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Formulation and Evaluation of Rosuvastatin Sustained Release Matrix Tablet

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ABSTRACT

The objective of the present study was to develop sustained release (SR) matrix tablets of Rosuvastatin. Tablets are prepared by direct compression technique using polymers HPMC K15M,HPMC K50M,PVP-K-30 , ethyl cellulose, Citric acid, Sodium bicarbonate and Magnesium Stearate .Tablets were evaluated for their physical characteristics viz.,hardness, thickness, friability and weight variation, drug content and floating properties. In vitro buoyancy and dissolution studies were performed for all the formulations. FT 1 TO FT 10 by using 0.1N HCL solutions at 37c. All the formulations were floated except FT 3 and FT6. The formulation FT10 containing 90mg of HPMC K4 M, 45mg HPMC K 100 M and 45mg of ethyl cellulose showed more sustained drug release time (12 hours) than other formulations. The formulation FT10 showed the controlled release for 24 hours. Thus FT10 was identified as ideal batch based on its results.

***Keywords*:** Rosuvastatin, sustained tablets, gastric residence time, sustained drug delivery system.

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Introduction

Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms.Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing a sustained-release drug delivery system. Sustained release dosage forms are designed to enhance the pharmaceutical activity of the medicament so as to attain higher selectivity and longer period of action. Sustained release preparations are useful to cut back the dosage frequency and side effects of medication and improve patient's convenience. Sustained release matrix tablet is comparatively simple to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials. the foremost commonly used technique of modulating the drug release is to include it in a matrix system.

Rosuvastatin is a new generation HMG-CoA reductase inhibitor that exhibits some distinctive pharmacological and pharmacokinetic properties. It has low extrahepatic tissue penetration, low potential for CYP3A4 interactions and substantial LDL-C lowering capacity and therefore has distinct advantages. Rosuvastatin is in a group of drugs called HMG CoA reductase inhibitors, or "statins." Rosuvastatin works by blocking enzymes in your liver that make cholesterol. Rosuvastatin reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood, while increasing levels of "good" cholesterol (high-density lipoprotein, or HDL). The oral bioavailability of rosuvastatin is 20%, which is comparable to atorvastatin, pravastatin and fluvastatin, and qualitatively higher than simvastatin and lovastatin. Approximately 90% of rosuvastatin is protein bound mainly to albumin; other statins have approximately 95% protein binding except pravastatin which has a lower protein binding of 50%.The mean volume of distribution is 134 litres in steady state. Rosuvastatin has a plasma half life of 19 hours which is longer than atorvastatin (15 hours) and simvastatin (2–3 hours). It is primarily eliminated in the faeces (90%) compared with 10% renal excretion. Approximately 72% of absorbed rosuvastatin is eliminated in bile and 28% via renal excretion.

The objective of the present study is to design and formulate a sustained release matrix tablet comparable to the marketed formulation with better stability, high production feasibility, and excellent patient acceptability.

Materials and Methods

Drugs & Chemicals

1. Rosuvastatin was generously gifted by SKN Oragnics Pvt Limited, India

2. HPMCK15M, HPMCK50M, PVP-K-30 and Ethylcellulose were gifted by Colorcon Asia Pvt. Ltd,India.

3. Citric acid (anhydrous) was procured from Aromatic Pvt. Ltd,India.

4. Talc was purchased from Ranbaxy Fine Chemical Ltd.,New Delhi.

5.Sodium bicarbonate, Magnesium Stearate were purchased from Loba chemie Pvt. Ltd, Mumbai.

Table: 1. Instruments

Equipments	Company
Electrical balance	SHIMADZU Scientific Instrument,Japan
Tablet compression	machine Cadmach Machinery Co. Pvt. Ltd,India
Hardness Tester	Monsanto,st. Louis,Mo
Friabilitor	Roche Friabilator
Bulk Density test apparatus	Vergo Instrument Corporation,Mumbai
Tap Density Tester (U.S.P.)	Electro Lab, ETD-1020, India
Ph Meter	Cyber Scan
Dissolution Apparatus	Minicon Equipments Pvt Ltd
UV Apparatus	SHIMADZU Scientific Instrument,Japan
FTIR	SHIMADZU Scientific Instrument,Japan

Pre-Compression Parameters of Blend

a) Angle of Repose

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose.

Method:

The angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4cm). A graph paper was placed below the funnel on the table**.** The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

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

Where, h = Height of the pile, r = Radius of the pile

b) Bulk Density

Bulk density is used as a measuring to describe packing Materials or granules.

Method:

Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weight amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

Bulk density = W/V_0 g/ml

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

c) Tapped Density

Method:

Tapped density was measured by transferring a known quantity of blend into a graduated cylinder and was placed on the density apparatus.

The initial volume was noted. The apparatus was set for 500,750 and 1250 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

Tapped density = W/V_f g/ml

Where, W = Mass of the blend, V_f = Tapped volume

d) Compressibility Index

It is the propensity of a powder to be compressed.

Method:

It is measured by tapped density apparatus for 500,700 and 1250 taps for which the difference should be not more then 2% . based on the apparent bulk density and tapped density the percentage compressibillity of the blend was determined using the following formula.

% Compressibility = $[(V_0-V_f)/V_0]X100$

or

% Compressibility = [(Tapped density – Bulk density)/Tapped density]X100

e) Hausner's Ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called hausne's ratio.

Hausners ratio = tapped density/bulk density.

Table 2: Limits of flow properties, angle of repose, compressibility index, hausner ratio.

S.no	Flow Properties	Angle of Repose(ɵ)	Compressibility Index (%)	Hausner Ratio
1	Excellent	25-30	<10	1.0-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Possible	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	>66	>38	>1.60

Loss on drying:

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

Drug exicipents compatibility studies:

Drug-exicipents compatibility studieds lay the foundation for designing a chemically stable formulation for clinical and commercial development. Drug exicipents compatibility studies are conducted during preformulation to select the most appropriate exicipents.

Objective:

To study compatibility of the active ingredients with selected exicipents and to prove that the selected exicipents are compatible with the active ingredient.

Design plan:

The active ingredients and the exicipents were mixed in the selected ratio using the motor and pestle. The mixtures are transfered to glass vials and sealed. The samples were placed as first set of initial samples and second set of samples were kept at RH for 4 weeks. The samples were analyzed for physical parameters.

Fourier transform infrared spectroscopy (FTIR):

FTIR spectra were obtained on a perkin-elmer 1600 FTIR spectrometer(1600 series perkin-elmer inc.norwalk,ct). Samples were prepared in KBR disks (2mg sample in 200mgKBr). The scanning range was 400 to 4000 cm and the resolution was 1 cm. The spectrum of drug, exicipents and their mixture was shown in figure.

Differential thermal analysis(DTA):

In DTA, the chemical and physical changes of the substance are recorded as a function of temperature or time as substance as heated at a liner rate. DTA is useful in investigation of solid state interaction.

In DTA thermograms are generated for the pure component and their physical mixture. In the absence of any interaction, thermogram of mixture shows paterns corresponding to those of the individual components. DTA studies also revealed that amlodipine besylate is compatiable with the exicipents used in the formulation.

FORMULATION OF ROSUVASTATIN SUSTAINED RELEASE

Table No. 3: Formulation of Rosuvastatin sustained release

S.NO	INGREDIENTS	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
1	Rosuvastatin	20	20	20	20	20	20	20	20	20	20
2	HPMCK 4M	80	-	-	90	-	-	-	45	45	45
3	HPMCK 100M	-	85	-	-	95	-	50	-	45	30
4	Ethylcellulose	-	-	85	-	-	95	45	50	-	35
5	Sodiumbicarbonate	85	80	80	75	75	70	70	75	75	70
6	Citric acid(anhydrous)	25	25	20	25	20	25	25	20	25	20
7	PVP-K-30	25	25	30	25	25	25	25	25	25	25
8	Magnesium Sterate	8	8	8	8	8	8	8	8	8	8
9	Talc	7	7	7	7	7	7	7	7	7	7
10	TOTAL WEIGH	250	250	250	250	250	250	250	250	250	25

Total weight of tablet=250mg

All quantities were in milligrams

All the batches contained 1% w/w talc and 0.5% w/w magnesium state.

Direct compression:

Direct compression is one of the popular techniques for preparation of these dosages forms. The advantages of this method include easy implementation. Use of conventional equipments along with commonly available excipents limited number of processing steps and cost effectiveness.

Disintegration and solubilization of directly compressed tablets depend on single or combined action of disintegrates, a water soluble excipents and effervescent agents. The basic principle involved in development of these dosage

form using this technique is addition of super disintegrates in optimum concentrations so as to achieve rapid disintegration along with pleasant mouth feel.

It is considered as the best method to prepare orally disintegrating dosage forms since the prepared tablets after higher disintegration due to absence of binder and low moisture contents.

NARRATIVE DESCRIPTION OF MANUFACTURING PROCESS

Formulation of oral disintegrating tablets of rosuvastatin 10mg were carried out by direct compression technique. The procedure followed for each of the trial has been direct compression technique. The procedure followed for each of the trial has been described as follows:

As the drug substance are hygroscopic the amount of drug substance weighed may not be quantity to the desired weight (because of the presence of moisture). Therefore the quantity of substance to be weighed was calculated as follows:

$$\text{Quantity of substance} = \frac{\text{Strength } \mathbf{X} \text{ Assay purity } \mathbf{X} \text{ LOD purity}}{\text{Assay of substance } \mathbf{X} \text{ (100 – LOD of substance)}}$$

PROCEDURE FOR FORMULATION OF F-1 TO F-15

- Rosuvastatin was weighed and filled individually through #20,40 mess and then blended in a polybag for 5 minutes.
    - The required super disintegrant (i.e.crospovidone, cross carmellose sodium explotab, kyron based on trial) were weighed and sifted through#30 mesh and added individually to the above mixture and mixed for 5 minutes.

- Aspartame and mint were weighed and passed through #60 meshes separately and added to the above mixture one after the other and for each addition the mixture was blended thoroughly for 5 minutes.
- The lubricant was weighed and sifted through #60 and added to the above blend.
- The final blend was mixed thoroughly for 5-10 minutes in the poly bag and tablets were compressed using 8mm round flat shaped punches with break line.

Post Compression Parameters Physical Appearance

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour, embossing, debossing etc.

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The tablet thickness should be controlled with in a 5% variation of a standard.

Disintegration time:

Disintegration time is the time taken by the tablet to breakup into smaller particles.The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75cm in length and 2.15mm in diameter the bottom of which consists of a #10 mesh sieve.

The basket is raised and lowered 28-32 times per minute in a medium of 900 ml saliva buffer pH 6.8 which is maintained at 37+2c.

Six tablets were placed in each of the tubes and the time required forcomplete passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet.The disintegration time that patients can experience for oral disintegration tablets ranges from 5 to 30 seconds.

Percentage of water content:

Karl fischer reagent (sulphur dioxide and iodine dissolved in pyridine and methanol) is used to determine the water content of the tablets using karl fischer titrator.

Weight Variation

20 tablets were selected randomly from a batch and were individually weighed and the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Table No. 4: Weight variation limits

Average Weight of Tablet (Mg)	% Difference
130 or less	10%
From 130 to 324	7%
>324	5%

Hardness test:

The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm.

Percentage friability:

In friability testing the tablets are subjected to abrasion and shock.it gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping.

Method:

If the tablet weight is >650mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650mg the number of tablets equivalent to a weight of 6.5g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25rpm. The tablets were dedusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets is being tested.

The percentage friability is expressed as the loss of weight and calculated by the formula:

Dissolution studies:

Dissolution is a process by which the disintegration solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

Method:

The dissolution test was carried out in USP apparatus type II (paddle) with 0.1 N hydrochloric acid as the dissolution medium of 500ml quantity at 50 rmp. The samples were drawn at 0,5,10,15,30 and 45 min.fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed by using UV-Visible spectrophotometer at 239nm for assessing the percentage of drug released.

Dissolution parameters:

Dissolution apparatus : USP apparatus type ll(paddle)
Dissolution medium : 0.1 N hydrochloric acid Volume : 500 ml

Temperature : 37+ 2c

Rpm : 50

Sampling intervals(min) : 0,5,10,15,30&45 min

Specification : NLT80%(Q) of the labelled amounts of rosuvastatin.

Standard calibration curve of rosuvastatin:

Procedure:

A stock solution of rosuvastatin (100mg/ml) was prepared by accurately weighing approximately 10mg of the drug into 100ml a grade volumetric flask and making up to volume with methanol. Aliquots of the standard stock solution of rosuvastatin were prepared with double distilled water to give the required final concentration of 10mg/ml. At absorbance was measured for the standard solutions of varying concentrations like 10,20,30,40,50,60,70, and 80mg/ml.

Drug release kinetics:

O study the release kinetics,data obtained from in vitro drug release studieswere plotted in various kinetic modules:zero order as the cumulative percentage of drug release vs time. First order as the log of the amount of the drug remaining to be drug released vs time. Higuchi model as the cumulative percentage of drug release vs. Square root of time,krosmeyer-peppas release model as the log time vs.log % of drug release and hixon-crowell release model as the time vs. Cubic root of % drug remaining.

Zero order kinetic:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly,assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation-

$$\mathbf{Q_t = Q_0 + K_0 t}$$

Where, Q_t = amount of drug dissolved in time t,

Q_0 = Initial amount of drug in the solution

K_0 = zero order release constant.

First order kinetics:

To study the first order release rate kinetics the release rate data were fined to the following equation.

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

Where, Q_t is the amount of drug released in time t,

Q_0 is the Initial amount of drug in the solution

K_1 is the first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study the release of water- soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expression were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media,the equation is

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

Where, Q_t = amount of drug released in time t, K_H = Higuchi dissolution constant.

Korsmeyer-peppas release model:

Korsmeyer et al derived a simple relationship which descriped drug release from a polymeric system. To find out the mechanism of drug release first 60% drug release data were fitted in korsmeyer-peppas model.

$Mt/M\infty=Ktn$

Where,

Mt/M∞ is a fraction of drug released at time t, K is the release rate constant and

N is the release exponent.

The n value is used to characterize different release for cylindrical shaped matrices.

Table No. 5: Interpretation of diffusion release mechanisms.

Release exponent(n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	t -0.5
0.45<n=0.89	Non-fickian transport	t n-1
0.89	Case ll transport	Zero order release
Higher than 0.89	Super case ll transport	t n-1

Hixson-crowell model:

To study the hixson-crowell model the release rate data are fitted to the following equation

$$W_o^{1/3} - W_t^{1/3} = K_s t$$

Where, W_o = amount of drug in the dosage form,

W_t = remaining amount of drug in the pharmaceutical dosage form.

K_s=is a constant incorporating the surface volume relationship.

Moisture uptake studies:

Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation, as several exicipents used are hygroscopic.

Moisture uptake studies were carried out by weight method.

Method:

Clean and dry petriplates were taken and their empty weights were recorded.

- 10 tablets were placed into each partiplates and the total weight of each petriplate with the test substance was recorded.
- Finally the partiplates were placed in desiccators saturated 75% relative humidity at 25 c using various standard salt solutions.
- The weights of all the particles were recorded at the end of 1,2,4,6,8,24,48,72 hr.
- The partiplates were carefully wiped tissue paper to remove any adhering moisture before the weight was recorded.
- The percentage of moisture absorption was determined using the formula.

Assay (UV method):

From the tablet an amount equivalent to 5mg of Rosuvastatin was weighed &dissolved in 50 ml of methanol & sonicated for 10 min. Then the solution was filtered through whatman filter paper no.41,final volume made upto 50 ml with methanol to get a stock solution of 100 mg/ml of rosuvastatin. The absorbance of resultant solution was measured at 239 nm. The concentration of drug present in sample solution calculated by using the equation generated from the calibration curve.

Stability Studies

In designing a solid dosage form it is necessary to know the inherent stability of the drug substance. To have an idea of what excipients to use, as well as how best to put them together with the drug and to know that no toxic substance are formed. Limits of acceptability and therefore compromises must be reasonably defined. Because the measurements of these aspects of stability as well as determination of shelf life or expiration date for the final dosage form require long term stability studies for confirmation, they can be expensive and time consuming. Consequently it is necessary to define those study designs and conditions that show the greatest probability of success. The objective therefore of a stability study is to identify and help avoid or control situations where the stability of the active ingredient may be compromised. For a drug substance to be developed into a table dosage form, this objective may be achieved by investigating the stability of the drug under the following three categories, (1) solid state stability of drug alone, (2) compatibility studies in presence of recipients, (3) solution phase stability.

Rationale for stability studies

There may be chemical degradation of active leading to a substantial lowering of the quality of therapeutic agent in the dosage form.Although chemical degradation of the active drug may not be expensive, a toxic product may be formed in the decomposition process.Instability of drug product can lead to substantial lowering in the therapeutic

efficiency of the dosage form. RH for the optimized formulations. The procedure was divided into two parts,

ICH Guidelines for Stability Study

Table No. 6: ICH guidelines for stability study

Study	Minimum Storage condition		Time
	Temperature	Relative humidity (%)	
Long term	25°C2°C	60%5%RH	12 Months
Intermediate	30°2°C	65%5%RH	6 Months
Accelerated	40°2°C	75%5%RH	6 Months

The analyst can select any one of the three study conditions. Stability study was carried out at 40°C/75%

Part One

Achieving of 60% RH

26.66 gm of sodium hydroxide was weighed and dissolved in 100ml of distilled water to get 26.66% sodium hydroxide solution. The solution was placed in the desiccators over which a wire mesh was placed, over which the dosage form was placed and the desiccators was sealed. The desiccators was placed in the oven maintained at 25°C to create the Relative Humidity OF 60%.

Achieving of 75% RH

Saturated solution of sodium chloride was prepared and placed in the desiccators over which a wire mesh was placed, over which the dosage form was placed and the

desiccator's was sealed. The desiccators was kept in oven maintained at 40°C to create the relative humidity of 75%.

Part Two

The sealed formulation were placed in amber colored bottles, tightly plugged with cotton and capped. They were then stored at 25°C/60% RH and 40°C/75% RH for two months and evaluated for their physical appearance and drug content.

The analyst can select any one of the three study conditions. Stability study was carried out at 40°C/75%

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26.66 gm of sodium hydroxide was weighed and dissolved in 100ml of distilled water to get 26.66% sodium hydroxide solution. The solution was placed in the desiccators over which a wire mesh was placed, over which the dosage form was placed and the desiccators was sealed. The desiccators was placed in the oven maintained at 25°C to create the Relative Humidity OF 60%.

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Results and Discussion

Pre-Formulation Study

Organoleptic Properties

Table No. 7: Observation of Organoleptic Properties of Rosuvastatin

Test	Observations
Colour	Creamy white Odourless powder
Nature	Crystalline powder

Solubility Study

Table No. 8: Solubility profile of Rosuvastatin

Time (Min)	% SOLUBILITY				
	Water	0.01N Hcl	0.1N Hcl	pH 4.5	pH 6.5
30	97.5	95.2	98.8	98.9	101.6

Results indicated that the solubility of Rosuvastatin is not influenced much by ph. it has shown a solubility of 97.55% in water, 95.2% in 0.01N HCl, 98.8% in 0.1N HCl, 98.9% in acetate buffer and 101.6% in phosphate buffer.

As per the above solubility data, the API is more soluble in pH 6.8 phosphate buffer USP when compared with other buffers water, 0.01N HCl, pH 4.5 acetate buffer USP. Rosuvastatin API is more than 90% solubility in all USP buffers.

Melting Point Determination

Theoretical Melting point of Rosuvastatin drug 120^0C

Observed melting point of Rosuvastatin drug is 118-120.5^0C

Standard Curve of Rosuvastatin

The absorbance was measured in a UV spectrophotometer at 222 nm against phosphate buffer solution of pH of 6.8. The absorbance so obtained was tabulated as in Table 3. Calibration curve was plotted and shown in Figure 1.

Table No. 9. Spectrophotometric data for the estimation of Rosuvastatin

S.No.	Concentration (µg/ml)	Absorbance (222nm)
1	0	0
2	2	0.091
3	4	0.178
4	6	0.254
5	8	0.343
6	10	0.428

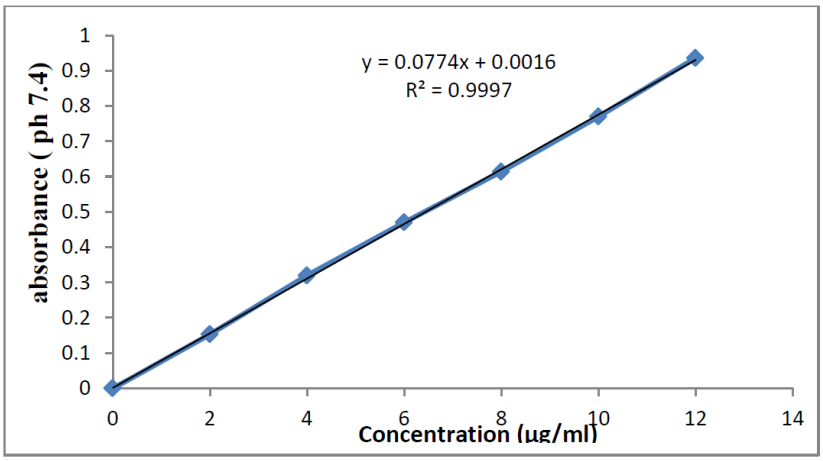

Fig. 1: Standard curve of Rosuvastatin by phosphate buffer

Development of calibration curve:

Calibration curve of the pure drug Rosuvastatin was prepared in the concentration range of 2 to 10|ig/ml at the wavelength of 222nm. The calibration curve showed good linearity and regression coefficient was 0.999(r2).

Compatibility Study by Using FTIR Spectroscopy:

FTIR:

The possible interaction between the Rosuvastatin and the polymers such as HPMC K15M ,HPMC K100M and Sodium CMC was studied by IR spectroscopy. The IR spectra for Rosuvastatin, HPMC K15M, HPMC K100M, Sodium CMC and its physical mixtures are shown in figures 5.2 to 5.5.

Table No. 10. Interpretation of FTIR spectra of Rosuvastatin

S.No	Function group	Wave number (cm^1)	Drug (pure)	Drug + Physical mixture
1	Enoic acid	1413	1546.96	1545.03
2	Aromatic C-H stretch	3040-3010	2970.48	2970.48
3	Secoundary alcohol CH_2OH	1100	1072.46	1072.46
4	Amide N=H	3140-3500	3389.04	3408.33
5	$C-(CH3)_2$	1385-1380	1384.94	1386.86
6	Fluoride C-F	1400-1100	1329.00	1329.00
7	Sulphonamide	1370-1335 1170-1155	1228.70 1153.47	1230.63 1153.47
8	Pyrimidine	750-800	777.34	777.34

Major functional groups present in Rosuvastatin shows characteristic peaks in IR spectrum. Figures +++ and +++ shows peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different polymer. The major peaks are identical to functional group of Rosuvastain. Hence, it was conformed that there was no incompatibility between drug and various polymers.

Fourier Transform Infrared Spectroscopy (FTIR)

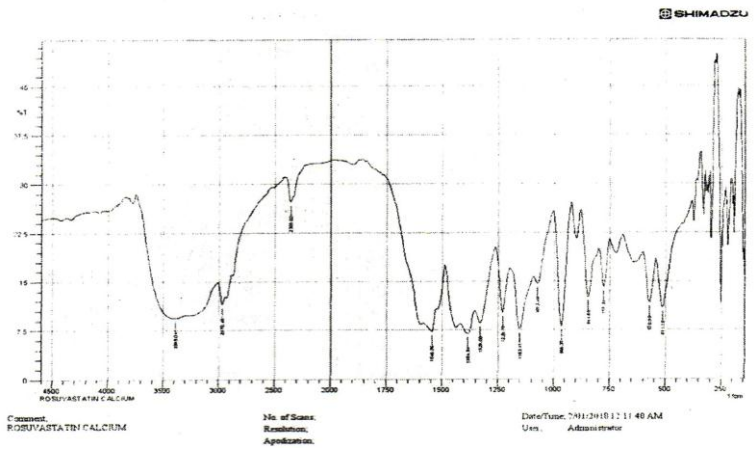

Fig. 2: FTIR Spectra of Rosuvastatin pure

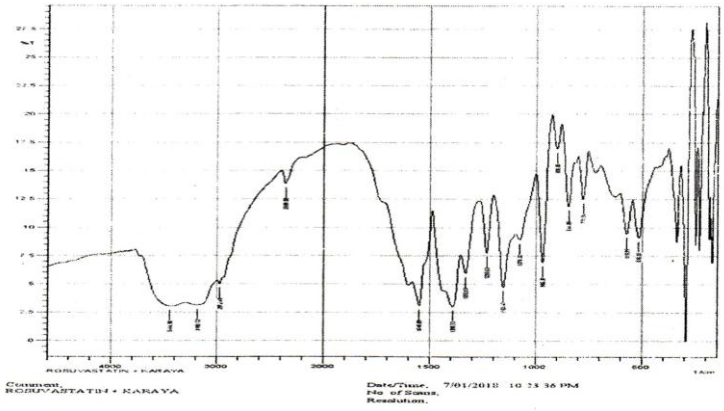

Fig. 3: FTIR Spectra of Rosuvastatin with physical mixture

Differential Scanning Calorimetry:

The DSC thermogram of Rosuvastatin pure, exhibiting a sharp exothermic peak at 101.18^{o}C corresponding to its melting and decomposition. The thermogram of the physical mixture of drug with other excipients showed the showed the existence of the drug exothermic peak which could indicate the absence of interaction between rosuvastatin and other excipients. The DSC thermogram of pure and its physical mixture is given in fig +++ and +++++.

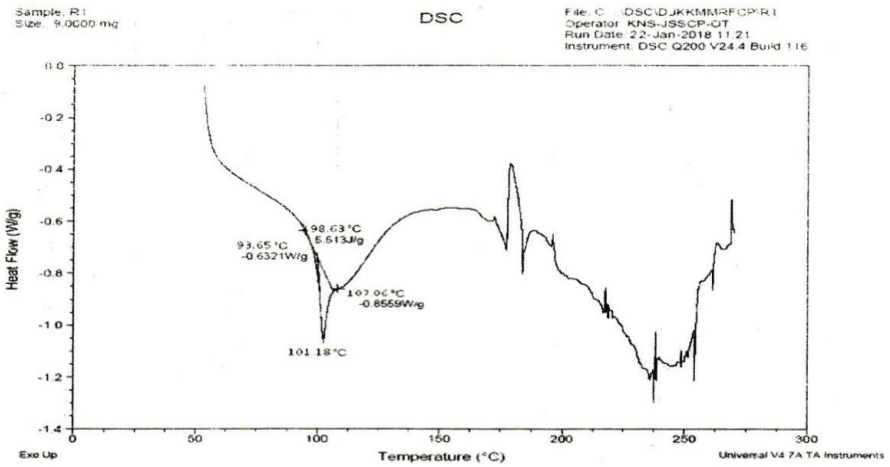

Fig. 4: DSC thermograms of Rosuvastatin pure

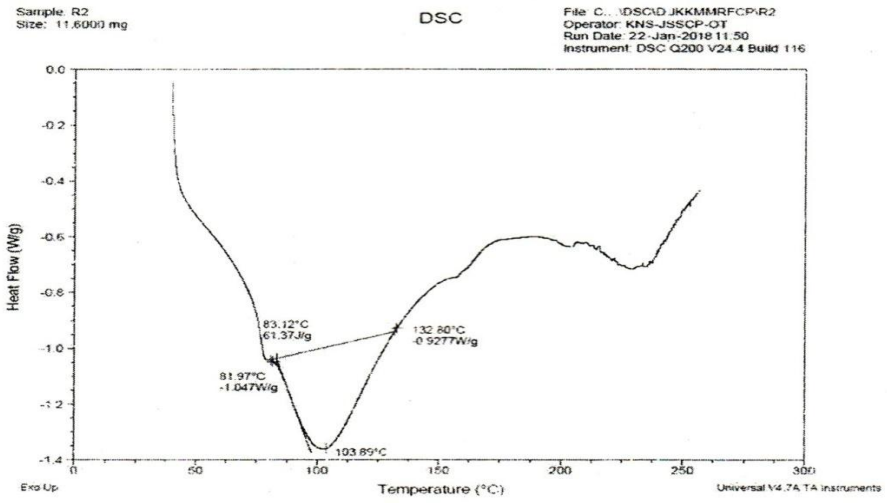

Fig. 5: DSC thermograms of Rosuvastatin with physical mixture

Table No. 11: Physical evaluation of Precompression Blend

Formulation	Bulk Density G/CC	Tapped Density G/CC	Hausner Ratio	Compressibility Index %	Angle of Repose
F1	0.49±0.04	0.57±0.02	1.17±0.03	4.04±0.04	278.40±0.05
F2	0.48±0.06	0.55±0.03	1.14±0.02	12.72±0.02	26.06±0.02
F3	0.46±0.01	0.53±0.01	1.15±0.05	13.20±0.04	24.38±0.01
F4	0.43±0.02	0.49±0.02	1.14±0.04	12.24±0.03	23.72±0.06
F5	0.41±0.02	0.47±0.03	1.13±0.01	12.76±0.05	21.94±0.03
F6	0.45±0.03	0.48±0.05	1.12±0.05	11.36±0.02	20.48±0.04
F7	0.55±0.04	0.59±0.01	1.16±0.04	14.06±0.01	26.21±0.01
F8	0.53±0.01	0.56±0.02	1.15±0.03	13.11±0.03	25.74±0.02
F9	0.50±0.03	0.58±0.03	1.16±0.02	13.79±0.02	24.02±0.05
F10	0.51±0.05	0.57±0.03	1.18±0.01	13.85±0.06	24.54±0.04

*AI1 values are mean ± S.D,n=3

Physical Evaluation of Precompression Blend

a. Bulk Density:

It is the ratio between a given mass of powder and its bulk volume. The bulk densities of the powder blends of all the formulations ranged from 0.41 to 0.55 gm/cc.

b. Tapped Density:

Tapped density is the ratio between weight of the sample powder taken and the tapped volume. The Tapped densities of the powder blends of all the formulations ranged from 0.47 to 0.59 gm/cc

c. Hausners Ratio:

Hausners ratio is the ratio of tapped density and bulk density. Hausners ratio is an indirect index of ease of powder flow. The Hausners ratio values ranged from 1.12 to 1.18. Evaluated values of Hausners ratio obtained were less than 1.25 indicating good flow. It means that the powder flow properties were within the pharmacopoeial limits.

d. % Compressibility or Carr's index:

It indicates powder flow properties. The Carr's index was within the pharmacopoeial specifications and the values ranged from 11.36 to 14.04%. 12-16 Carr's index value indicates good flow, 18-21 Carr's index value indicates fair.

e. Angle of Repose:

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. The angle of repose of the powder blends of all the formulations were determined and the values ranged from 20.48 °to 27.40° and it was observed to within the pharmacopoeial limits. The results of angle of repose (< 25) indicate excellent flow properties of granules, and it was observed to be within the pharmacopoeial limits.

Table No. 12: Physical evaluation of matrix tablets

Formula Code	Hardness (kg/cm2)	Thickness (mm)	Weight variation (mg)	Friabiity (%)	Assay *%)
F1	4.4±0.15	4.12±0.17	313.5±0.13	0.18±0.15	97.98±0.13
F2	4.2±0.11	4.25±0.15	313.3±0.12	0.22±0.16	100.15±0.12
F3	4.6±0.13	4.21±0.12	316.3±0.15	0.20±0.12	99.12±0.15
F4	4.1±0.15	4.42±0.15	313.5±0.14	0.19±0.17	99.53±0.14
F5	4.3±0.12	4.10±0.13	316.1±0.11	0.16±0.11	100.24±0.12
F6	4.7±0.13	4.37±0.15	316.5±0.13	0.14±0.12	98.57±0.11
F7	5.1±0.14	4.22±0.12	313.6±0.12	0.21±0.14	98.25±0.04
F8	4.9±0.12	4.13±0.11	316.2±0.11	0.17±0.15	99.15±0.13
F9	5.0±0.15	4.28±0.13	313.7±0.12	0.18±0.12	98.34±0.12
F10	4.8±0.13	4.14±0.12	316.4±0.13	0.21±0.14	99.28±0.14

Where,

*Al1 values are mean ± S.D, n=20

Evaluation of Formulated Matrix Tablets

a. Hardness:

The hardness of all the formulations ranged from 4.1 to 5.1 kg/cm2. The pharmacopoeial limit for hardness is 3-5 kg/cm2. Hence all the formulations passed the test for hardness.

b. Thickness:

The thickness of all the formulations was between 4.12 to 4.42 mm which was according to the pharmacopoeial specifications.

c. Weight variation: The weight variation test was performed and the weights of the tablets were between 313.3 to 316.5 mg. The pharmacopoeial specification for weight variation limit is ±7.5.Hence all the formulations passed the weight variation test and the % weight variation was within the pharmacopoeial specifications.

d. Friability (F):

Friability of the tablets was determined by using Roche friabilator. The friability of all the formulations was determined, and the values were in the range from 0.14 to 0.22 %. Friability values below 1% were an indication of good mechanical resistance of the tablets. Hence all the formulations was within the pharmacopoeial limits

e. Assay:

The percentage drug content of all the tablets was found to be in the range of 97.98 to 100.24 % . This was within the acceptable limits. The preparation complies with the test if each individual content is S5 to 115% of the average content. Hence all the formulations were passes the test and the values are within the pharmacopoeial limits.

5.4.In-Vitro Drug Release Studies

The in-vitro dissolution studies were performed using the USP-I1 (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900ml of phosphate buffer pH 6.8,

maintained at 37±0.5 C. An aliquot (5ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer at 222nm.

Table No. 13. In-vitro drug release data of Rosuvastatin from formulations F1 to F10 and comparative with Marketed product

Time in Hrs	**0**	**1**	**4**	**8**	**20**
% Drug release in F1	0	9.56±1.6	24.58±1.1	40.10±2.2	64.05±1.4
% Drug release in F2	0	10.70±0.2	24.62±1.3	40.18±2.0	69.31±2.2
% Drug release in F3	0	11.31±0.9	26.81±1.6	44.31±2.3	76.84±1.5
% Drug release in F4	0	11.40±1.1	27.91±1.7	44.38±1.3	77.96±2.6
% Drug release in F5	0	13.51±1.4	29.0±0.8	46.94±1.9	79.35±2.4
% Drug release in F6	0	21.3±1.9	42.1±2.4	72.4±1.6	95.1±1.1
% Drug release in F7	0	19.2±0.2	42.8±1.9	64.5±2.1	92.3±0.5
% Drug release in F8	0	18.9±2.5	42.3±1.4	63.7±0.7	90.6±1.7
% Drug release in F9	0	14.8±1.6	34.2±2.1	51.4±1.9	86.9±0.4
% Drug release in F10	0	15.6±0.4	35.6±1.1	53.5±0.2	88.09±2.6
% Drug release in marketed product.	**0**	**13.3**	**33.8**	**51.5**	**88.02**

Where,

*Al1 values are mean ± %, n=6

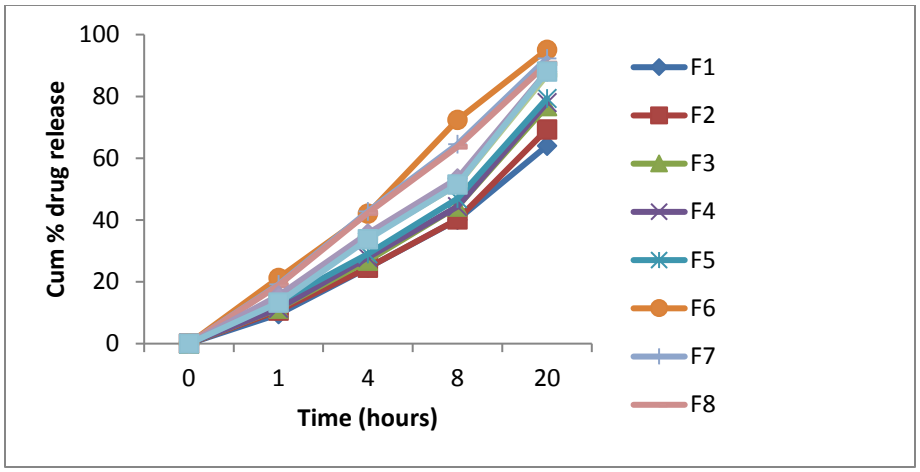

Fig. 6: In-vitro drug release profiles of Rosuvastatin from F1 to F10 and comparative with Marketed product

Table No. 14: In-vitro drug release data of Rosuvastatin from optimized formulation F10 and Marketed product

Time in Hrs	0	1	4	8	20
% Drug release in F10	0	15.6	35.6	53.5	88.09
% Drug release in marketed product	0	13.3	33.8	51.5	88.02

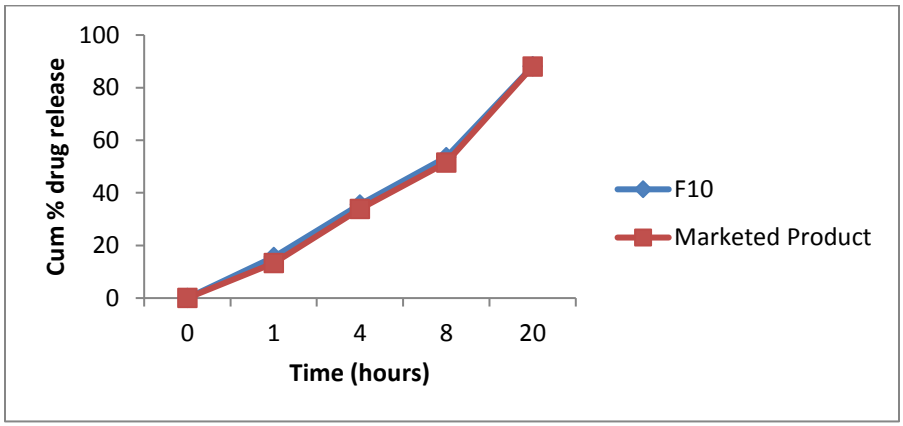

Fig. 7: Comparison of In-vitro drug Release profiles of Rosuvastatin from optimized formulation F10 and Marketed product

Drug Release Kinetics

Table No. 15: Mathematical modelling and drug release kinetics of HPMCK4M matrix tablets

Formulation	Drug release kinetics (r^2)				Release exponential (n)
	Zero-order	First-order	Higuchi	Korsmeyer	
F1	0.934	0.987	0.992	0.988	0.783
F2	0.956	0.997	0.989	0.998	0.699
F3	0.959	0.999	0.987	0.996	0.533
F4	0.959	0.998	0.988	0.999	0.644
F5	0.950	0.998	0.991	0.998	0.595

Fig. 8. Mathematical modelling and drug release kinetics of HPMCK4M matrix tablets

Table No. 16: Mathematical modelling and drug release kinetics of HPMCK100M and Ethyl cellulose matrix tablets

Formulation	Drug release kinetics (r^2)				Release exponential (n)
	Zero-order	First-order	Higuchi	Korsmeyer	
F6	0.934	0.987	0.992	0.999	0.790
F7	0.956	0.997	0.989	0.999	0.711
F8	0.959	0.999	0.987	0.999	0.513
F9	0.959	0.998	0.988	0.998	0.523
F10	0.934	0.995	0.996	0.999	0.579

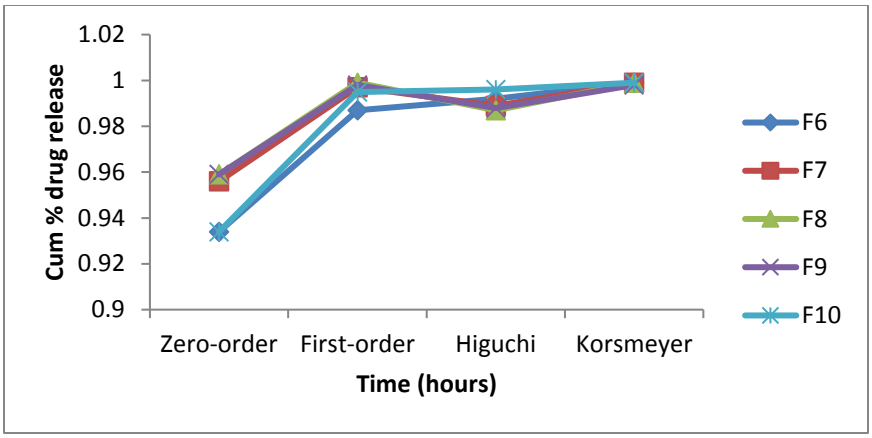

Fig. 9: Mathematical modelling and drug release kinetics of HPMCK100M and Ethyl cellulose matrix tablets

Table No. 17: Mathematical modelling and drug release kinetics of optimized formulation F10 and marketed product

Formulation	Drug release kinetics (r^2)				Release exponential (n)
	Zero-order	First-order	Higuchi	Korsmeyer	
F10	0.934	0.995	0.996	0.999	0.579
Marketed product	0.948	0.995	0.992	0.998	0.599

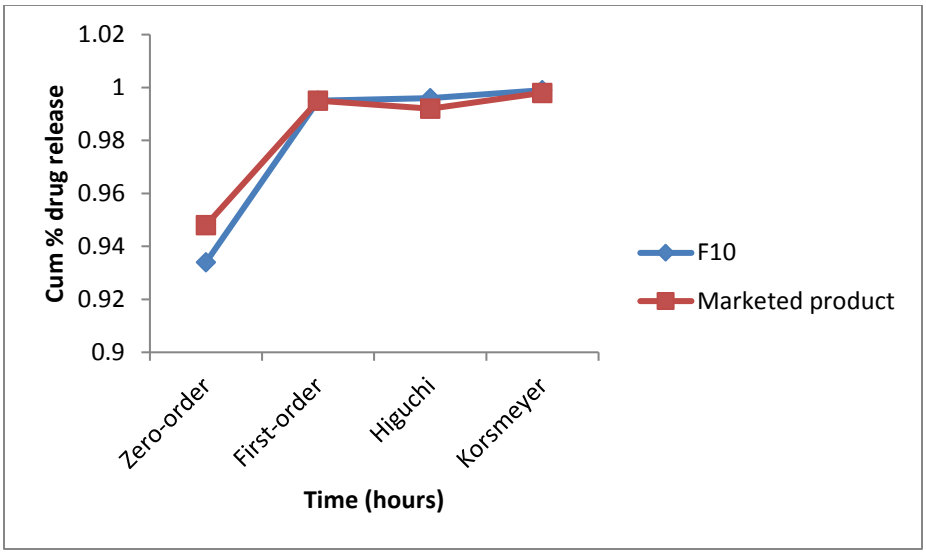

Fig. 10: Mathematical modelling and drug release kinetics of optimized formulation F10 and marketed product

The drug release data obtained were extrapolated by zero order, Highuchi, First order, Korsemyer peppa's to know the mechanism of drug release from the formulations. the release rate kinetic data for all the formulations was shown in Table 5.13 to 5.15. The release kinetics shows that the release of drug followed first order release in all the formulations. as the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

Table No. 18: Rosuvastatin stability studies

Parameters Tested	Storage Conditions			
	Initial	$40^0C \pm 2^0C$ / 75% ± 5% RH		
		1st month	2nd month	3rd month
Description	White coloured flat faced round shaped tablets with breakline	No change	No change	No change
Weight (mg) variation	316	316	316	315
Thickness (mm)	4.14	4.14	4.14	4.13
Hardness (kp)	4.8	4.8	4.8	4.6
Friability (%)	0.21	0.21	0.21	0.20
Assay (sec)	99.28	99.28	99.28	99.00

Rosuvastatin is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate,an early rate-limiting step in cholesterol biosynthes. Review of literature indicated that floating drug delivery system and minimize the fluctuation of plasma level and can be used to maintain drug concentration at a therapeutic level by means of controlled drug release.

The aim of the study was to develop and physic-chemically characterized sustained release matrix tablet of Rosuvastatin based on a matrix polymer. Rosuvastatin has a biological half-life (19 hours). Development of sustained release most of the drug at the colon,thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. Being weak acid, pka-4.55, the rosuvastatin well absorbed from the upper portion of the duodenum. Moreover, less solubility in alkaline ph of rosuvastatin is partly responsible for the poor bioavailability of rosuvastatin from the colon. These properties of rosuvastatin favour the

traditional approach to sustained release delivery. Hence, clinically acceptable sustained release dosage forms of rosuvastatin prepared with conventional technology may not be successful.

Different types of matrix forming polymers were studied:

HPMC k4m, HPMC k100m,ethyl cellulose, for the study. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former. The release rate could effectively be modified by varying the "matrix-form polymer", the tablet geometry (radius) the type of matrix forming forming polymer. The use of polymer blends. The controlled behaviour of the matrix drug delivery system could successfully be combined with accurate control of the drug release patterns. The batch optimization was done using HPMC K4 M, HPMC K100 M and ethyl cellulose as matrix polymers as they gave optimum SDDS as well as long acting affect and no/ least eroding effect. It was also found that the tablet formulations released more than 90% drug in 12 hours as desired.

The use of HPMC K4 M, HPMC K100 M polymer in matrix tablets as density reducing agent has given a different look while ethyl cellulose used as release retardant polymer. During the study with the polymer various characteristics of the material were observed; like highly porous spherical structure, good compressibility, good flow property with drug and other polymers, no significant effect on drug release and compatibility with drug and other polymers as seen through IR spectra.

Thus it is summarized and concluded that HPMC K4 M, HPMC K100 M and ethyl cellulose can be successfully used in the formulation of rosuvastatin sustained release drug delivery system.

Conclusion

From the compatibility studies it was concluded that HPMC K4 M, HPMC K100 M, and ethyl cellulose were compatible with rosuvastatin and thus suitable for the formulation of rosuvastatin sustained tablets.

In vitro buoyancy studies were performed for all the formulations. FT 1 TO FT 10 by using 0.1N HCL solutions at 37c. All the formulations were floated except FT 3 and FT6. The formulation FT10 containing 90mg of HPMC K4 M, 45mg HPMC K 100 M and 45mg of ethyl cellulose showed more sustained drug release time (12 hours) than other formulations. In vitro dissolution studies were also performed for all formulations. The formulation FT10 showed the controlled release for 24 hours. Thus, FT10 was identified as ideal batch based on its results.

Finally, it was concluded that HPMC K4 M, HPMC K100 M and ethyl cellulose can be successfully used in the formulation of Rosuvastatin sustained release drug delivery system.

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