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To Formulate And Evaluate Microwave Generated Nanocomposites For Solubility Enhancement Of Rosuvastatin Calcium.

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Abstract: Rosuvastatin calcium is anti-hyperlipidaemic agent has low aqueous solubility resulting in low oral bioavailability thus presents a challenge in formulating a suitable dosage form to improve the aqueous solubility. Nanocomposites are novel technology for enhancing the solubility of Rosuvastatin calcium. Nanocomposite's formulation of Rosuvastatin Calcium was prepared by microwave induced diffusion method (MIND). The natural polymers like gum acacia, Chitosan and HPMC K4M were used as carrier in the formulation. Four different formulations were prepared with varying ratios of drug and carriers and corresponding physical mixtures were also prepared. The selections of natural carriers were based on their surfactant and wetting properties. The optimum drug-to-carrier ratio was found to be 1:4 which enhanced solubility as compared to pure drug. In vitro drug release exhibited cumulative release of 84.72% as compared to 27.38% for the pure drug. The optimized nanocomposites were characterized by Fourier transform infrared spectroscopy, X-ray diffraction, these results suggest that nanocomposites using natural carrier is a promising approach for oral delivery of Rosuvastatin calcium.

Keyword: *Rosuvastatin Calcium, Acacia, HPMC K4M, Nanocomposites, Chitosan*

I. INTRODUCTION

Oral administration of drug is highly preferred and commonly used route of drug administration. A specific drug's oral bioavailability is decided based on its solubility and its permeability within the gastrointestinal tract, an aqueous environment. according to the Pharmacopoeia of United States, 40% of the drugs so far being manufactured are either insoluble or poorly soluble in aqueous environments. The pharmaceutical researchers face a big challenge in front of them i.e., enhancing the oral bioavailability of poorly water-soluble drugs by increasing its solubility so that the therapeutic application can be effective. The primary idea used in the researcher is the enhancing effects of microwave heating on mass transport, which might result in a sustainable and efficient instrument for developing such dispersions. Nowadays, microwave heating (MW) is the latest and newer technology is processing of materials, manufacturing of chemicals and it comes up with favorable advancements when compared to the older thermal treatments. The pharmaceutical nanocomposites that were developed as a result of MW processing were separate molecular clusters of drug adsorbed onto the surface. But there seems to be no definitive inhibition of re-crystallization since the drug molecules are highly mobile on inorganic surfaces. In order to prevent the drug re-crystallization, in the current approach, the inorganic surface is replaced with inert 3D-matrices. [1,2,3,4,5]

Rosuvastatin have a class of drugs which is statins and it used for lowering blood cholesterol level. It has very good intestinal permeability and short half-life. However, the factors like low aqueous solubility(0.1mg/mL), crystalline nature and hepatic first pass metabolism responsible for low oral

bioavailability. Due to the poor performance, drugs have to be administrated in higher doses which can causes liver abnormalities, rhabdomyolysis, arthralgia and kidney failure. To avoid such side effects, salt formation has been tried. A nanocomposite is a combination of two or more different materials with different properties of each and that are fused, by an effort to blend the best properties of both and combination of those shows improvement in their properties greater than that of individual. The melting or fusion technique is one of the simple and efficient technique in the preparation of nanocomposites for the solubility and dissolution enhancement. Particle size reduction provides more surface area for absorption and rapid dissolution.

Microwave radiation consists of electromagnetic waves with frequencies between the infrared and radio waves, which is in the range of 0.3–300 GHz. It passes through materials and oscillate their molecules, which generating heat. The ability of microwave to penetrate any substance, which produced the heat in a sample at any point at a given time. The first and unique attempt was proposed by Kerk et al in the direction of bioavailability enhancement. The pharmaceutical nanocomposites which prepared by MW processing which was silicon dioxide substrate with isolated molecular clusters which adsorbed on the surface. Nevertheless, it seems that re-crystallization is not definitively inhibited, as drug molecules have high mobility on inorganic surfaces. This approach consisting the replacement of inorganic surface with inert 3D-matrixes that have suitable microstructural properties to prevent re-crystallization of the drug.

In the present work, we developed a nanocomposite of rosuvastatin calcium using natural carriers such as gum acacia, Chitosan and HPMC K4M. The rosuvastatin nanocomposites were evaluated for drug content, solubility and dissolution studies. Varying ratios of drug and carrier were formulated and evaluated. To deduce the possible effects of the carrier on the drug, their physical mixtures were also formulated and compared with nanocomposites and plain drug for solubility analysis. Optimized nanocomposites were followed by studies for confirmation of formation of nanocomposites. Finally, in-vivo studies were carried out to elucidate the anti-hyperlipidemic potential of optimized nano composites with comparison to pure drug.

II. MATERIALS AND METHODS

Materials

Rosuvastatin Calcium IP was brought from Arti distributors, Mumbai. Gum acacia, Chitson, HPMC K4M and Methanol were received from Research Lab Fine Chem, Industry, Mumbai. All the materials were of analytical grade. The materials were used as received without any further purification.

Selection of Natural Gum

Gum acacia, Chitosan and HPMC K4M were studied for swelling index, foaming index, viscosity method which described by Murali M. B GV et al

Swelling Index

The modified method was used for determination of Swelling index of gums. 1 mg of Gum acacia, Chitosan gum, HPMC K4M were measured in accurate weight and then transferred to 100ml measuring cylinder. After this, the occupied initial volume by gum was noted down for calculations. Using distilled water, the volume was then adjusted. The cylinder (open end) is sealed with aluminum foil and kept aside for 24 Hours. After 24 hours of storage the volume of swelled gum was noted. Using the formula given below,

$$SI = \frac{H_f - H_i}{H_i} \times 100$$

Where,
SI- Swelling index of gum,
Hi - Initial height of powder,
Hf - Final height of powder after 24 hours

Foaming Index

The foaming index of Gum acacia, Chitosan gum, HPMC K4M were calculated to check the surfactant properties of the gum. 1 gm of gum was weighed accurately and then shifted to 250 ml measuring cylinder. The 100ml of distilled water was incorporated in measuring cylinder to make dispersion. The resultant dispersion was shaken vigorously for 2mins. The foaming index of each polymer calculated by the following equation

Foaming Index = $H_f - H_i$

Where,
H f = Height of solution of gum after shaking.
H i = Height of solution of gum before shaking.

Viscosity

Viscosity of gums was calculated by dissolving one gram of each acacia gum and modified gum karaya and gaur gum in 100 ml of water (1% w/v solution). The viscosity of the carrier dispersions of acacia and modified gum karaya were measured by Brookfield viscometer using spindle 00 at 200 rpm.

Formulation of Physical Mixtures

Physical mixture of Rosuvastatin calcium with polymers like Gum acacia, Chitosan and HPMC K4M were prepared by simple blending of drug with polymer in the ratio 1:1 to 1:4. Different physical mixtures of Rosuvastatin calcium and various polymers were developed as reported

table no 1: physical mixtures of rosuvastatin calcium and polymers

Ratio for physical Mixture	**Drug: Polymer 1:1**	**Drug: Polymer 1:2**	**Drug: Polymer 1:3**	**Drug: Polymer 1:4**
Formulation code	**RTGP1**	**RTGP2**	**RTGP3**	**RTGP4**
Rosuvastatin Calcium	500	500	500	500
Gum Acacia	500	1000	1500	2000
Formulation code	**RTCP1**	**RTCP2**	**RTCP3**	**RTCP4**
Rosuvastatin Calcium	500	500	500	500
Chitosan	500	1000	1500	2000
Formulation code	**RTHP1**	**RTHP2**	**RTHP3**	**RTHP4**
Rosuvastatin Calcium	500	500	500	500
HPMC K4M	500	1000	1500	2000

Formulation of Nanocomposites

The nanocomposites were developed by homogenous mixing of accurately weighed amount of Rosuvastatin calcium with individual polymer. In preparation the 1:1 to 1:4 ratio of drug to polymer (w/w) was taken from by keeping amount of mixture constant. The quantity of Rosuvastatin calcium and polymer for different ratios were taken as shown in Table 9.4.2. The nanocomposites of drug with Gum acacia having ratio 1:1, 1:2, 1:3 and 1:4 was formulated & denoted by RTGN1, RTGN2, RTGN3, RTGN4 respectively.

The nanocomposites of drug with Chitosan having ratio 1:1, 1:2, 1:3 and 1:4 was formulated & denoted by RTCN1, RTCN2, RTCN3, RTCN4 respectively. Similarly, nanocomposites of drug with HPMC K4M having ratio 1:1, 1:2, 1:3 and 1:4 was formulated & denoted by RTHN1, RTHN2, RTHN3, RTHN4

To the mixture of polymer and drug in different ratios, the 4 ml of water was incorporated for each gram of polymer to make uniform slurry. The fixed (constant) amount of slurry was taken in beaker and was irradiated with microwave radiation at power 556 W with continuous stirring for 5. The formulated nanocomposites were grounded in pestle and mortar and sieve to achieve the desired particle size of 80 to 250 µm.

table no 2: nanocomposites of Rosuvastatin calcium and polymers

Ratio for physical Mixture	**Drug: Polymer 1:1**	**Drug: Polymer 1:2**	**Drug: Polymer 1:3**	**Drug: Polymer 1:4**
Formulation code	**RTGN1**	**RTGN2**	**RTGN3**	**RTGN4**
Rosuvastatin Calcium	500	500	500	500
Gum Acacia	500	1000	1500	2000
Formulation code	**RTCN1**	**RTCN2**	**RTCN3**	**RTCN4**
Rosuvastatin Calcium	500	500	500	500
Chitosan	500	1000	1500	2000
Formulation code	**RTHN1**	**RTHN2**	**RTHN3**	**RTHN4**
Rosuvastatin Calcium	500	500	500	500
HPMC K4M	500	1000	1500	2000

Optimization of Ratio (Drug: Polymer [29,30,37,38]

Solubility study:

The solubility study of Rosuvastatin calcium, Physical mixtures, and Nanocomposites (NCs) was calculated methanol and water. In the solubility study Rosuvastatin calcium, physical mixtures, and Nanocomposites excess quantity of drug (10 mg) and Nanocomposites of Rosuvastatin Calcium (equivalent to 10 mg of drug) was incorporated in 10 ml of methanol and water. The samples were placed in an orbital shaker at 37±0.5°C for a period of 24 hours and at 50 rpm. The supernatant fractions were separated from the vials and let to filter through a membrane filter (0.45 micron). The sample which was filtered was analyzed at a wavelength of 244 nm by UV-visible spectrophotometer (Shimadzu, Japan). Based on results obtained for solubility, the ratio optimization (drug: carrier) was carried out.

In-vitro dissolution [29,30,37,38]

The In-vitro powder dissolution test was carried out on USP XXIV apparatus II (Paddle) on Rosuvastatin calcium and nanocomposites by using 900ml 0.1N HCl as a dissolution media. Powder containing accurate dose of drug was incorporated in the dissolution media drug (equivalent to 10 mg of Rosuvastatin calcium) maintaining temperature at 37± 0.5°C and rotating speed of paddle at 75 rpm. The 5 ml of sample were withdrawn at an interval of 0, 5, 10, 15, 20, 25, 30 minutes. The sink condition is maintained by replacing about 5 ml of 0.1 N HCl in dissolution media. The samples were then filtered and analyzed spectrophotometrically at wavelength of 244 nm.

Drug content analysis [29,30,37,38]

The analysis of drug content was conducted to measure the amount of drug incorporated into nanocomposites. The developed nanocomposites were dissolved in 25ml of methanol. The subsequent solution was then filtered and analyzed at wavelength 244 nm by UV-visible spectrophotometer against methanol as a blank.

Characterization of optimized nanocomposites [26,27]

Out of the results retrieved from dissolution studies and solubility, the NCs which expressed good results were scrutinized for further characterization.

Fourier –transform infrared spectroscopy (FTIR) [26,27]

The optimized ratio of the nanocomposites was characterized by FTIR analysis. These nanocomposites were mixed in a ratio of 1:100 with (KBr) potassium bromide of IR grade which was then compressed at 15 tons pressure using pellet press. A FTIR spectrophotometer (Shimadzu 8400S) was then used to screen the pellets and the obtained spectra of optimized nanocomposites were compared with that of the pure drug. The changes in the principal peaks of spectra in the optimized nanocomposites were recorded.

X-ray diffraction studies (XRD) [26,27]

The optimized nanocomposites and Rosuvastatin calcium were characterized by XRD to measure the crystallinity changes that occurred when the drug was mixed with polymer. Using Cu-kα radiation, the XRD pattern was then recorded. The scanning range is then kept in the range of 10° to 80° of 2θ. XRD study was conducted so as to measure the changes occurred in the crystallinity at the time when drug was mixed with carriers. Figures 10.1.13 and 10.1.14 show the XRD pattern of pure drug and nanocomposites.

Stability Study of Optimized Nanocomposites. [41]

Accelerated stability study was carried out as per ICH guidelines. The sample of optimized nanocomposites was placed at room temperature for 3 months in stability chamber and 75 ±5% RH. Various parameters such as drug content, appearance and in- vitro drug release was measured after 1, 2 and 3 months of stability study.

III. Results and Discussion

Pre-formulation Study of Drug

Organoleptic properties:

table no 3: organoleptic properties of Rosuvastatin calcium

Properties	Observed Results	Reported Results	Inference
Color	White	Off white to creamish white	Complies with IP
Odor	Odorless	Odorless	Complies with IP
Appearance	Crystalline powder	Crystalline powder	Complies with IP

In Pre-formulation study, the identification of sample was performed, and results of organoleptic properties and melting point of drug was found to be similar to that mentioned in books, literature and official monograph.

Melting point of Rosuvastatin calcium:

table no 4: melting point of Rosuvastatin calcium

Sample	Observed Results	Reported Results	Inference
Rosuvastatin Calcium	178^0 C	173-188^0 C	Complies with IP

Solubility of Rosuvastatin calcium:

table no 5: solubility of Rosuvastatin calcium

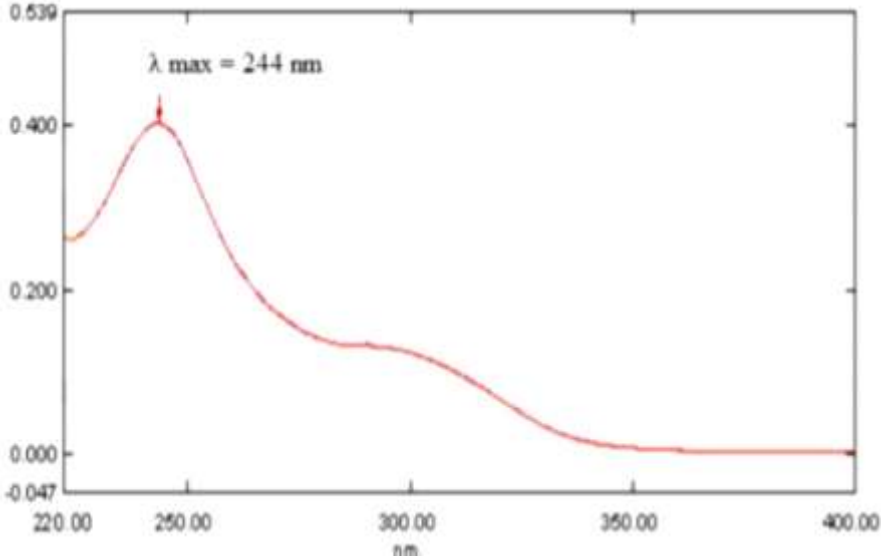
Solvent	Observed Solubility (mg/ml)	Reported Solubility (mg/ml)	Inference
Distilled water	0.028	0.05	Complies with IP
Methanol	0.121	0.118	Complies with IP

UV Spectrophotometric analysis of Rosuvastatin calcium [2,4]

The UV spectrum was recorded in the range 200-400 nm. The (λmax) wavelength of maximum absorption was determined from the results obtained and then further preparation of (standard) curve was carried out at the detected wavelength of maximum absorption (λmax) in water:

Rosuvastatin calcium was showing the maximum absorbance at 244 nm in water.

figure no 1: UV spectra of Rosuvastatin calcium



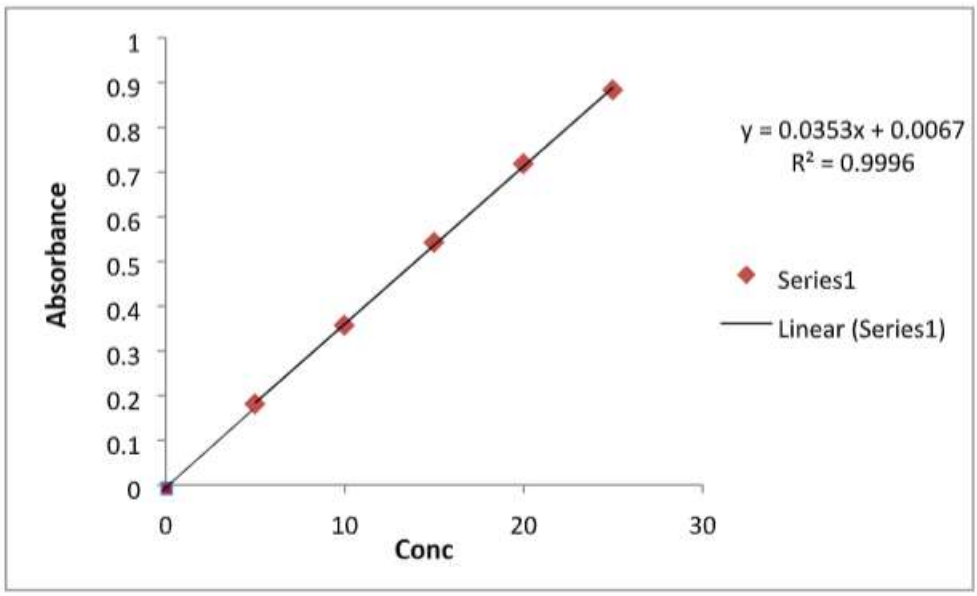
Construction of Beer's lamberts plot of Rosuvastatin calcium in methanol:

The Beer's lamberts plot for Rosuvastatin calcium in water was constructed. The regression coefficient of the lines obtained in water was found to be 0.9996 The linearity in water was found in the concentration range of 5-25 µg/ml.

table no 6: UV spectroscopy

Sr No	Concentration (µg/ml)	Absorbance
1	5	0.210
2	10	0.442
3	15	0.651
4	20	0.867
5	25	1.060

Figure no 2: Beer's lambert's curve for Rosuvastatin calcium



Fourier transforms infrared spectroscopic studies (FTIR)

The powdered mixture of Rosuvastatin calcium and Potassium bromide was taken in a sampler and scanned in the wavelength region of 4000- 400 cm -1 and recorded with the help of FTIR spectrophotometer. FTIR spectrum of Rosuvastatin calcium was showed all the peaks corresponding to the functional groups presents in the structure of Rosuvastatin calcium.

table no 7: FTIR of Rosuvstatin calcium

Wave Number (cm^2)	Interpretation
3395	N-H stretching
3200-3550	O-H stretching
3080	C-H aromatic phenol
2970	Alkane C-H stretching
2873	Aldehyde C-H stretching

Characterization of Polymer

The Gum acacia, Chitosan, HPMC K4M were studied for the organoleptic properties. The identification of sample was performed and results of organoleptic properties, melting point of drug were found to be like that mentioned in literature, books and also official monograph.

table no 8: characterization of polymers

Polymer	Properties		
	Color	**Odor**	**Appearance**
Gum Acacia	White or yellowish-white powder	Odorless	Crystalline powder
Chitoson	Creamy white powder	Odorless	Crystalline powder
HPMC K4M	White	Odorless	Crystalline powder

All the organoleptic parameters for gum acacia, chitosan and HPMC k4M comply with IP.

Melting point determination:

table no 7: melting point of polymers

Polymer	Observed Results	Reported results	Inference
Gum Acacia	259^0 C	$250\text{-}260^0$ C	Complies with IP
Chitoson	128^0 C	$127\text{-}129^0$ C	Complies with IP
HPMC K4M	251^0 C	$250\text{-}255^0$ C	Complies with IP

Physical characterization of polymer

table no 8: physical characteristics of polymers

Polymer	% Swelling	Viscosity	Foaming Index	Inference
Gum Acacia	63.26 ± 1.21	2.93 ± 0.83	11 ± 0.59	Complies with IP
Chitoson	71.87 ± 1.09	3.74 ± 0.62	10 ± 0.89	Complies with IP
HPMC K4M	90.23 ± 1.40	7.87 ± 0.89	8 ± 0.65	Complies with IP

Identification by FTIR:

The FTIR spectra of each polymer were taken for identification of polymer.

Figure no 3: FTIR spectra of Gum Acacia

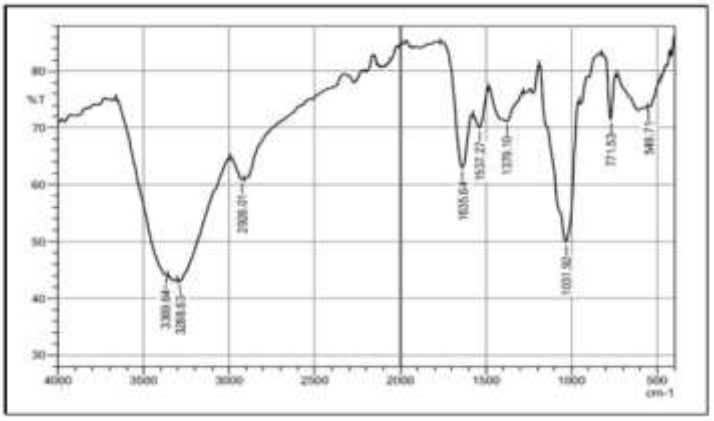


table no 9: FTIR of Gum Acacia

Remarks	Observed peak cm^1	Standard range cm^1
C-H Stretching	2926	2990-2850
C-O-C Stretching	1031	1200-1020
C-O Stretching of hydroxyl	1379	1380-1300
O-H Stretching	3369	3550-3200

Figure no 4: FTIR spectra of Chitoson

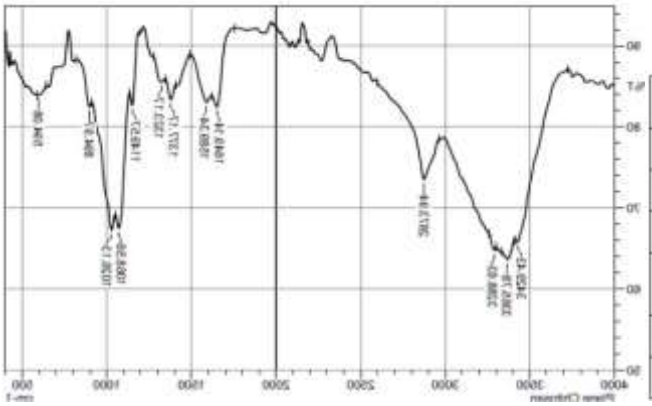


table no 9: FTIR of Chitoson

Remarks	Observed peak cm^{-1}	Standard range cm^{-1}
C-H Stretching	2873	2990-2850
C-O-C Stretching	1068	1200-1020
N-H Stretching	3429	3500-3350
C-O Stretching of hydroxyl	1323	1350-1260
C-N Stretching	1377	1380-1250
O-H Stretching	3365	3550-3200

Figure no 4: FTIR spectra of HPMC K4M

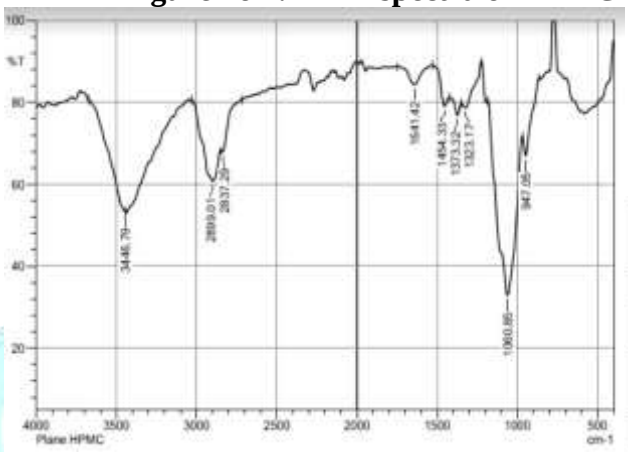


table no 9: FTIR of HPMC K4M

Remarks	Observed peak cm^{-1}	Standard range cm^{-1}
C-H Stretching	2899	2990-2850
C-O-C Stretching	1060	1200-1020
C-O Stretching of hydroxyl	1373	1350-1260
O-H Stretching	3446	3550-3200

Solubility studies of Physical Mixtures (Drug: Polymer)

table no 10: solubility of physical mixture

Mixture	Physical Mixture	Solubility
Rosuvastatin Calcium and Gum Acacia	RTGP1	0.054± 0.001
	RTGP2	0.065± 0.006
	RTGP3	0.069± 0.007
	RTGP4	0.0801± 0.004
Rosuvastatin Calcium and Chitosan	RTCP1	0.034± 0.007
	RTCP2	0.052± 0.009
	RTCP3	0.068± 0.006
	RTCP4	0.075± 0.005
Rosuvastatin Calcium and HPMC K4M	RTHP1	0.046±0.005
	RTHP2	0.039±0.008
	RTHP3	0.053±0.003
	RTHP4	0.063± 0.009

Solubility studies of Physical Mixtures (Drug: Polymer)

table no 11: solubility of nanocomposites

Nanocomposites	Physical Mixture	Solubility
Rosuvastatin Calcium and Gum Acacia	RTGN1	0.105±0.002
	RTGN2	0.142±0.004
	RTGN3	0.147±0.004
	RTGN4	0.162±0.008
Rosuvastatin Calcium and Chitosan	RTCN1	0.082±0.003
	RTCN2	0.106±0.008
	RTCN3	0.116±0.102
	RTCN4	0.140±0.002
Rosuvastatin Calcium and HPMC K4M	RTHN1	0.045±0.005
	RTHN2	0.064±0.008
	RTHN3	0.076±0.003
	RTHN4	0.113± 0.009

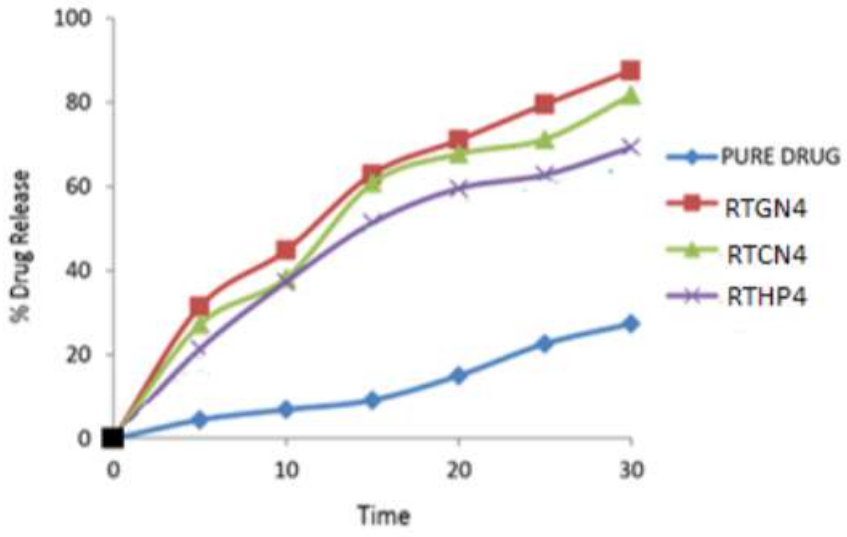
In vitro Drug release:

Table no 11: in vitro drug release of Rosuvastatin calcium

Time	Pure Drug % Drug Release	RTGN4 % Drug Release	RTCN4 % Drug Release	RTHN4 % Drug Release
0	**0**	**0**	**0**	**0**
5	3.46±0.49	30.35±0.81	25.14±0.76	20.73±1.68
10	5.86±0.85	42.51±1.57	36.28±0.56	35.43±1.21
15	8.10±0.49	60.79±0.91	58.74±1.39	50.43±0.87
20	14.04±0.66	70.05±0.74	68.54±0.87	58.45±0.45
25	22.41±1.87	77.65±0.43	70.16±0.97	61.75±0.98
30	27.38±0.91	**87.59±0.97**	81.72±1.64	69.32±0.65

Based on the results retrieved from the dissolution study of the nanocomposites, it was inferred that a notable improvement in the dissolution rates were recorded in all the nanocomposites when compared with pure drug Rosuvastatin Calcium. At the end of 30 minutes among all of the nanocomposites the best result was shown by RTGN4, which showed 87.59% drug release in comparison to pure Rosuvastatin which released 27.38%.

figure no 5: drug release of Rosuvastatin calcium



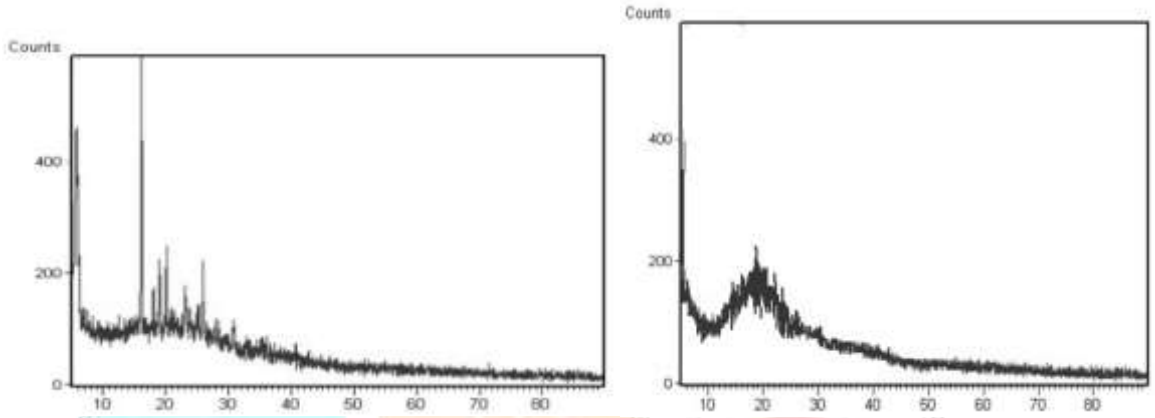
Drug content analysis of nanocomposites

The amount of drug in the nanocomposites can be determined by drug content analysis. It was observed that around 69 to 91 % drug can be incorporated in the nanocomposites. RTGN4 (1:4) showing maximum amount of drug content as compare to other batches So it was chosen for further studies**.**

table no 12: drug content in nancomposites

Nanocomposites	**RTGN4**	**RTCN4**	**RTHN4**
Drug content	91.12 ± 0.54%	85.83 ± 0.50 %	69.42 ± 0.66%

Characterization of Optimized Nanocomposites XRD studies of plain drug and Nanocomposites



Stability Study

table no 13: stability data of nanocomposites

Duration (Months)	**Appearance**	**Drug content (%)**	**In vitro drug release (%)**
0	Brownish fine powder	91.12 ± 0.54	87.59 ± 0.97
1	No change	90.76 ± 0.51	86.91± 1.26
2	No change	90.52 ± 0.49	86.12± 1.31
3	No change	90.48 ± 0.60	85.94± 1.29

Stability study of optimized ratio of powder nanocomposites of Rosuvastatin calcium (RTGN4) was done to see the effect of temperature and humidity on powder nanocomposites during the storage time. Nanocomposites were evaluated periodically at 0 and 1, 2, 3 months for its drug content, appearance, and in-vitro drug release. From the stability study results, it can be understood that there was no noteworthy change brought in drug content, appearance and in-vitro drug release of the formulation which is tabulated. Hence, we can conclude that Nanocomposites were stable after the 3 months of stability study.

IV. Conclusion

In solubility enhancement experiments of Rosuvastatin calcium, the nanocomposites prepared by Gum Acacia as a carrier at 1:4 ratios (RTGN4) expressed the best results with regards to the improvement of solubility and dissolution. From the stability studies, it is assured that the NCs are stable. It is evident from the stability studies conducted for all the optimized formulations containing different matrices that the stability of drug is promising over a studied range of period. There seems to be no degradation of optimized formulation as well. Further, similar dissolution profile was achieved from the same optimized formulation even after three months of storage at accelerated stability conditions. It is likely achievable to improve the solubility of poorly soluble BCS class II drugs with the help of cheap natural as well as synthetic polymers using MIND technique. As a final note, from the results, it can be concluded that microwave generated NCs can successfully be utilized to enhance solubility, dissolution and eventually the bioavailability of poorly soluble BCS class II drug.

V. References

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