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Development and Evaluation of Floating Drug Delivery System of Rosuvastatin Calcium Dosage Form

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ABSTRACT: The objective of the present study was to develop floating drug delivery system(FDDS) of rosuvastatin calcium is one method to accomplish tedious gastric residence times, provide convinience for both local & systemic drug action. Thus, gastroretention could help to provide higher availability of new products and subsequently improved therapeutic activity and considerable benefits to patients. In this article aims at summarizing the floating drug delivery system along with types, access for designing the floating dosage form, advantages & disadvantages of FDDS. In this article, aims to maintain increasing floating retention time at the gastric site to reinforce the bioavailability and release rate of drug. The floating dosage form was processed by direct compression method adopting sodium bicarbonate as gas generating agent. The release rate was sustained up to 20hrs with 1: 1.5 ratio of HPMC K4M and Xanthan gum, but the Floating Lag time was construct to be more with the combination. Evaluations of granules like physical parameters, weight variation, drug content uniformity, bulk density, tapped density, buoyancy studies, Swelling Index, angle of repose was done.
Similarly, the aggregate between HPMC K4M and Guar gum also controlled the release more than 20hrs was detected. The aggregate between HPMC K100M and Carbopol 934P with the ratio of 2:1 was found to be acceptable with release profile. Hence the Formulation F10 was optimized by for further studies. The formulation (F10) also gratify the Swelling Index, Buoyancy time controlled the drug release up to 24hrs. The mechanism of drug release pursued the Zero order kinetics with the co-efficient (R^2) value 0.996.
KEYWORDS: Floating drug delivery, matrix, compression, in-vitro, gastric residence time

I. INTRODUCTION

Rosuvastatin is recommended to be used for the treatment of dyslipidemia only after other limit such as diet, exercise, and weight reduction have not augmented cholesterol levels. Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase, with mechanism of action comparable to one of other statins. It has close elimination half-life of 19 hrs & time to extent peak plasma concentration within 3–5 hrs following oral administration.

Dose: Start with 5 mg OD, increase if needed up to 20 mg/day, (max 40 mg/ day).

Oral drug delivery is the highest favored and convenient route for the administration of therapeutic agents or drugs for systemic action. This route is favored over other routes because it administer augmented therapeutic advantages, such as ease of administration, patient compliance, cost-effectiveness and compliance in formulations.

There are many access to controlled the drug release in the gastric region. Out of these O-CDDS is a recent access for the formulation of an extended-release dosage form which can furnish a zero-order release profile independent of pH and hydrodynamics of dissolution.

In the present study core tablets of rosuvastatin calcium were prepared using sodium bicarbonate just as gas generating agent.by direct compression method.

II. MATERIALS &METHODOLOGY

Materials &Equipments:

Materials:

Table: List of materials used.

Ingredients	**Manufacturer/ Suppliers**
Rosuvastatin calcium	SAIN Medicaments Pvt.Ltd., Hyderabad.
Calcium Phosphate,Tri basic	Loba Chemie Pvt. Ltd., Mumbai
Carbopol 934P	Loba Chemie Pvt. Ltd., Mumbai
HPMC K100	Loba Chemie Pvt. Ltd., Mumbai

Xanthan gum	Loba Chemie Pvt. Ltd., Mumbai
Guar gum	Loba Chemie Pvt. Ltd., Mumbai
Sodium Bicarbonate	Loba Chemie Pvt. Ltd., Mumbai
Citric acid	A to Z pharmaceuticals, Chennai.
Lactose	SD Fine chemicals Ltd., Mumbai
Magnesium Stearate	Loba Chemie Pvt. Ltd., Mumbai
Talc	SD Fine chemicals Ltd., Mumbai

Equipments

Table No: List of Equipments used

Instruments	**Manufacturer**
Electronic Weighing balance	Shimadzu, Japan. (ELB300)
Sieves	Retsch, Hyderabad. (FR – 019)
Blender	Cadmach, Ahmadabad.
Friabilator	Electro lab, Mumbai. (EF-2)
UV-Visible spectrophotometer	Shimadzu, Japan. (UV-L700)
HPLC	Agilent technologies, Japan. (LC-10 Ai)
FTIR	Shimadzu, Japan. (8400S)
Differential Scaning Calorimetry	Universal V4.7A TA Instruments, USA. (DSC Q200 V24.4 Build 116)
Disintegration apparatus	Electrolab, Mumbai. (ED-04)
Digital Vernier calipers	Wenzhou Shahe, China. (0 -300mm;12)
Dissolution apparatus USP Type II	Electrolab, Mumbai. (TDL-08L)
Single punch machine	Shimadzu, Japan. (CMD3)
Hardness tester	Cadmach, Ahmadabad. (Monsanto)
Friability tester	Electro lab, Mumbai. (EF-TW)

Formulation Preparation:

Preparation of Rosuvastatin calcium floatingtablets:

Tablets containing 150 mg Rosuvastatin calcium were processed, according to the design depicted in table-5, by direct compression method. The respective powders, namely Rosuvastatin calcium, release-retarding polymer(s) Xanthan gum, Guar gum, HPMC K100 and Carbopol 934, a gas-forming agent (Sodium Bicarbonate), and all excipients as given in table -5 were passed through sieve no. 20, separately. Mixing of powders was borne out using a pestle and mortar for 10 min. Magnesium Stearate and talc were then added to the mixed powders. Mixing was last for another 3 min. Finally, 150 mg of each mixture were weighed and fed manually into the die of a single punch tableting machine and compressed. The hardness of the tablets was adopted at 4- 5 kg/cm^{2}using a Monsanto hardness tester.

Steps in Direct CompressionProcedure:

- **Screening:**

Weigh all ingredients except the lubricant and screen them (20 - 45 mesh screen). Add the low density material first and the high density material at the end. It is beneficial to combine materials with poor flowability, small particle size or static charge with another material in order to improve the overall handling of the powder blend. Sometimes a pre-blending step is done to facilitate screening.

- **Mixing:**

Mix the powder blend to achieve content uniformity. Add the lubricant to the powder blend and mix for 2 - 5 minutes (avoid over mixing and over lubrication).

- **Compression:**

Compress the powder blend to target weight and hardness.

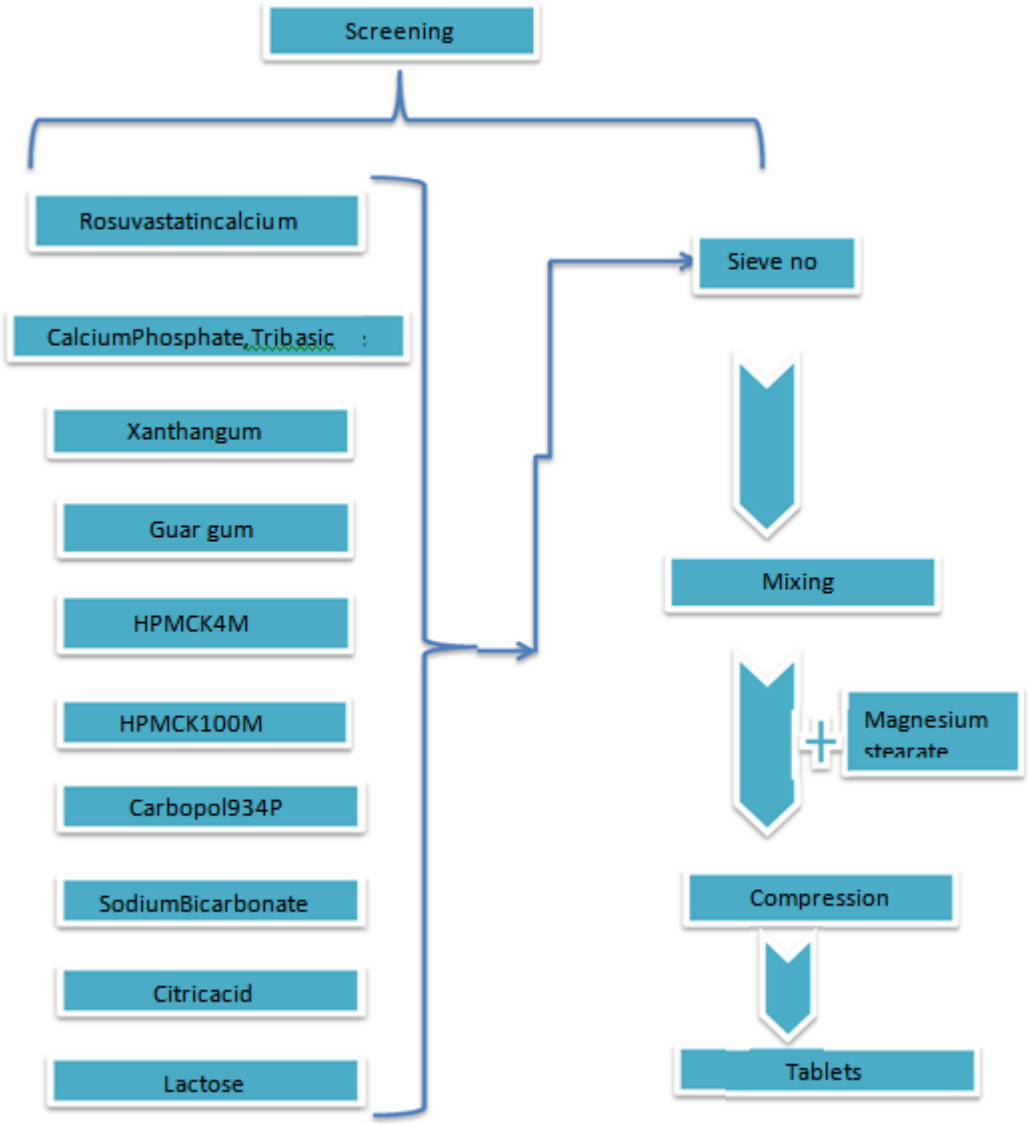

Fig. No. 31: Schematic representation of Preparing Floating table

Formulation development:

Rosuvastatin Calcium is a lipid lowering agent, which is used for the treatment of Dyslipidemia. Because of it's severe adverse effects, side effects, deleterious in high plasma concentration have been made to develop a controlled release formulation to maintain the Therapeutic Index. Due to moisture sensitive nature of Rosuvastatin and to prepare matrix tablets in cost effective and easy manner here preffered the most effective method; Direct compression method. HPMC K 100 M, Carbopol 934P, Xanthan gum, Guar gum polymers, which swell and form a hydrogel matrix, when comes in contact with aqueous solutions and facilitates Floating Drug Delivery system, which is effectively deliver Sparingly soluble drugs (Rosuvastatin) used in view of this study. Here Sodium Bicarbonate is used as gas generatingagent.

Calcium Phosphate Tri basic and Lactose Anhydrous were used as tablet diluents and their reaction on the drug release remain was studied. Calcium Phosphate Tri basic is stabilizing agent for Rosuvastatin and it will prevent the Lactone formation, Oxidation decomposition products. Lactose Anhydrous is used as a diluent in this Direct Compression method, because of moisture sensitivity ofRosuvastatin.

III. RESULTS ANDDISCUSSION:

3. 1. Rosuvastatin and excipients Compatibility Studies:

3. 1. 1. Rosuvastatin and excipients compatibility studies by FTIR Spectroscopy:

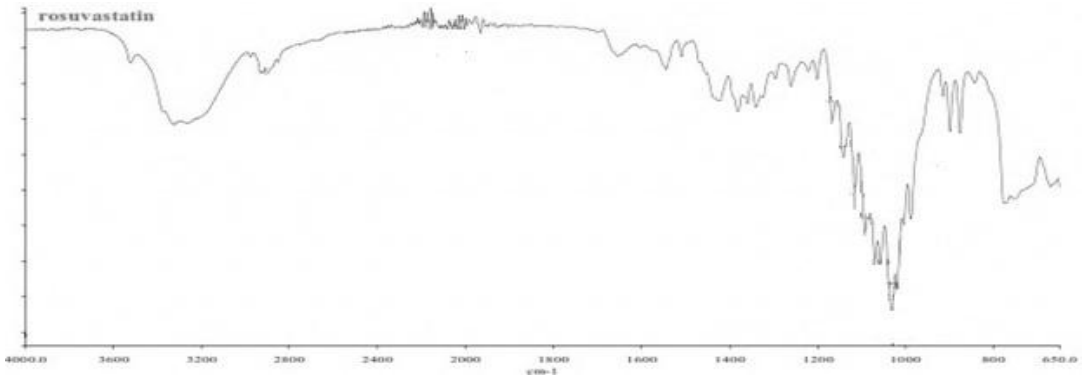

Fig. No. 32: FTIR Spectrum of Rosuvastatin calcium

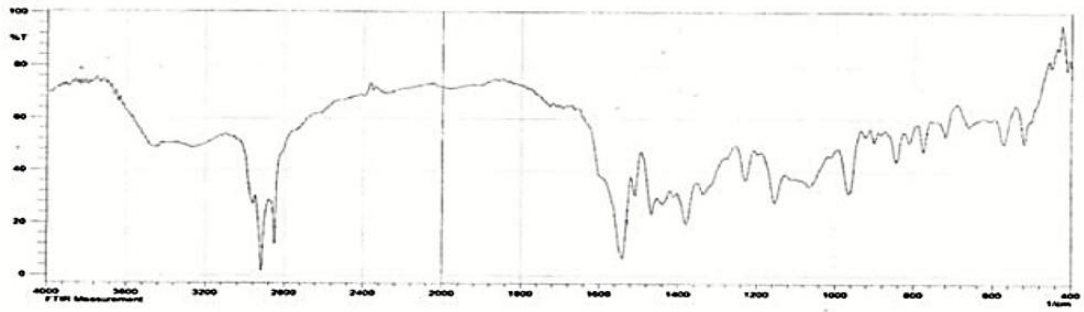

Fig. No. 33: FTIR Spectrum of Optimized batch (F10)

Absorption Peak[13]	**Associated To**
1500	C_6H_5
400-800	-F
1075-1010	-OH

3.1.2.DrugandexcipientscompatibilitystudiesbyPhysicalappearanceandAssay:

TableNo.21:DiffernetratiosofdrugandexcipientsappropriatedforCompatibilityStudy.

Name of Excipients	**Ratio**	**Assay (%)**	**Final observation**		**Conclusion**
			40 ° C / 75 % RH		
			2nd week	**4th week**	
Rosuvastatin calcium	-	98.04	No colour Change	No colour change	Compatible
Rosuvastatin calcium : Tri basic calcium phosphate	1:1	99.46	No colour change	No colour change	Compatible
Rosuvastatin calcium : Xanthan gum	1:1	98.84	No colour change	No colour change	Compatible
Rosuvastatin calcium : Guar gum	1:1	98.08	No colour change	No colour change	Compatible
Rosuvastatin calcium : HPMC K4M	1:1	97.47	No colour change	No colour change	Compatible
Rosuvastatin calcium : HPMC K100M	1:1	99.02	No colour change	No colour change	Compatible
Rosuvastatin	1:1	98.44	No colour	No colour	Compatible

calcium : Carbopol 934P			change	change	
Rosuvastatin calcium : $NaHCO_3$	1:1	99.47	No colour change	No colour change	Compatible
Rosuvastatin calcium : Citric acid	1:1	98.29	No colour change	No colour change	Compatible
Rosuvastatin calcium : Magnesium stearate	1:1	97.26	No colour change	No colour change	Compatible
Rosuvastatin calcium : Talc	1:1	99.48	No colour change	No colour change	Compatible
Rosuvastatin calcium : Lactose	1:1	99.06	No colour change	No colour change	Compatible

Characterization of Rosuvastatin and polymers by DSCanalysis:

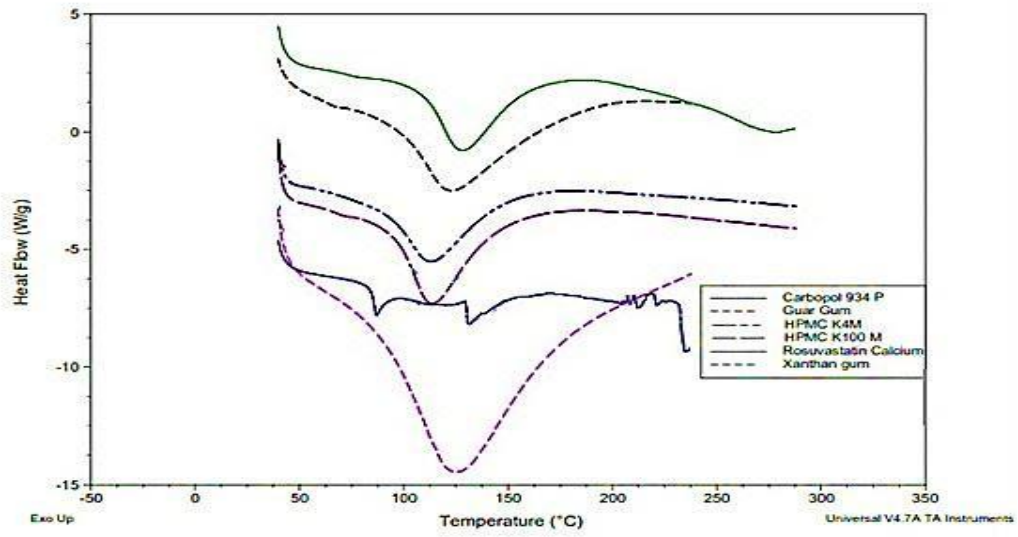

Fig.No. 34: Characterization of pure Rosuvastatin and Polymers by DSC Thermogram

Determination of* λmax of Rosuvastatin *by Simple U.V. Spectrophotometric method:

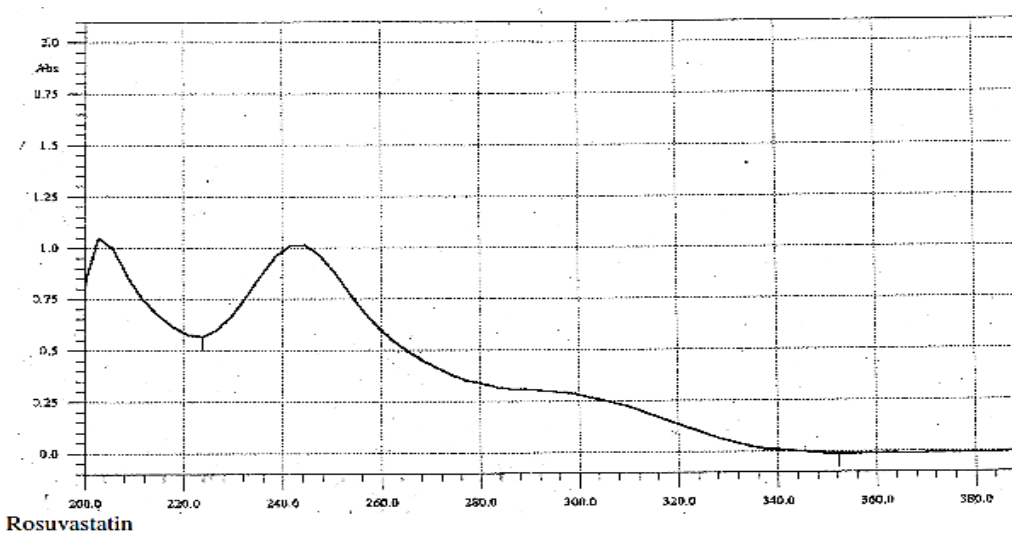

Fig. No. 35: U.V. spectrum of Rosuvastatin calcium in methanol.

1) λmax of Rosuvastatin =244nm

Calibration curve of Rosuvastatincalcium:

Table No. 22: Calibration of Rosuvastatin calcium

Nominal Concentration (µg/mL)	AVG Peak area	Practical concentration (µg/mL)	Accuracy (%)
25	1186360	25.01	100.08
30	1421245	29.98	99.96
40	1895067	40.01	100.03
50	2369727	50.05	100.10
60	2847064	60.14	100.25
70	3324742	70.25	100.36
75	3530504	74.60	99.47

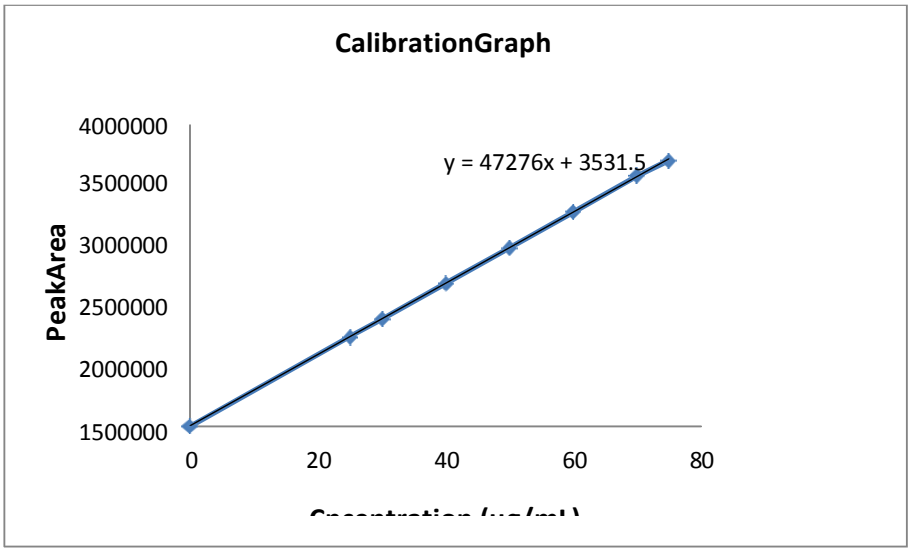

Fig. No. 36: Calibration curve of Rosuvastatin calcium in methanol at 244 nm

3. 5. Preformulation:

3. 5. 1. API characterization:

Table No. 23: Preformulation parameters of blended Rosuvastatin powder:

Parameters	Mean readings
Bulk Density	0.67
Tapped Density	0.86
Hausner's ratio	1.28
Angle of repose	36.5^0
Carr's index	22.09

3. 5. 2. Flow properties:

Table No.24 : Flow properties of blended formulations:

Formulation Code	Blend Characterization				
	Bulk density (BD) (g/cc)	Tapped density (TD) (g/cc)	Compressibilty Index (%)	Hausner's ratio	Angle of repose
F1	0.468 ± 0.009	0.586 ± 0.013	20.13 ± 1.49	1.25 ± 0.03	24.55 ± 1.53
F2	0.464 ± 0.004	0.583 ± 0.012	20.41 ± 1.64	1.25 ± 0.04	28.98 ± 1.57
F3	0.464 ± 0.003	0.584 ± 0.015	20.54 ± 1.34	1.26 ± 0.04	29.85 ± 1.44
F4	0.472 ± 0.005	0.589 ± 0.014	19.86 ± 0.76	1.24 ± 0.08	25.30 ± 1.45
F5	0.466 ± 0.006	0.584 ± 0.017	20.20 ± 0.87	1.25 ± 0.06	28.97 ± 1.58
F6	0.469 ± 0.004	0.588 ± 0.0019	20.23 ± 1.36	1.25 ± 0.04	29.13 ± 1.23
F7	0.490 ± 0.009	0.594 ± 0.013	17.50 ± 1.49	1.21 ± 0.06	29.85 ± 1.44
F8	0.486 ± 0.003	0.586 ± 0.015	17.06 ± 1.34	1.21 ± 0.08	25.98 ± 1.57
F9	0.486 ± 0.004	0.578 ± 0.012	15.67 ± 1.62	1.18 ± 0.04	24.41 ± 1.53
F10	0.484 ± 0.004	0.581 ± 0.013	16.69 ± 1.64	1.20 ± 0.04	24.55 ± 1.53

Post compressionalparameters:

Physical characteristics of Rosuvastatin calcium floating matrixtablets:

Table No25.: Physical characteristics of Rosuvastatin calcium floating matrix tablets:

Formulation Code	Physical properties		
	Weight variation (mg)	Hardness (Kg/cm^2)	Diameter (mm)
F1	150 ± 0.46	4.8± 0.34	7 ± 0.01
F2	150 ± 0.64	4.3± 0.15	7 ± 0.12
F3	150 ± 0.48	4.2 ± 0.44	7 ± 0.14
F4	150 ± 0.60	5.6 ± 013	7 ± 0.14
F5	150 ± 0.38	5.6 ± 0.34	7 ± 0.23
F6	150 ± 0.64	5.9 ± 0.15	7 ± 0.26
F7	150 ± 0.55	5.9 ± 0.23	7 ± 0.18
F8	150 ± 0.54	5.3 ± 0.17	7 ± 0.10
F9	150 ± 0.53	5.2 ± 0.14	7 ± 0.04
F10	150 ± 0.42	5.2± 0.49	7 ± 0.08

Table No. 26: Physical characteristics of Rosuvastatin calcium floating Tablets

Formulation Code	Physical properties		
	Thickness (mm)	Friability (%)	Drug content (mg)
F1	3.19 ± 0.01	0.339 ± 0.011	39.65
F2	3.17 ± 0.14	0.352 ± 0.014	39.26
F3	3.20 ± 0.08	0.410 ± 0.012	39.24
F4	3.14 ± 0.04	0.328 ± 0.016	38.31
F5	3.16 ± 0.06	0.340 ± 0.01	38.18
F6	3.21 ± 0.13	0.350 ± 0.24	38.97
F7	3.15 ± 0.17	0.225 ± 0.42	39.83
F8	3.16 ± 0.06	0.246 ± 0.23	39.27
F9	3.22 ± 0.05	0.251 ± 0.15	39.40
F10	3.23 ± 0.03	0.286 ± 0.38	39.52

Floating behavior of Rosuvastatin calcium Floating MatrixTablets:

Table No.27: Floating behavior of tablets with Sodium Bicarbonate

Formulation Code	Parameter		
	Amount of $NaHCO_3$	Floating lag time (sec)	Floating duration (Hrs)
F1	10	86	> 10
F2	20	77	> 10
F3	30	64	> 10
F4	10	84	> 10
F5	20	73	> 10
F6	30	62	> 10
F7	20	58	> 10
F8	20	63	> 10
F9	25	60	> 10
F10	30	54	> 10

Fig.No.37.Imagetakenduring*invitro*buoyancystudyofformulaF10in200mL 0.1N HCl at particular timeintervals.

Swelling index of Rosuvastatin calcium Floating MatrixTablets:

Table No.28 : Swelling Index of tablets:

Formulation Code	Time (Hrs)				
	1	2	4	6	8
F1	58.46	89.38	141.65	189.52	199.86
F2	68.75	97.47	163.41	213.76	225.39
F3	79.43	119.59	177.66	228.53	243.69
F4	32.74	70.87	132.94	174.88	181.57
F5	54.63	86.36	141.88	183.36	195.49
F6	67.71	99.47	157.59	198.58	218.38
F7	49.83	67.69	104.71	121.77	135.25
F8	36.55	52.31	89.43	99.50	117.74
F9	34.79	55.27	83.33	104.26	119.56
F10	37.47	56.76	84.47	101.51	125.32

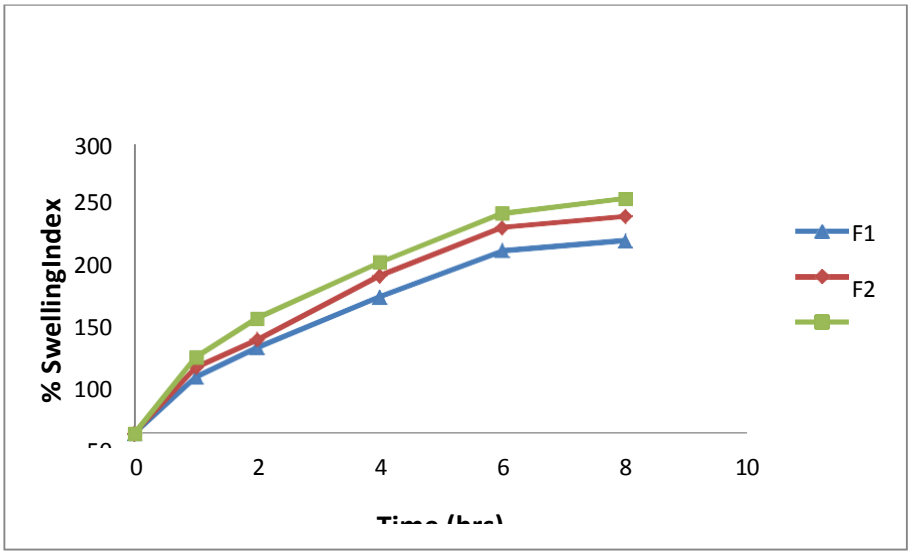

Fig. No. 38: Comparitive Swelling Index for F1, F2 & F3

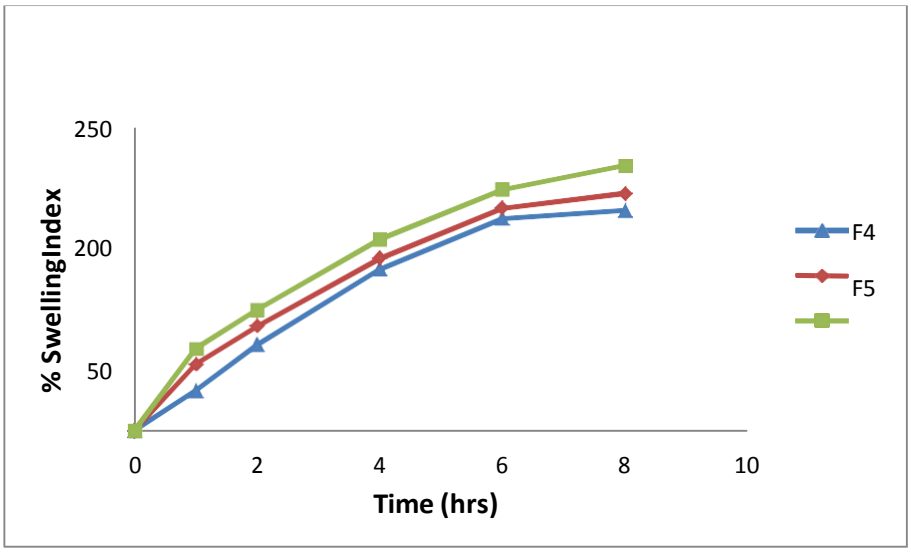

Fig. No. 39: Comparitive Swelling Index for F4, F5 & F6.

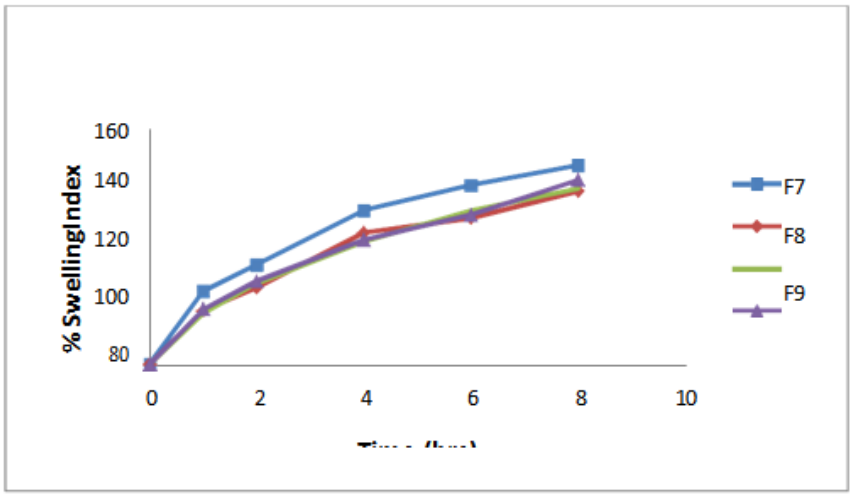

Fig. No. 40: Comparitive Swelling Index for F7, F8, F9 & F10.

In Vitro Dissolution Studies of Rosuvastatin calcium Floating MatrixTablets:

Table No.29 : *Rosuvastatin calcium Floating Matrix Tablets In Vitro* drug release studies (F1 to F6):

Time (hr)	% Drug release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	11±1.39	9± 1.32	8± 1.62	10±1.62	7± 1.39	6± 1.95
4	37±1.55	35±0.89	33±1.55	34±1.25	31±1.63	27±1.07
8	59±1.32	56±1.63	54±1.65	56±1.63	52±1.83	46±1.19
12	83±1.63	81±1.19	79±1.39	80±0.89	78±1.39	63±1.19
16	91±1.42	90±1.55	87±1.19	88±1.19	85±1.63	78±1.19
20	99±1.06	99±1.25	95±1.32	99±1.63	93±0.89	85±1.39
24	-	-	99±0.89		99±1.25	93±1.42

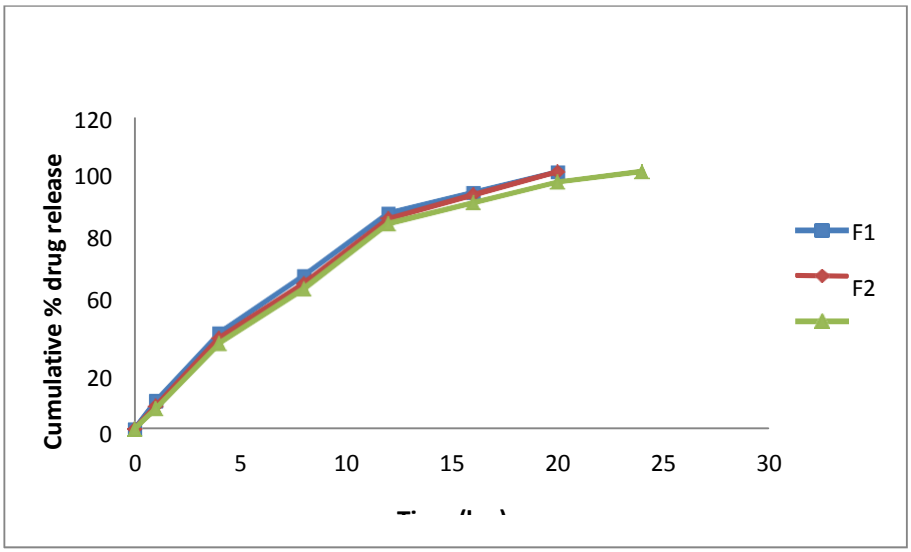

Fig. No.41 : Comparitive dissolution profile for F1, F2 & F3

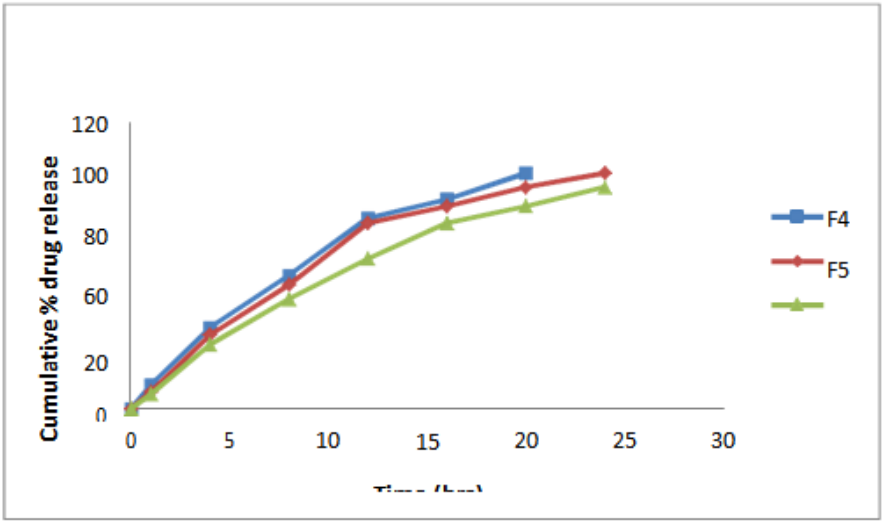

Fig. No. 42: Comparitive dissolution profile for F4, F5 & F6

Table No. 30: ***Rosuvastatin calcium Floating Matrix Tablets In Vitro*** **drug release studies (F7 to F10):**

Time (hr)	% Drug release			
	F7	**F8**	**F9**	**F10**
1	2± 1.77	4± 1.51	6± 1.57	7± 1.57
4	13± 1.32	18± 1.05	26± 1.32	22± 1.46
8	24± 1.07	31± 1.23	48± 1.83	39± 1.63
12	37± 1.62	47± 1.63	65± 1.69	54± 1.28
16	49± 0.89	56± 1.62	79± 1.19	71± 1.09
20	55± 1.55	73± 1.83	87± 1.25	88± 1.42
24	68± 1.63	84± 1.19	99± 1.55	99± 1.69

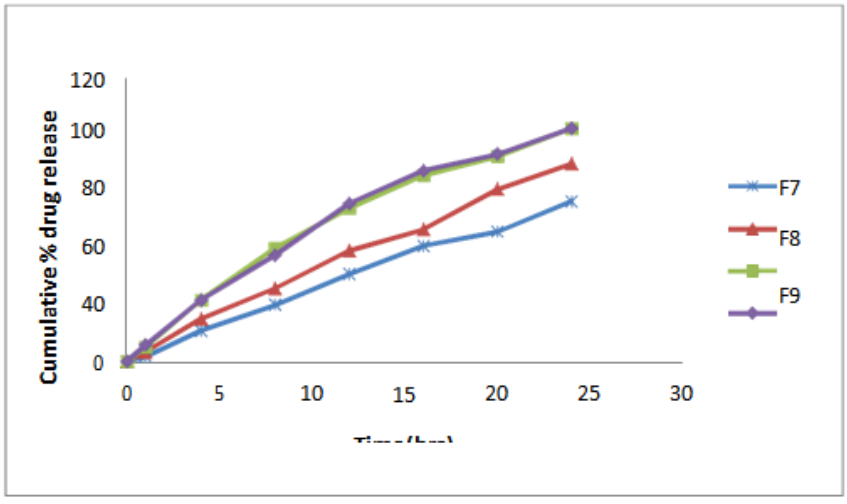

Fig. No. 43: Comparitive dissolution profile for F7, F8, F9 & F10.

3. 10. Drug release kinetics of **Rosuvastatin calcium Floating Matrix Tablets** ***:***

Table No. 31: Regression co-efficient (R^2) values of drug release data obtained from various kinetic models and Release exponent (n) values from Korsmeyer-Peppas.

Formulation Code	kinetic models					
	Zero order	**First order**	**Higuchi**	**Korsmeyer- Peppas**		**Hixson- crowell**
	R^2	**R^2**	**R^2**	**R^2**	**n**	**R^2**
F1	0.939	0.935	0.990	0.987	0.746	0.994
F2	0.948	0.919	0.992	0.985	0.812	0.996
F3	0.913	0.965	0.981	0.976	0.802	0.988
F4	0.955	0.897	0.992	0.991	0.773	0.994
F5	0.919	0.942	0.982	0.976	0.837	0.989
F6	0.957	0.979	0.996	0.985	0.862	0.996
F7	0.993	0.985	0.979	0.989	1.093	0.995
F8	0.995	0.951	0.997	0.996	0.945	0.989
F9	0.966	0.856	0.998	0.988	0.877	0.990
F10	0.996	0.872	0.992	0.993	0.838	0.993

3. 10. 1. Graphs of drug release kinetics for optimized batch (F10):

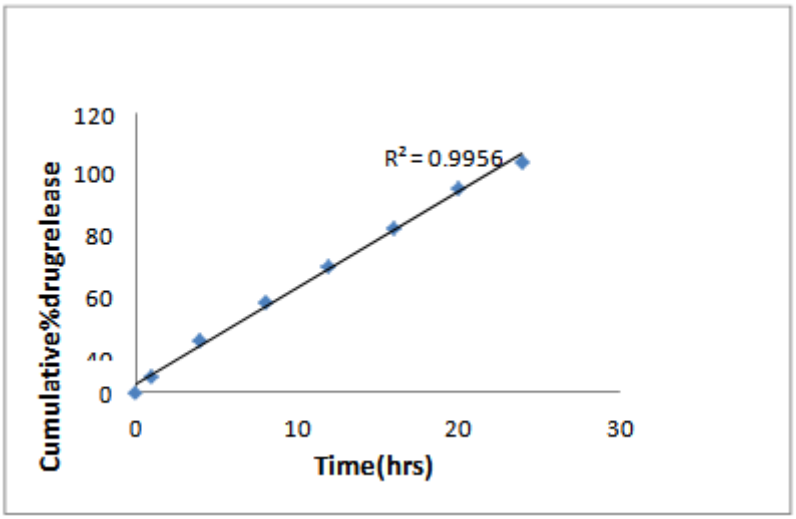

Fig.No.44:Zeroorderkinetics

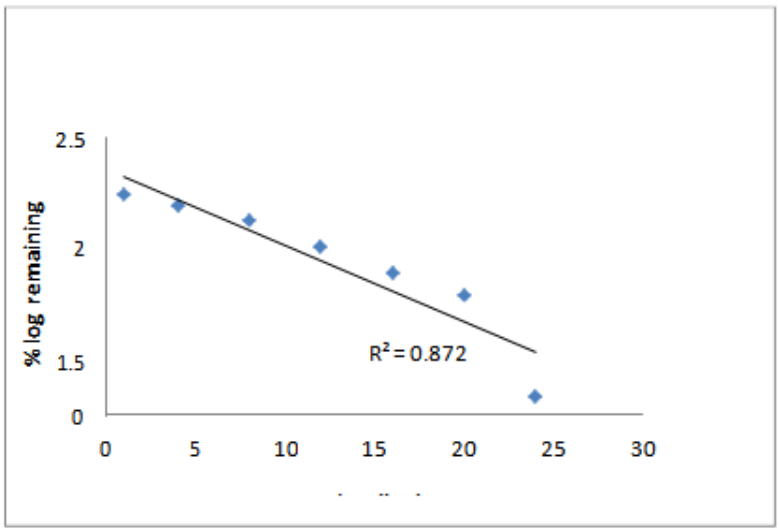

Fig.No.45:Firstorderkinetics

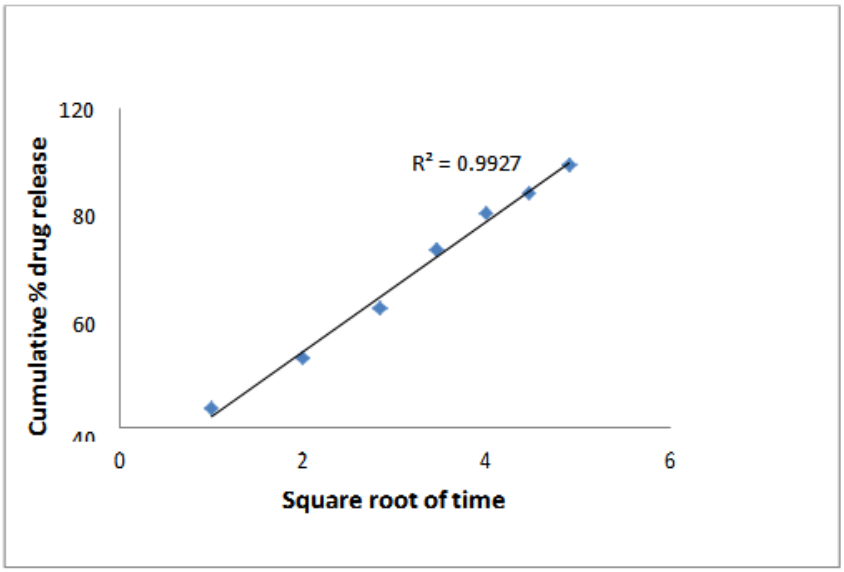

Fig. No. 46: Higuchi drug release kinetics

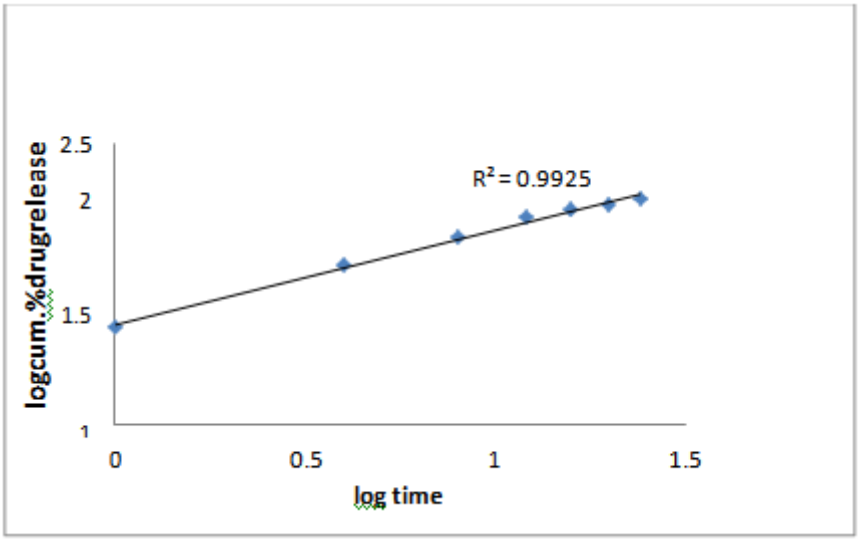

Fig. No. 47: Krosmeyer - Peppas drug release kinetics

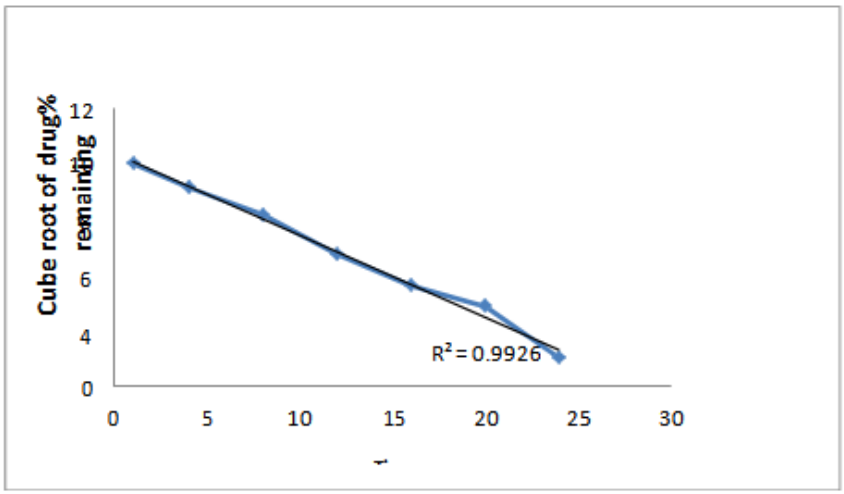

Fig. No. 48: Hixson-crowell drug release kinetics

3. 11. Stability studies:

Table No. 32: Optimized formulation (F10) Stability studies:

Specifications	Duration		
	After 15 days	**After 30 days**	**After 45 days**
Physical appearance	No change	No change	No change
Weight variation (mg)	150 ± 1.26	150 ± 1.44	149 ± 0.86
Hardness (Kg/cm^2)	5.2 ± 0.89	5.1 ± 1.18	4.9 ± 0.45
Diameter (mm)	7 ± 0.08	7 ± 0.16	6.9 ± 0.03
Friability (%)	0.286 ± 0.82	0.431 ± 0.03	0.524 ± 0.12
% Drug content at 25^0C/65%RH	99.46 ± 0.43	98.86 ± 0.62	98.73 ± 0.91
% Drug content at 25^0C/70%RH	99.26 ± 0.26	98.42 ± 0.18	98.25 ± 0.28
% Drug content at 40^0C/65%RH	98.88 ± 0.21	98.34 ± 0.32	98.16 ± 0.44
% Drug content at 40^0C/70%RH	98.36 ± 0.32	98.16 ± 0.41	97.89 ± 0.16
Bouyancy lag time (sec)	55 ± 1.23	56 ± 2.20	56 ± 3.13
Duration of Bouyancy (Hrs)	> 10	> 10	> 10

3. 12. Discussion:

Oral route of administration is the better extensively preferred route of delivery expected to the calm of administration, prevention of pain and other hazards such as parenteral administration and include good patient conformity. The absolute advantage of the oral continuous d release dosage form is that it preserve the therapeutic concentration over an prolonged period of time. Distinct new advancement technologies have been refined to overwhelmed the physicochemical and pharmacokinetic characteristic of drugs, at the same time improving the patient conformity. In this article, technologies is the Floating matrix category of dosage forms.

3. 12. 1. Formulation development:

Rosuvastatin Calcium is a lipid lowering agent, which is used for the treatment of Dyslipidemia. Because of it's severe adverse effects, side effects, deleterious in high plasma concentration have been made to develop a controlled release formulation to maintain the Therapeutic Index. Due to moisture sensitive nature of Rosuvastatin and to prepare matrix tablets in cost effective and easy manner here preffered Direct compression method. HPMC K 100 M, Carbopol 934P, Xanthan gum, Guar gum polymers, which swell and form a hydrogel matrix, when comes in contact with aqueous solutions and facilitates Floating Drug Delivery System, which is effectively deliver Sparingly soluble drugs (Rosuvastatin) used in this studies. Here Sodium Bicarbonate is used as gas generating agent.

Calcium Phosphate Tri basic and Lactose Anhydrous were used as tablet diluents and their effective response on the drug release was studied. Calcium Phosphate Tri basic is stabilizing agent for Rosuvastatin and it will prevent the Lactone formation, Oxidation decomposition products. Lactose Anhydrous is used as a diluent in this Direct Compression method, because of moisture sensitivity of Rosuvastatin.

3. 12. 2. Drug and excipients compatibility studies:

The affinity of drug and formulation ingredient is important imperative before formulation. It is therefore necessary to affirm that the drug does not react with the polymers and excipients beneath experimental conditions and alter the shelf life of product or any other undesirable issues on the formulation. Through FTIR analysis, The IR spectra of Rosuvastatin calcium is characterized by the absorption frequency of two stretching band at 3394.72 cm^{-1} and that of carbonyl group at 1604.77 cm^{-1}. The results indicate that has no interactions or bondings between drug and polymers/excipients, so there was no chemical incompatibility between drug and excipients used in the formulation.

The vials, in which the drug and excipients are in different ratio was exposed to 40˚c / 75 % RH and observed physical appearance, made at initially, 2 week, and 4week. The samples should not change in colour. From the Assay of solid admixtures samples also gives good percentage of drug content. So it's showing good compatibility for the formulation development with the mentioned polymers and excipients.

3. 12. 3. Characterization of Rosuvastatin and polymers by DSC analysis:
Rosuvastatin and polymers were identified by DSC analysis,the characteristic peaks indicating melting points of Rosuvastatin, HPMC K100M, Carbopol 934P, HPMC K4M, Xanthan gum, Guar gum are 129.38°c, 142.78°c, 153.96°c, 142.30°c, 154.85°c and 162.51°crespectively.

3. 12. 4. Determination of λmax of Rosuvastatin in simple UV Spectrophotometric method:
The method showed an absorption maximum for Rosuvastatin calcium at 244 nm, the λ max which is similar to the obtained reference (244 nm) and the result showed in **Figure No.36.**

3. 12. 5. Calibration curve of Rosuvastatin calcium:
The results from HPLC method showed that, there was an excellent correlation and linearity between peak area and analyte concentration. The linearity result showed in **Table No22.**

3. 12. 6. Flow Properties:
A flow property plays an important role in pharmaceuticals especially in tablet formulation by virtue of improper flow may cause more weight variation. Values of Carr's Index (Compressibility) 12 to 18 % usually give rise to good flow properties but readings above 25% signify poor flow properties. It was initiate that the compressibility values of the powders were in the range from 17.50 ± 1.49, 17.06 ± 1.34, 15.67 ± 1.62, 16.69 ± 1.64 (F7, F8, F9, F10) hence exhibit good flow characteristics. Values of angle of repose are infrequently 20^o and values up to 40^o indicate moderate flow properties. Above 50^o yet the powder flows only with great complications. Dynamic angle of repose assessments can be depict with relative standard deviations of approximately 2%. They are specifically sensitive to change in particle size distribution and to the moisture content, and they furnish a rapid compelling batch to batch differences in these respects. The angle of repose of the powders were in the range of 29.85 ± 1.44, 25.98 ± 1.57, 24.41 ± 1.53, 24.55 ± 1.53 (F7 – F10) which indicate a good flow property of the powders. Here the angle of repose was found to be below 40^o. This shows that the reasonably flow property of powders. The results are shown in **Table No.24.**

3. 12. 7. Evaluation of Rosuvastatin calcium Floating Matrix Tablets:
2. Physical Parameters (Shape, Size,Hardness &Friability):
The shape and size of the tablets were found to be in a period of the limit. The results are given in **Table No. 25 & 26.** The hardness of the tablets was establish to be in the range of 5.2 ± 0.15 to 5.9 ± 0.23 Kg/ cm^2. It was be in the range of monograph specification. The friability of the tablets was establish to be less than 1% and it was within the range of standard requirement.
3. Weight Variation:
Weight variation test cooperate to identify if the tablet contain pertinent quantity of the drug. From each of the formulations twenty tablets were inconstantly selected and weighed. The results are given in **Table No. 26.** The average weights of the tablets were found to be in reach the prescribed official limits(IP).
4. Drug content Uniformity:
Drug content for each of the formulations was predicted. The drug content for all the batches was found to be in the limit of 99.45 to 101.40 %. The results are given in **Table No. 26.**

3.12.8.EffectofGasgeneratingagent(SodiumBicarbonate)onFloatinglagtimeand Floatingduration:
The inspected gastric floating systems occupied Sodium Bicarbonate as a gas-forming agent dispersed in a hydrogel matrix (HPMC K100, Carbopol 934P, Xanthan gum, Guar gum). The buoyancy study acknowledged the ability of most formulae to maintain buoyant more than 10 h **(Table No. 27** and **Fig. 41**). This suggests that the gel layers, formed by the investigated polymers, empower efficient entrapment of the generated gas bubbles. The conceivable increase in tablet porosity made it float on the test medium (0.1 N HCl) for this extended period of time. These matrices are fabricated so that consequent arrival in the stomach, carbon dioxide gas is redeem by the acidity of the gastric contents and is entrapped in the thicken hydrocolloid. A decrease in specific gravity generate the dosage form to float on the chime. The extended residence time of drug in stomach could induce increased absorption due to the evidence that the stomach and upper intestine was the main absorption site for Rosuvastatin calcium. One of the factors influencing the behavior of the effervescent systems is their floating lag time. As shown in **Table No. 27.** The floating lag time of formulaF1,F2,F3,F4,F5,F6,F7,F8,F9,F10are86,77,64,84,73,62,58,63,60 and 54seconds .This could be explained with view to the rate of the test medium penetration into these matrices and consequently the time appropriate for gel formation. From the above results concluded that as the percentage of Sodium Bicarbonate increases, the floating lag time decreases. This experience might be due to the generation of larger amounts of effervescence with higher Sodium Bicarbonate percentages. This would edge to an increase in the rate of pore formation and consequently accelerated hydration of the tablet's matrices. It is aid to note that high amount of Sodium

Bicarbonate containing formulae (F10) have shorter floating lag time than the interrelated formulae prepared with low amount of Sodium Bicarbonate.

3. 12. 9. Swelling Behavior:

The hydration ability of the formula is important because it impact: (i) tablet buoyancy, (ii) adhesion ability of swellable polymers as HPMC K100, Carbopol 934, Xanthan gum, Guar gum in contact with the test fluid and (iii) drug release kinetics. It could be achieve that the test medium uptake of the prepared matrices depends on the type of polymer **(Figures35,36,37)**. Formulaton1 showed the highest swelling indices throughout the study period. This may be related to the high affinity of Xanthan gum containing matrices to the test medium. The maximum swelling index of this formula 243.69 was achieved after 8 h. The maximum swelling indices of F1, F2, F3, F4, F5, F6, F7, F8, F9and F10 formulae 199.86, 225.39, 243.69, 181.57, 195.49, 218.38, 135.25, 117.74, 119.56, 125.32**(Table. No. 28)** were achieved after 8 h. Throughout the study period, low the swelling indices was achieved with formula F9 & F10. This could be relevant to the lower affinity of Carbopol 934 containing matrices to the test medium. As sugessted by Bertram and Bodmeier, the ability of hydrogels to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water access into the polymer network leading to expansion and therefore an ordering of the polymer chains. Peppas and Khare suggested that the swelling equilibrium (maximum swelling index) is attained when the osmotic forces of the functional groups are balanced by the restrictive forces of the higher ordering of the polymer chains. As the water continues to enter the tablet, a highly concentrated polymer solution is formed, designate as a gel layer. The solvent endure to penetrate the tablet, and the gel layer and the dimensions of the swollen tablet increase, a process normally assigned to as the swelling process. In a parallel line, Ju et al. suggested that a polymer concentration gradient is formed in the tablet, starting at a high concentration in the more or less dry core and declining through the gel layer tagainst the gel layer surface. At the surface of the gel layer, denoted as the erosion front, the polymer concentration is assumed to coincide to the critical polymer concentration.

3. 12. 10. *In- vitro* studies of Rosuvastatin Calcium Floating matrix tablets:

Depending on the type and concentration of the examined polymer(s) in the current study, variable drug release profiles were successfully bespoke. Tablets formulated using guar gum and xanthan gum alone and combine were eroded faster and dissolved completely within 14 - 16 hr, while tablet containing HPMC remain intact and provided slow release up to 20-24 hr. The influence of HPMC K100, Carbopol 934, Xanthan gum, Guar gum on the release of Rosuvastatin calcium from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5 ^{0}C was shown in **Fig. No. 38, 39, 40.** It was clear that all formulae flourish in controlling the rate of drug release. However, the drug release rate was dependent on the type and concentration of the investigated polymer(s). At 12 hr the percentage of drug releaseof F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 formulations were found as 83± 1.63, 81±1.19,79±1.39,80±0.89,78±1.39,63±1.19,37±1.62,47±1.63,65±1.69and 67± 1.28 respectively. At 20 Hr the percentage of drug release of F1,F2, F3, F4,F5, F6, F7, F8, F9 and F10 formulations were found as99± 1.06, 99± 1.25, 95± 1.32, 99±1.63, 93± 0.89, 85± 1.39, 55± 1.55,73± 1.83,87± 1.25 and 88± 1.42 respectively. At 24 Hr the percentage of drug release of F3, F5, F6, F7, F8, F9 and F10 formulations were establish as 99±0.89,99±1.25,93±1.42,68±1.63,84±1.19,99±1.55and99± 1.69 respectively.

3.12.11.Effect of Xanthan gum and HPMCK4M polymer mixture on Rosuvastatin Calcium Floating Matrix tablets:

The formulations F1, F2, F3, which contain 20%, 26%, 33% of the polymer mixture of Xanthan gum and HPMC K4M, exhibit good swelling behavior but formulation F3only succeeded in predominant the rate of drug release for 24 hrs.

3. 12. 12. Effect of Guar gum and HPMC K4M polymer mixture on Rosuvastatin Calcium Floating Matrix tablets:

The formulations F4, F5, F6, which are containing 20%, 26%, 33% of the polymer mixture of Guar gum and HPMC K4M, showing good swelling behavior and Floating duration (more than 10hrs) and F5 only succeeded in predominant the rate of drug release for 24hrs. The F6 formulation showing only ≈85% drug release at 24hr. So we can conclude that from the first six formulations (F1 – F6), increase in amount of polymer/ viscosity results decrease in drug release rate.

3.12.13. Effect of HPMCK100M and Carbopol934P polymer mixture on Rosuvastatin Calcium Floating Matrix tablets:

The formulations F7, F8, F9, F10 which are containing 33%, 26%, 20%, 20% of the polymer mixture of Guar gum and HPMC K4M showing much lower drug diffusivity. F9, F10 formulations, which are having

less amount of polymer mixture succeeded in controlling the rate of drug release for 24hrs, because of the higher viscosity of Carbopol 934, HPMCK100M would boost the synergic effect, formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rate. In a parallel line, Siepmann and Peppas proposed that the drug release from Carbopol 934P and HPMC K100M matricesis basically governed as follows:

(i) At the beginning, steep water concentration gradients are developed at the polymer/water interface resulting in water impregnations into the matrix.

(ii) Due to the impregnation of water, polymers swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system.

(iii) Upon contact with water, the drug dissolves and diffuses out of the appliance due to concentration gradients.

(iv) With increasing water content, the diffusion coefficient of the drug increases substantiallyextensively

It is aid to note that, sometimes a blowout effect was observed with all formulations. This could be due to the fact that the gel layer, which maintains the drug release rate, needs some time to become adequate. The rapid drug dissolution from the surface of the tablets could be another possible clarifications.

Uncertainly, this effect was less prevailing with those formulae have synergic effect of carbopol 934P and HPMC K100M amount. Formation of gel like grid surrounding these matrices, upon contact with aqueous media, would produce enegetic surface barriers that would effectively reduce the burst drug release. Taking into consideration the intention of the work of achieving a compromise between excellent floating behaviour (very short floating lag time and extended floating duration), extended gastro retentive period and sustained drug release characteristics, formula F9 was chosen for further studies. The formulation (F10), which is containing highest gas-forming agent concentration present the highest drug release rate and short Floating Lag time than F9 formulation. The ascent of the gas-forming agent concentration would generate larger amounts of effervescence well known to an increase in the rate of pore formation, rapid hydration of the tablets matrices and consequently a faster drug release rate.

3. 12. 14. Drug Release Kinetics for Rosuvastatin Calcium Floating Matrix tablets:

Different models like Zero order, First order, Higuchi's, and Peppa's were drawn for the formulations. The conclusions of linear regression investigation of data including regression coefficient are compiled in **Table No. 31** and **Figure No. 44 - 48.** When the regression coefficient 'R^2' value of zero order and first order plots were correlated, it was observed that the 'R^2' values of zero order were in the range of 0.913 to 0.995 although the 'R^2' values of first order plots were found to be in the range of 0.856 to 0.985 indicating drug release from all the formulations were found to follow zero order kinetics. The good fit of the Higuchi model to the dissolution profiles of all the formulations suggested that diffusion is the prevailed mechanism limiting drug release since the 'R^2' values of Higuchis plots were nearer to linearity (0.985-0.996). Korsmeyer-Peppas plots, slope equal to "n" states that kind of drug release, $0.45 < n < 0.89$, Non – Fickian/anomalous release for the optimized formulation F10. From the drug release kinetics stuy the optimized formulation F10 gives the "R^2" values, Zero order (0.965), First order (0.872), Higuchi (0.992), Korsmeyer-Peppas (0.838), so it has concluded that formulation follows zero order controlled release and Diffusion controlledmechanism.

3. 12. 15. Stability studies:

Stability studies were operated for the optimized formulation F10. The stability study was performed at 25^0C/65%RH, 25^0C/70%RH, 40^0C/65%RH, 40^0C/70%RH for a specific period of time. The tablets were analysed for Physical appearance, Weight variation, Hardness, Diameter, Friability, Drug content, Bouyancy lag time, Duration of Bouyancy. The overall results showed particular formulation is stable at the above mentioned storage conditions. shown in **Table No. 32.**

IV. SUMMARY

In this current study Controlled-release effervescent floating matrix tablets of Rosuvastatin calcium were processed by direct compression technique, using HPMC K100, Carbopol 934P, Xanthan gum, Guar gum as release retardant components. Different parameters like hardness, friability, weight variation, drug content uniformity, Floating lag time and duration, swelling index and in-vitro drug release were evaluated for these formulations. The hardness of the floating tablets was accomodate in the current work ≈ 4 - 5 kg/cm^2. The thickness of all tablet batches ranged from ≈3.2mm. All the tablet formulae showed satisfacotry physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ≈150 ± 0.66mg. All the prepared formulae meet the USP requirements. Drug uniformity results were found to be good among different batches. The percentage of drug content ranged from 99.65% to 101.40%. The percentage friability for all formulae was less than 1%, indicating better mechanical resistance.

The floating lag time of formula F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 are 86,77, 64, 84, 73, 62, 58, 63, 60 and 54 seconds. This could be elucidated with regard to the rate of the test medium penetration into these matrices and therefore the time required for gel formation. From the above results concluded that as the percentage of Sodium Bicarbonate increases, the floating lag time decreases. *Invitro* drug released studies were evaluated for 24 hr. At 12 hr the percentage of drug release of F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 formulations were found as 83 ± 1.63, 81±1.19,79±1.39,80±0.89,78±1.39,63±1.19,37±1.62,47±1.63,65±1.69 and 67 ± 1.28 respectively. At 20hrs the percentage of drug release of F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 formulations were found as 99 ± 1.06, 99 ± 1.25, 95 ± 1.32, 99± 1.63, 93± 0.89, 85± 1.39, 55± 1.55, 73± 1.83, 87± 1.25 and 88± 1.42 respectively. At 24hrs the percentage of drug release of F3, F5, F6, F7, F8, F9 and F10 formulations were establish as 99 ± 0.89, 99 ± 1.25, 93± 1.42, 68 ± 1.63, 84 ± 1.19, 99 ± 1.55 and 99± 1.69 respectively (Values have shown in **Table. No. 29 & 30**). It was found that increase in the concentration of HPMC K100, Carbopol 934, Xanthan gum, Guar gum decreases the drug release.

Polymers accumulate in gastric fluid to produce a highly viscous coating around the tablet through which the drug must dispersed. This property makes them useful ingredients for sustained release matrix tablet. All the formulations have shown good sustained drug release and the formulations F7 to F10 containing Carbopol 934P and HPMC K100M have shown better controlled effect for 24 hr than other formulations. Those formulations have synergic effect of carbopol 934P and HPMC K100M amount in retarding drug release, reduce accelerated drug dissolution from surface of the tablets.

Different models like Zero order, First order, Higuchi's, and Peppa's were drawn for the formulations. The results of linear regression analysis of data including regression coefficient are summarized in **Table. No. 31 and Figure. No. 44 - 48.** When the regression coefficient 'R^{2}' value of zero order and first order plots were compared, it was observed that the 'R^{2}' values of zero order were in the range of 0.913 to 0.995 whereas the 'R^{2}' values of first order plots were found to be in the range of 0.856 to 0.985 indicating drug release from all the formulations were estimated to follow zero order kinetics. The good fit of the Higuchi model to the dissolution profiles of all the formulations recommended that diffusion is the predominant mechanism confined drug release since the 'R^{2}' values of Higuchis plots were nearer to linearity (0.981-0.998), Hixsoncrowell range is between 0.988 – 0.996. Korsmeyer-Peppas plots, slope equal to"n" states that kind of drug release, $0.45 < n < 0.89$, Non – Fickian/anomalous release for the optimized formulationF10.

V. CONCLUSION

The Floating matrix tablets of Rosuvastatin Calcium were processed and evaluated. The Gastric Residence Time (GRT) of the tablet was considerably increased up to 24hrs time by optimizing the polymer concentration. The release was sustained up to 20hrs with 1: 1.5 ratio of HPMC K4M and Xanthan gum, but the Floating Lag time was establish to be more with the combination.

Similarly, the combination between HPMC K4M and Guar gum also controlled the release more than 20hrs was observed. The HPMC K100M and Carbopol 934P combination with the ratio of 2:1 was found to be satisfactory with release profile. Hence the Formulation F10 was optimized by for further studies. The formulation (F10) also satisfies the Swelling Index, Buoyancy time controlled the drug release up to 24hrs. The mechanism of drug release pursued the Zero order kinetics with the co-efficient (R^{2}) value 0.996.

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