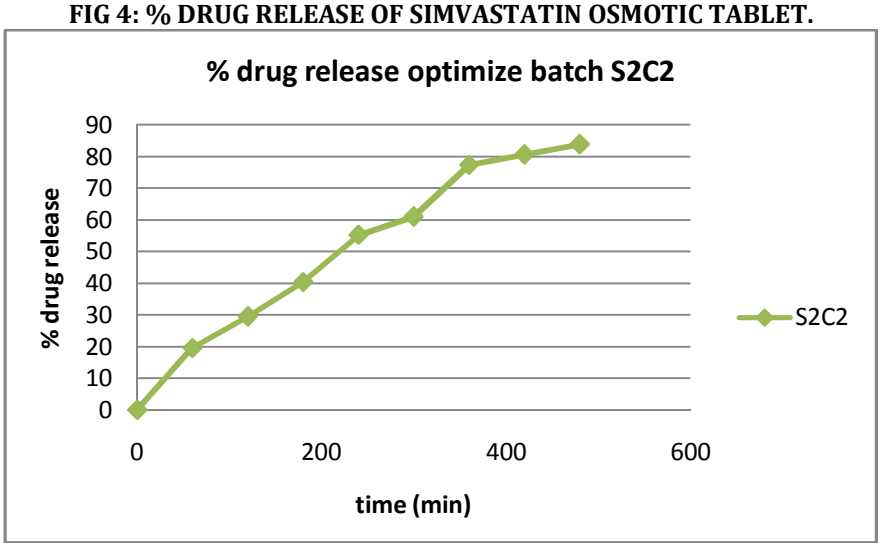

TABLE. 8 *IN-VITRO* DRUG RELEASE OSMOTIC TABLET OF OPTIMIZE BATCH (S2C2)

time min	
0	0
60	19.5
120	29.5
180	40.3
240	55.2
300	61
360	77.3
420	80.6
480	83.8

KINETICS MODELS

Dissolution data of above osmotic controlled tablet was fitted in Zero order, First order, Higuchi equation, Hixson, and Kors-peppas equations.

TABLE. 9 DRUG RELEASE KINETICS OF OSMOTIC CONTROLLED TABLET OF SIMVASTATIN.

Time (Hr)	cumulative % drug released	% Drug Remaining	Square Root Time	Log Cumu % Drug Remainining	Log time	Log cumu % drug released	% drug released	Cube root of % drug remaining (wt)	Wo-wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
60	19.5	80.5	7.746	1.906	1.778	1.290	19.5	4.318	0.324
120	29.5	70.5	10.954	1.848	2.079	1.470	10	4.131	0.511
180	40.3	59.7	13.416	1.776	2.255	1.605	10.8	3.908	0.734
240	55.2	44.8	15.492	1.651	2.380	1.742	14.9	3.552	1.090
300	61	39	17.321	1.591	2.477	1.785	5.8	3.391	1.251
360	77.3	22.7	18.974	1.356	2.556	1.888	16.3	2.831	1.811
420	80.6	19.4	20.494	1.288	2.623	1.906	3.3	2.687	1.955
480	83.8	16.2	21.909	1.210	2.681	1.923	3.2	2.530	2.112

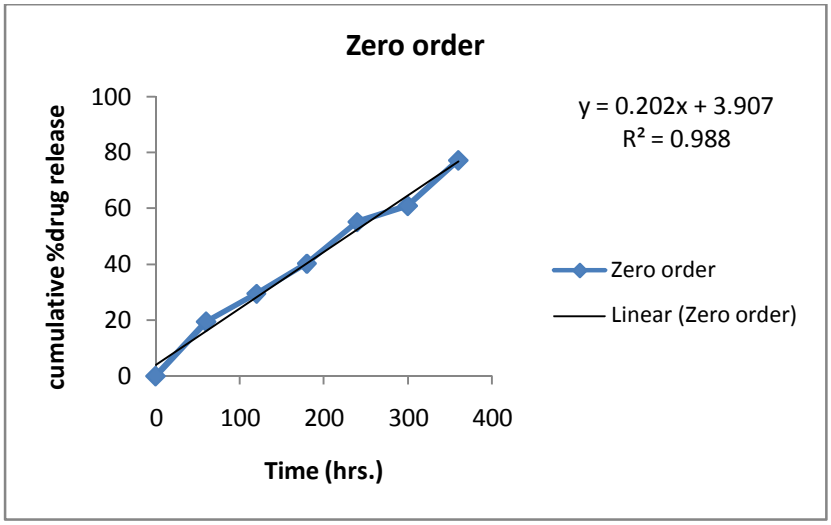

FIG 5: DRUG RELEASE KINETICS OF OSMOTIC CONTROLLED TABLET OF SIMVASTATIN.

CONCLUSION

The prepared tablet indicate satisfactory results for various evaluation parameter such as hardness, thickness, weight uniformity, friability, drug content, in-vitro dissolution study. Optimized formulation i.e. (S2C2) Simvastatin osmotic controlled tablet having 50 mg mannitol and 20 mg sodium chloride are osmotic agent, and 0.6 mg Sorbitol are pore forming agent are successfully comply with the requirement of controlled release formulation. The osmotic pressure generated in core tablet by means of osmotic agent and pore forming agent release drug controlled manner through semi-permeable membrane. The drug release mechanism was found to be zero order release pattern depend on the drug diffusion through semipermeable Membrane.

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CONFLICT OF INTEREST

There is no conflict of interest in this article.

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