ISSN No:-2456-2165

Studies on Formulation and in-Vitro Evaluation of Mucoadhesive Microbeads of Rosuvastatin Calcium by using Central Composite Design

Dr. T. AYYAPPAN[1], G. SARANYA[1], R.VIGNESWARAN[1] and Dr. T. VETRICHELVAN[2]
*1Department of Pharmaceutics,2Department of Pharmaceutical Analysis,
Adhiparasakthi College of Pharmacy, Melmaruvathur-603319, and affiliated to
The Tamil Nadu Dr M.G.R. Medical University, Chennai-28, Tamil Nadu, India

For Correspondence*
Dr. T. AYYAPPAN,
M.Pharm, Ph.D., Associate Professor,
Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur 603 319

Abstract:- The Mucoadhesive drug delivery system was a new approach in pharmaceutical field and drug retention for a prolonged time has been achieved. Rosuvastatin calcium is a HMG-CoA Reductase inhibitors (statins) used in the treatment of percholesterolemia or hyperlipidemia. Mucoadhesive micro beads of Rosuvastatin calcium were successfully prepared by Ionotropic gelation technique. Central composite design was applied for the preparation and optimization of mucoadhesive microbeads using Statease-Design of Experiment Version–12 software. The results of preformulation studies showed that there was no interaction between the drug and polymer. The polymers used in the microbeads are Sodium Alginate, HPMC. Mucoadhesive microbeads were obtained by Ionotropic gelation method for all the formulations from F1 to F9. Formulations F1 to F9 were prepared with different concentration of polymer and with constant drug ratio of Rosuvastatin Calcium. All formulations were evaluated for the Percentage yield, Particle size, Drug content, Entrapment efficiency, Scanning electron Microscopy, Swelling study, mucoadhesion testing, *in-vitro* drug release profile. From the overall studies it can be concluded that the formulation F9 considered as the best formulation among nine formulations by comparing all the evaluated parameters.

Keywords:- *Microbeads, Central Composite Design, Rosuvastatin calcium, in-vitro drug release studies.*

I. INTRODUCTION

Drug delivery is a carriage of medicinal agents through the physiological systems to get their targeted site for pharmacological action. Micro particulate drug delivery systems have various well-known advantages over single unit dosage form. Microbeads are nearly spherical, small with diameter of 0.5- 1000 µm. The solid and free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form allow a sustained release or multiple release profiles of treatment with various active agents without major side effects. Central composite design can be an excellent choice. In the process of Optimization and finding the best possible product from the ongoing batches, an Experimental design called the central composite design (CCD). During the run, the microbeads were evaluated for physiochemical characterization and responses were recorded. In our study it measures the DT, and in response to that the polynomial regression equation was plotted and tested for the significance.

After generating the polynomial equations relating the dependent and independent variables, the process was optimized to obtain the levels of A, B, and C, which gives optimum values of Y at constrained conditions. To verify these values, a new formula was prepared according to the predicted levels of A, B, and C. Then, the microbeads was prepared as per the optimized value and compared with the predicted value. Formulation of Mucoadhesive Microbeads includes formulation by using Central Composite experimental design, Evaluation of Mucoadhesive Microbeads includes physico-chemical properties of microbeads, Swelling study, Entrapment efficiency, mucoadhession testing, in-vitro drug release study, and include stability studies. In the present study Mucoadhesive microbeads of Rosuvastatin were prepared by using polymer of sodium alginate in different concentration. Nine formulations were going to designed using the polymer of Sodium alginate. Mucoadhesive microbeads were prepared by using Ionotropic Gelation Techniques.

A. Objective:

The objective of the present work is to formulate and evaluate the Rosuvastatin calcium micro beads by using ionotropic gelation method.

To formulate the nine different formulation with different concentration of polymer using Central Composite Design.

II. MATERIALS AND METHODS

The chief material Rosuvastatin calcium were brought from Shasun pharmaceuticals where as Sodium alginate, Calcium chloride were brought from Loba Chemie Pvt Ltd, and HPMC K100M were procured from Colorconasia Pvt. Ltd. Electronic balance, Digital pH meter, UV spectrophotometer, FTIR spectrophotometer, SEM, etc. were brought from different companies.

III. PRE-FORMULATION STUDIES

A. Identification of Drug:

As per IP specification, the white precipitate was obtained that result indicate presence of Rosuvastatin calcium in given sample.

B. Determination of λ max:

The absorption maximum for Rosuvastatin calcium in pH 6.8 phosphate buffer was found to be 242 nm.

IV. FORMULATION OF MUCOADHESIVE MICRBEADS

Formulation by Central Composite experimental design (Design expert, version 12)

Formulation Code	Rosuvastatin Calcium(mg)	Sodium Alginate(mg)	HPMC K100M (mg)	Calcium Chloride (%)
F1	40	341.421	30	10
F2	40	100	40	10
F3	40	200	15.8579	10
F4	40	200	30	10
F5	40	300	20	10
F6	40	200	44.1421	10
F7	40	58.5786	30	10
F8	40	100	20	10
F9	40	300	40	10

Table 1: Formulation designing of mucoadhesive microbeads

V. PROCEDURE FOR FORMULATION DESIGNING

Central composite design technique was used for formulation designing, total 9 experimental formulation of SA–HPMC microbeads containing Rosuvastatin calcium were prepared by ionotropic gelation taking two variable factors like polymer blend (sodium alginate & hydroxy propyl methyl cellulose) with cross linker Calcium chloride. Overview of the experimental plan & observed response values are founded by CCD. First to enter responses in CCD, and then click fit summary and then select model by suggested. The outcome of model analysis like sum of squares, mean square, F – value, P – values were found from ANOVA. All plots like normal plot of residuals, residuals vs. predicted plots, box–cox plot for power transforms, cook's distance plot, contour plot, predicted vs. actual plot, 3D surface plot were studied by design of experiment software– version 12.

VI. EVALUATION OF MUCOADHESIVE MICRBEADS

A. Determination of λ max of Rosuvastatin calcium by using pH6.8 Phosphate Buffer:

The absorption maximum for Rosuvastatin calcium in pH 6.8 phosphate buffers was found to be 242nm and it is shown in figure.

B. Data of concentration and absorbance data for Rosuvastatin calcium in Ph 6.8 phosphate buffer:

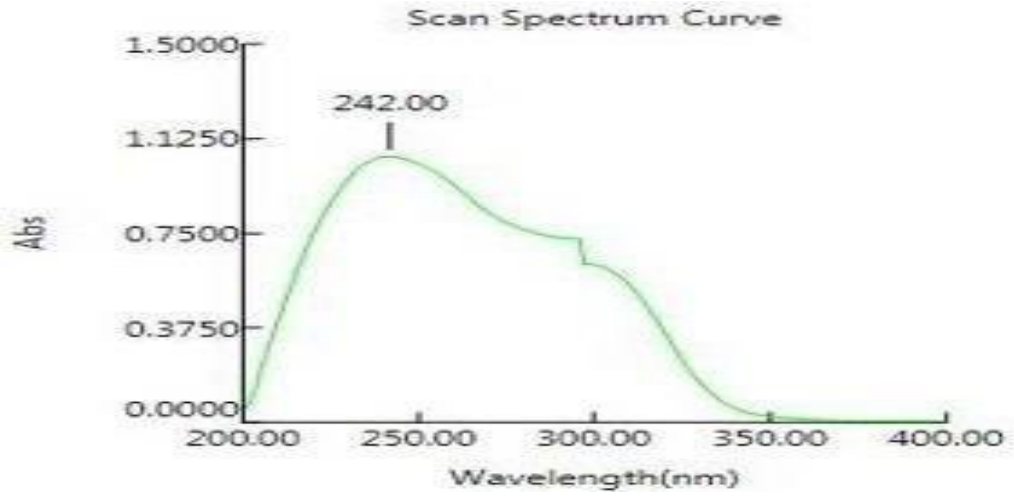

Fig. 1: Data of concentration and absorbance data for Rosuvastatin calcium in Ph 6.8 phosphate buffer

ISSN No:-2456-2165

S. No.	Concentration(µg/ml)	Absorbance at 242 nm
1	0	0
2	2	0.0848
3	4	0.1514
4	6	0.2264
5	8	0.2924
6	10	0.3617

Table 2: Calibration curve of Rosuvastatin calcium pH 6.8 phosphate buffer

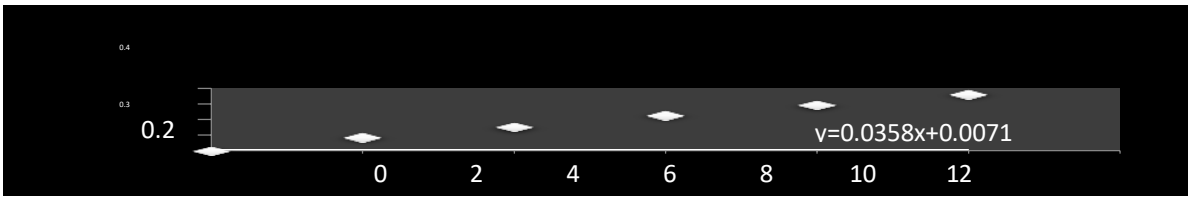

Fig. 1: Calibration Curve of Rosuvastatin Calcium in pH 6.8 Phosphate Buffer

The values of correlation coefficient(R), slope (M), Intercept(C) obtained from the calibration curve are given in the Table No 2.

S. No.	Parameters	Values
1	Correlation Coefficient(R)	0.9986
2	Slope(M)	0.0358
3	Intercept(C)	0.0071

Table 3: Correlation Coefficient, Slope, Intercept.

- **Percentage Purity of Drug:** The percentage purity of drug was calculated by using calibration curve method (least square method) and the data has been shown in Table No 3.

S. No.	Percentage Purity	Average Percentage Purity*
1.	99.05%	98.76±0.79%
2.	97.87%	
3.	99.38%	

Table 4: Percentage Purity of Drug

***All the values are expressed as mean ±SD, n=3**

The percentage purity for Rosuvastatin calcium in IP 2007 is not less than 98.0 % and not more than 102.0 % of the stated amount of Rosuvastatin calcium. The average percentage purity of Rosuvastatin calcium was found to be 98.76± 0.79%.So, it stands within the limits of IP 2007.

➢ *Fourier Transforms Infra-Red (FTIR) Spectroscopy:*

C. The FTIR spectrum of Rosuvastatin calcium shown in following Fig.No.2

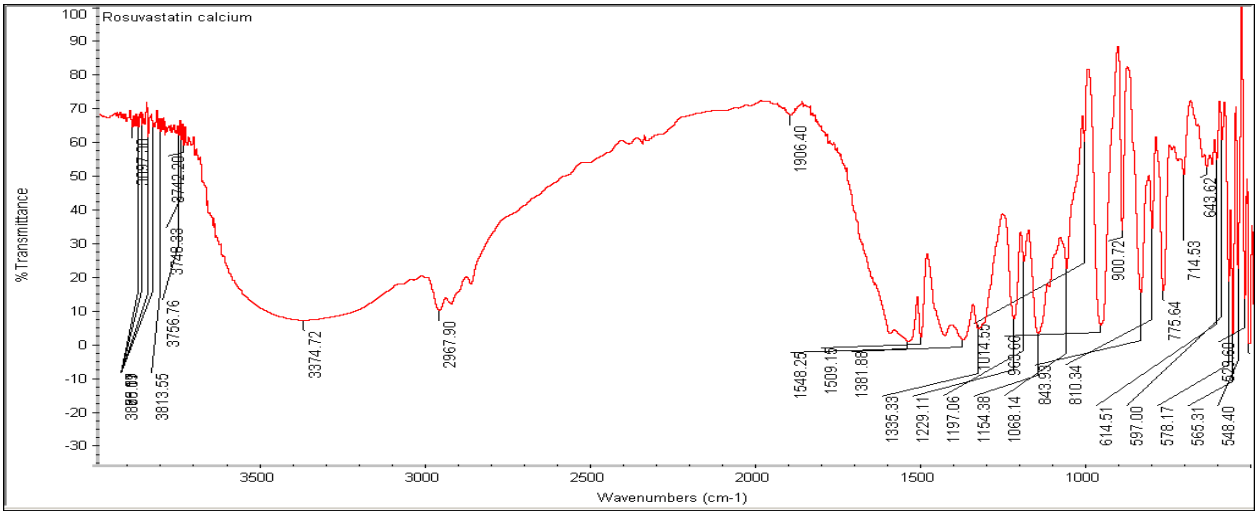

Fig. 2: FTIR spectrum of Rosuvastatin calcium

D. FTIR Spectrum of Rosuvastatin calcium with polymers are shown in following Fig. No. 3

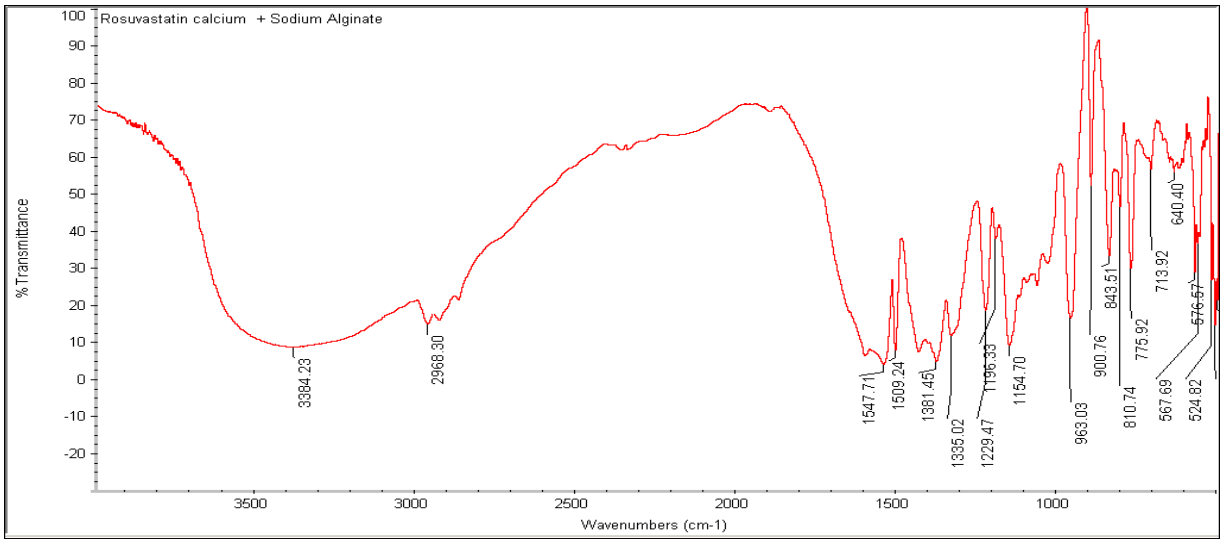

Fig. 3: FTIR Spectrum of Rosuvastatin calcium with polymers

E. FTIR Spectrum of Rosuvastatin Calcium with HPMC K100M in following Fig. No. 4

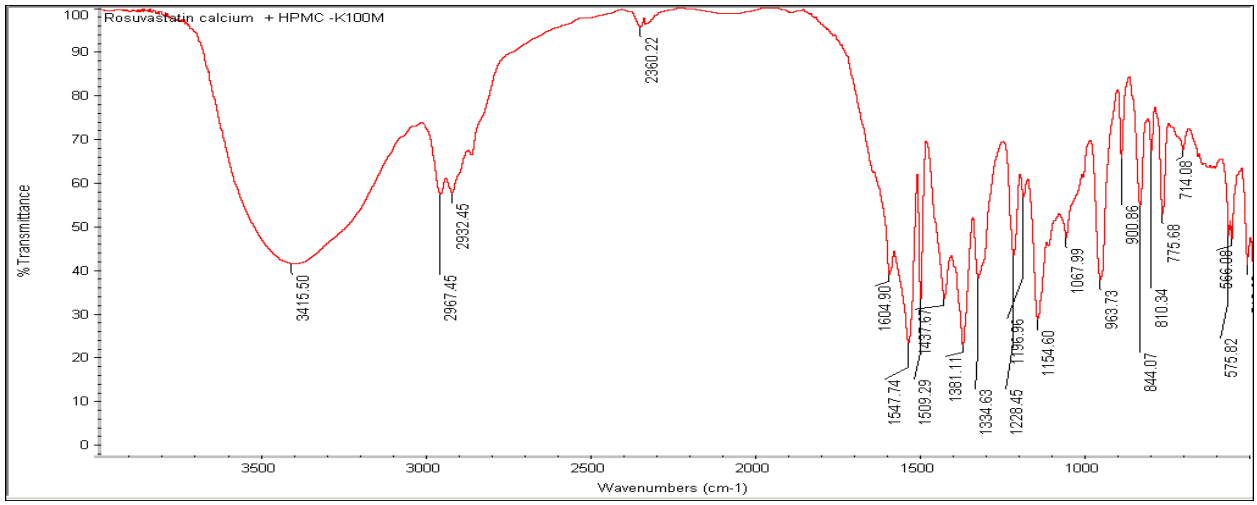

Fig. 4: FTIR Spectrum of Rosuvastatin Calcium with HPMC K100M

Interference	Wave Number (Cm^{-1})
C-F Stretching	1068.14
O-H Stretching	3374.72
C-O Stretching	1068.14
C-N Stretching	1335.33
SO_2 Stretching	643.62
C-H (aromatic C-H in plane)	1197.06
C-H (aromatic C-H out of plane)	900.72
C-C Skeletal Stretching (Aromatic)	1229.11
C-S Stretching	810

Table 5: Characteristics frequencies in FTIR spectrum of Rosuvastatin Calcium

F. FT-IR Frequencies:

Wave Number (cm^{-1})	Functional Group	Peak observed (Yes/No)		
		Rosuvastatin Calcium	Rosuvastatin with Sodium Alginate	Rosuvastatin with HPMC K100M
2970-2950	C-H Stretching	Yes	Yes	Yes
1300-700	C-C Stretching	Yes	Yes	Yes
3400-3200	O-H Stretching	Yes	Yes	Yes
1150-1050	C-O Stretching	Yes	Yes	Yes
1225-950	C-H Bending	Yes	Yes	Yes

Table 6: The major peak observed in FTIR spectrum of Rosuvastatin calcium and Rosuvastatin calcium with Different Polymers

The peaks of Rosuvastatin calcium Spectrum were compared to Rosuvastatin calcium with polymers spectrum. There was no interaction between Rosuvastatin calcium and polymers. The data was represented in table 6.

- **Loss on Drying:** The percentage loss on drying after 5 hours was found to be follows in Table 7.

S. No.	Percentage LOD	%LOD*
1	0.4	0.5666 ± 0.25
2	0.8	
3	0.7	

Table 7: Percentage Loss on Drying for Rosuvastatin Calcium

***All the values are expressed as a mean ± SD., n=3**

S. No	Formulation Code (F1–F9)	Percentage Yield (%)	Particle Size(µm ± S.D)*
1	F1	88.077 %	757±0.50
2	F2	81.48 %	743±0.32
3	F3	82.46 %	734±0.41
4	F4	84.44 %	746±0.43
5	F5	86.11 %	764±0.45
6	F6	83.14 %	764±0.32
7	F7	79.41 %	724±0.34
8	F8	80.33 %	804±0.41
9	F9	90.78 %	784±0.54

Table 8: Evaluation of Micro beads

*All the values are expressed as a mean ± SD., n=3

ISSN No:-2456-2165

G. Micromeritic Properties of Drug Loaded Microbeads:

Micromeritic properties like Angle of Repose, Loose bulk density and Tapped bulk density, Carr's Index and Hausner's Ratio were studied by triplicate. All the values are entered in to Table 9.

Formulation Code	Angle of Repose (θ)*	Loose Bulk Density (g/ml)*	Tapped Bulk Density (g/ml)*	Carr's Index (%)*	Hausner's Ratio*
1	22.84±0.26	0.58±0.00	0.66±0.0	11.8±0.0	1.13±0.00
2	23.61±0.06	0.63±0.02	0.67±0.03	6.39±0.24	1.06±0.00
3	23.71±0.06	0.60±0.02	0.63±0.02	6.01±0.20	1.06±0.00
4	25.01±0.09	0.58±0.00	0.62±0.00	5.89±0.00	1.06±0.00
5	23.75±0.09	0.62±0.00	0.69±0.01	10.41±1.80	1.11±0.02
6	22.76±0.72	0.58±0.00	0.66±0.00	10.78±1.69	1.12±0.02
7	24.03±0.19	0.58±0.00	0.64±0.02	7.84±3.39	1.08±0.04
8	24.24±0.09	0.62±0.00	0.68±0.01	8.33±1.80	1.09±0.02
9	24.82±0.12	0.60±0.01	0.67±0.01	11.39±0.96	1.13±0.01

Table 9: Micromeritic Properties of Drug Loaded Microbeads

*All values are expressed as Mean ± SD, n=3

H. Estimation of Drug Content and Entrapment Efficiency:

All the formulations Drug content and Entrapment efficiency data was showed in table 10.

S. No.	Formulations	Drug Content*	Entrapment Efficiency*
1	F1	91.24±0.94	63.85±1.63
2	F2	82.29±1.21	59.53±1.21
3	F3	84.17±1.71	61.42±1.08
4	F4	87.89±1.59	62.00±1.20
5	F5	89.86±1.57	62.67±1.23
6	F6	85.87±1.50	62.68±0.41
7	F7	80.49±1.37	60.14±1.42
8	F8	81.57±1.81	59.99±0.36
9	F9	94.56±1.25	65.58±1.35

Table 10: Drug Content and Entrapment Efficiency

*All values are expressed as Mean ± SD, n=3

I. Scanning Electron Microscopy (SEM):

Surface morphology and shape characteristics of microbeads were evaluated by means of scanning electron microscopy. The surface morphology of optimized best formulation (F9) shows the photomicrographs at different magnifications and voltages. Magnification, kilo voltages were mentioned in given table 11.

S. No.	Magnification	Voltages
1	25X	3.0KV
2	25X	5.0KV
3	35X	3.0KV
4	35X	5.0KV
5	50X	3.0KV
6	50X	5.0KV
7	100X	3.0KV
8	100X	5.0 KV

Table 11: Magnification, kilovolt ages

ISSN No:-2456-2165

J. Swelling Study / Degree of swelling:

Swelling study of Rosuvastatin Calcium mucoadhesive microbeads were performed in pH phosphate buffer up-to 8 hours. It was represented in table 12.

S. No	Hours	In 0.1N HCl (%)			In pH 6.8 Phosphate Buffer (%)		
		F5	F1	F9	F5	F1	F9
1	1	6	8	10	8	10	12
2	2	10	12	20	20	18	24
3	3	16	20	32	26	26	32
4	4	20	28	44	36	36	46
5	5	28	32	50	42	50	56
6	6	34	42	58	52	62	62
7	7	40	50	60	64	70	70
8	8	46	58	64	72	74	78

Table 12: Data of Swelling Test:

K. Mucoadhesion Testing/In-vitro Wash off Test:

The *in-vitro* wash off test for mucoadhesive for all formulations (F1 to F9) was studied in 0.1N HCl and pH 6.8 phosphate buffer. The result of *in-vitro* wash off test data were represented in table 13.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1hr	78	58	64	70	75	67	54	54	85
2hr	68	42	54	62	66	58	42	38	72
3hr	60	32	42	54	51	42	34	29	63
4hr	55	26	33	40	43	31	12	13	54
5hr	44	15	24	29	36	27	-	-	47
6hr	39	8	13	17	28	18	-	-	39
7hr	25	-	-	10	13	9	-	-	25
8hr	9	-	-	-	6	-	-	-	12

Table 13: Mucoadhesion Testing in 0.1N HCl

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1hr	78	56	60	70	75	65	50	54	80
2hr	69	46	50	61	67	51	38	40	71
3hr	55	35	47	53	51	43	21	21	61
4hr	43	26	38	45	43	35	10	10	51
5hr	35	14	29	34	36	28	-	-	42
6hr	25	-	15	21	28	20	-	-	32
7hr	12	-	-	9	14	12	-	-	25
8hr	-	-	-	-	-	-	-	-	10

Table 14: Mucoadhesion Testing in pH 6.8 Phosphate Buffer

L. In-vitro Drug Release Study:

In-vitro drug released profiles of Rosuvastatin Calcium microbeads were performed in pH 6.8 phosphate buffer up-to 8 hours.

Time(hr)	Percentage Drug Release (%DR)*								
	F1DR %	F2DR %	F3D R%	F4DR %	F5D R%	F6D R%	F7D R%	F8D R%	F9D R%
1	17.66± 1.03	13.14± 0.90	18.70± 1.40	21.30± 1.88	4.09±0 .86	8.54±0 .69	4.38±1 .54	19.37± 1.95	22.63± 1.17
2	19.26± 0.59	14.46± 1.14	20.75± 0.75	22.52± 1.03	6.50±0 .37	10.11± 1.24	4.91±1 .60	19.91± 0.97	23.88± 0.49
3	19.52± 0.19	15.54± 1.56	22.92± 1.55	23.60± 1.20	6.90±0 .34	12.03± 1.10	5.12±1 .76	21.29± 1.04	24.57± 1.31
4	24.50± 1.67	16.62± 0.86	24.16± 0.59	24.77± 1.19	9.92±0 .71	14.77± 1.65	6.40±1 .20	22.55± 1.04	26.36± 1.27
5	26.25± 1.04	22.44± 0.79	25.47± 1.59	25.93± 0.20	16.06± 1.38	22.20± 1.57	7.71±1 .87	23.67± 1.94	31.31± 1.23
6	26.79± 0.99	25.14± 0.91	25.98± 1.20	26.69± 0.86	20.21± 0.39	25.70± 1.23	9.45±1 .27	25.86± 1.20	36.79± 0.87
7	31.62± 0.69	26.02± 1.20	27.22± 0.68	27.91± 1.57	26.43± 1.20	27.81± 0.39	10.16± 1.29	26.90± 1.93	45.10± 1.81
8	33.73± 1.62	27.44± 1.69	28.18± 0.90	29.70± 0.71	31.80± 0.86	28.66± 0.39	16.19± 1.27	27.89± 1.04	58.68± 1.03

Table 15: Percentage Drug Release of Formulation F1-F9

*All the values were expressed as mean ± SD., n=3

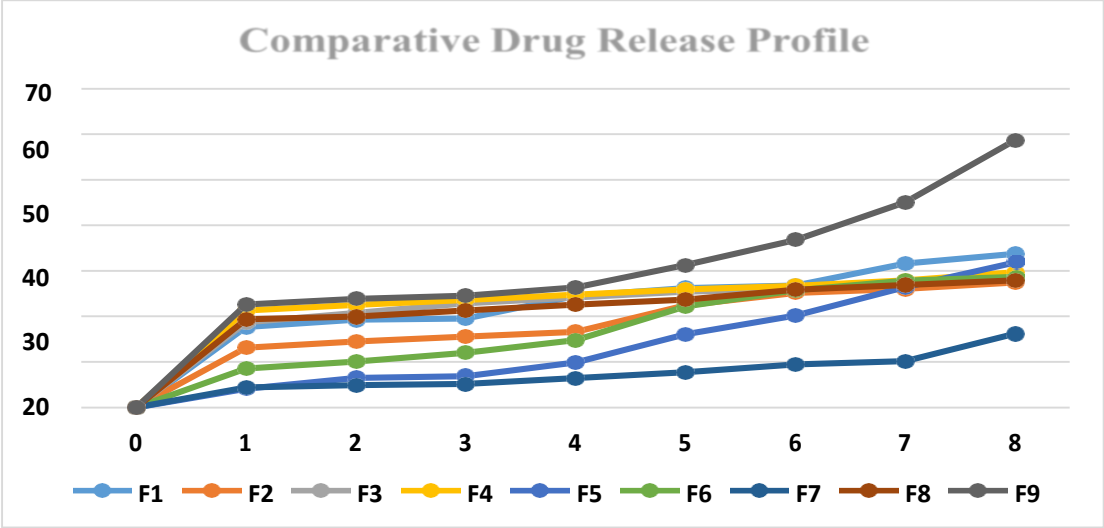

Fig. 5: Comparative Drug Release Profile between F1 to F9

Formulation Code	Best FTIR Values
F1	0.9613
F2	0.9546
F3	0.835
F4	0.8791
F5	0.8945
F6	0.9667
F7	0.8765
F8	0.9549
F9	0.8888

Table 16: Kinetics of *in-vitro* Drug Release Profile for All Formulation

ISSN No:-2456-2165

VII. STABILITY STUDY

The formulation F9 was observed after specified period stability studies as per ICH guidelines. Accelerated temperature: 40ºC± 2º at 75% RH ± 5 % for 3 Months. The formulations was monitored for drug content and *in-vitro* drug released profile and results were represented in Table 16.

Characteristics	Initials	1 Month	2 Month	3 Month
Drug content (%)	94.56 ± 1.25	94.46 ± 0.72	94.21 ± 1.81	94.03 ± 0.87
In-vitro drug Released (%)	58.68 ± 1.03	58.58 ± 1.52	58.47 ± 0.67	58.22 ± 1.12
Entrapment Efficiency (%)	65.58 ± 1.35	65.46 ± 1.21	65.25 ± 0.89	65.07 ± 1.42

Table 17: Data of Stability Studies of Formulation (F9)

*All the values are expressed as mean ± S.D. n=3

Fit summary Results for response Y1-DC (8h)				
source	**Sequential p-value**	**Adjusted R^2**	**Predicted R^2**	
Linear	0.0008	0.8767	0.7870	Suggested
2FI	0.2737	0.8864	0.7502	
Quadratic	0.6685	0.8552		
Cubic	0.7270	0.7704		Aliased
Fit summary Results for response Y2–DR (8 h)				
Linear	0.1068	0.3673	-0.1593	
2FI	0.1390	0.5309	-0.3284	Suggested
Quadratic	0.9260	0.2572		
Cubic	0.8151	-0.4807		Aliased

Table 18: Statistical Analysis Report by Design Expert Software: Table 17 : Fit summary Results for response Y1–DC & Y2–DR
The fit summary suggested linear with p-value 0.0008 for response Y1 - DC and 0.0985 for response Y2-DR.

ANOVA FOR LINEAR MODEL

ANOVA for linear model (responseY1-DC)					
Source	**Sum of Square**	**df**	**Mean Square**	**f-value**	**P-value**
Model	167.52	2	83.76	29.44	0.0008
A-SA	159.87	1	159.87	56.20	0.0003
B–HPMC	7.65	1	7.65	2.69	0.1521
Residual	17.07	6	2.84		
Cortotal	184.59	8			
ANOVA for 2 FI model (response Y2-DR)					
Model	727.92	3	242.64	4.02	0.0843
A-SA	449.33	1	449.33	7.44	0.0414
B–HPMC	91.86	1	91.86	1.52	0.2723
AB	186.73	1	186.73	3.09	0.1390
Residual	301.96	5	60.39		
Cortotal	1029.89	8			

Table 19: ANOVA for response Y1– DC & Y2 –DR

ANOVA for the DC & DR for until 8 hrs indicated that the separate and collective upshot of the two factors A–SA, and B–HPMC, in influencing the DC of mucoadhesive microbeads of Rosuvastatin Calcium is highly significant ($p<0.01$). The model F value of 29.44 (for response 1) and 4.02 (for response 2) suggests the model is significant. The model F-value of DC of 29.44 denotes the model is significant. There is an only a 0.08% chance that more F values are dueto noise.

- **Predicted Value vs. .Experimented Value Response Y1–DC & Y2-DR:**

ISSN No:-2456-2165

Ingredient	Composition (Maximum Conc.) mg	Response	Predicted value	Experimented value	Standard error (%)
Sodium alginate (SA)	300 mg	Drug Content	91.886	94.56	0.911
HPMCK 100M	40 mg				
Sodium alginate (SA)	300 mg	Drug release	49.079	58.68	0.911
HPMCK 100M	40 mg				

Table 20: Comparison of experimental results with predicted responses of mucoadhesive microbeads of Rosuvastatin calcium

From this results conclude that predicted values are near to experimental values with low standard error/ desirability.

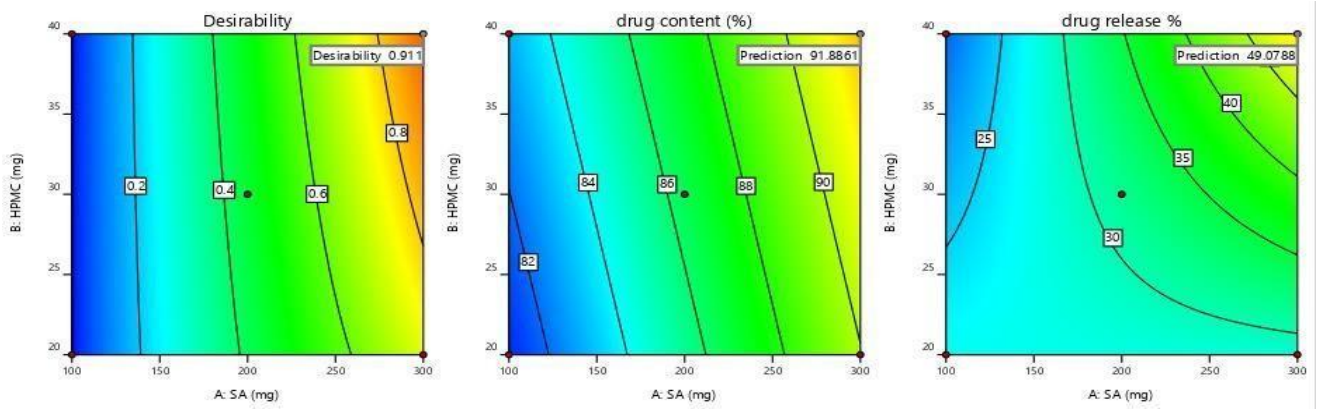

Fig. 6: Prediction value of DC & DR Responses

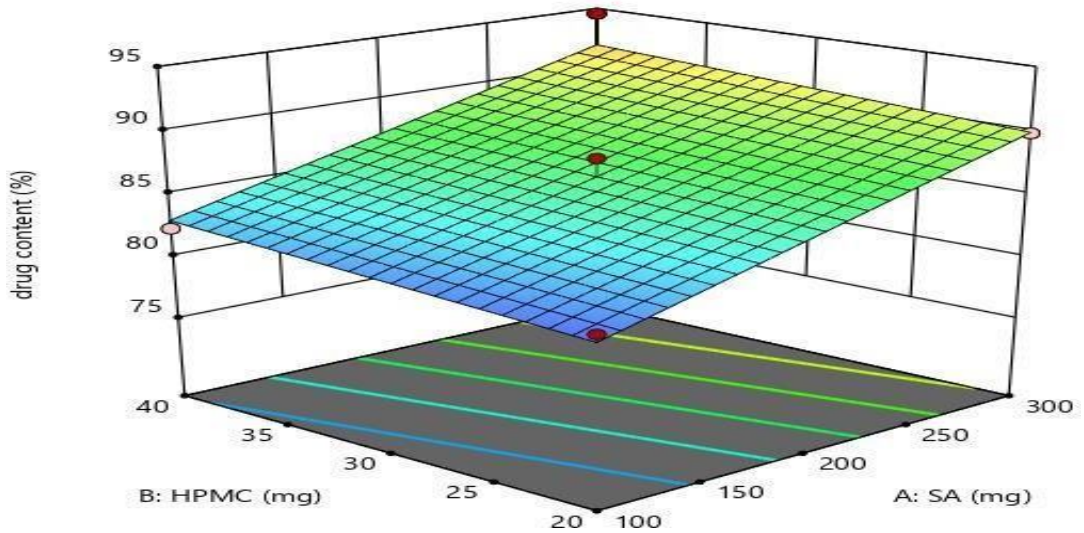

Fig. 7: Contour Plot of Drug Content 3D Response Plots of Y1–DC & Y2-DR

The based on the above polynomial equation, the optimized mucoadhesive microbeads of Rosuvastatin Calcium with 58% release in end 8 hrs could be formulated by employing Sodium Alginate at 300 mg and HPMC K100M at 40mg (F9). Hence, mucoadhesive microbeads with more dissolution rate in 8 hr could be optimized by Central Composite Design.

VIII. CONCLUSION

Mucoadhesive microbeads were obtained by ionotropic gelation method for all the formulations from F1 to F9. Formulations F1 to F9 were prepared with different concentration of polymer and with constant drug ratio of Rosuvastatin Calcium. All formulations were evaluated for the Percentage yield, particle size, Drug content, Entrapment efficiency, Scanning electron microscopy, swelling study, mucoadhesion testing, in-*vitro* drug release profile and the

ISSN No:-2456-2165

formulation F9 was selected as the best formulation, as it showed maximum percentage yield, drug content and Entrapment efficiency. It also showed a good Controlled drug release pattern up to 8 hrs. According to stability study it was found that there was no variation in drug content, entrapment efficiency, and *in-vitro* drug released profile of optimized formulation F9 for 3 months period. From the overall studies it can be concluded that the **formulation F9** considered as the best formulation among nine formulations by comparing all the evaluated parameters.

ACKNOWLEDGEMENTS

The authors are sincerely thankful to Adhiparasakthi College of pharmacy, Melmaruvathur, Kancheepuram, for providing us infrastructure facilities and moral support to carry out this research work. I sincerely express my gratitude to Shasun Pharmaceutical Limited, Pondicherry for providing Rosuvastatin calcium and Loba Chemie Pvt Ltd, Mumbai for providing Sodium alginate, Hydroxy propyl methylcellulose K100M, Calcium chloride.

REFERENCES

[1.] Adnan Burhan Qader., Ahmed Abbas Hussein. Development of Oral Self-Nano emulsifying Drug Delivery System (Snedds) Of Rosuvastatin Calcium: Formulation, Characterization, and In-Vitro Drug Release Study, *International Journal of Pharmaceutical Research*, 2021.

[2.] Mullaicharam Bhupathyraaj and Sushama pole. Study on effect of combination of sodium alginate and xanthan gum on drug release from Tacrolimus microbeads, *European Journal of Molecular & Clinical Medicine*, 2020, 7(11), 4584-4596.

[3.] Rachel B. Geevarghese., SatishV. Shirolkar. Formulation Development of Rosuvastatin Calcium Drug in Adhesive Transdermal System, *International Journal of Pharmaceutical Sciences andResearch*,2020, 11(8), 3902-3911.

[4.] Sankar.V., Arjun. S, Karthik. S., Arjunan. K., Hariharan. S., Seenivasan. P. Preparation And Evaluation of Rosuvastatin Calcium Nanosuspension and Solid Dispersion Tablets By Wet Granulation and Direct Compression Techniques Using Tamarind Gum As A Binder, *Indian Journal of Pharmaceutical Sciences*, 2020, 82(1), 32-40.

[5.] Satya Lakshmi. S.,Srinivasa Rao Yarraguntla. Formulation and Evaluation of Rosuvastatin Calcium Drug Transdermal Patch, *Research Journal of Pharmacy and Technology*, 2020, 13(10),4784-4790.

[6.] Suryawanshi Rhushikesh and Sudke Suresh. A Review on Mucoadhesive Drug Delivery System, *International Journal of Research and Analytical Reviews*, *2020*, 7(1), 793-808.

[7.] Taker Gurjeet Singh., Sonia Dhiman, and Sandeep Arora. Mucoadhesion Drug Delivery System: A Propitious Approach, *International Journal of Pharmaceutical Sciences Review and Research*, 2018, 50(2), 72-88.

[8.] Vinod K.R., Rohit Reddy T., Sandhya S., David Banji., Venkatram Reddy B. Critical Review on Mucoadhesive Drug Delivery Systems, *Journal for drugs and medicines*, 2012,4(1),7-28.

[9.] Yasmini. Formulation, evaluation and development of fast release tablets of Rosuvastatin calcium using sublimation method, World Journal of Pharmaceutical Research, 2017, 6(6), 1105-1130.

[10.] Adnan Burhan Qader., Ahmed Abbas Hussein. Development of Oral Self-Nano emulsifying Drug Delivery System (Snedds) Of Rosuvastatin Calcium: Formulation, Characterization, and In-Vitro Drug Release Study, *International Journal of Pharmaceutical Research*, 2021.

[11.] Juti Rani Devi and Bidyut Das. Microparticulate Drug Delivery System- A Review, *World Journal of Pharmaceutical and Life Sciences*, 2016, Vol.2, Issue 6, 243-258.

[12.] Marwa H. S. Dawoud., Ahmed M.Fayez., Reem A.Mohamed., Nabila M. Sweed. Enhancement of the Solubility of Rosuvastatin calcium by nano vesicular Formulation: A Systematic Study Based on a Quality by Design Approach, *Proceedings*, 2020, 78(34), 1-8.