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Use of Nanohybrid Material for Formulation, Development and Evaluation of Pharmaceutical Dosage Form Containing the Low Solubility Active Pharmaceutical Ingredient

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ABSTRACT

In oral absorption of a drug, the drug first dissolves and then is absorbed by diffusion through gastrointestinal membranes. The gastrointestinal environment is aqueous in nature and it is well-known that one-third of the drug population is water insoluble. Hence, there is a need for enhancement of the solubility and dissolution of such drugs. In this work, enhancement of the solubility and dissolution of the practically insoluble drug Rosuvastatin Calcium was achieved by formation of nanohybrids using microwave-induced diffusion (MIND), which ultimately leads to bioavailability enhancement. nanohybrids were formed by using natural carriers such as acacia,guar gum and PVP k-30 with the help of microwaves. Selection of carriers was based on their surfactant and wetting properties. Solubility studies were carried out to establish the solubility-enhancing property of the nanohybrids. To support solubility analysis results, dissolution studies (i.e. powder dissolution and in-vitro dissolution) were carried out. The nanohybrids were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction studies, scanning electron microscopy and transmission electron microscopy. It was found that as the concentration of polymer in the composite increased the solubility and dissolution of rosuvastatin calcium were enhanced. The optimised ratio (drug : polymer) for all the composites was found to be 1:4. The novelty of this work is the green and cost-effective way of forming drug nanocomposites with the help of microwave, which can be scaled up to an industrial level. The method gives an immaculate means of solubilisation by generating drug dispersion at the micro and nanoscale level in natural biodegradable stabilising media. Hence, this study demonstrates the use of nanohybrids in solubility and dissolution enhancement.

Keywords- BCS Class II, Nanohybrids, Solubilization, Enhancement of solubility, Optimized drug dissolution and drug release.

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INTRODUCTION

The oral route is the major way of dosing both existing and new drugs. Most of the drugs which administrated by oral route are absorbed by passive diffusion through the gastro-intestinal (GI) cellular membranes. The solubility and permeability are the most important tools for determining the oral bioavailability of a specific drugs within the GI tract, which have aqueous environment. According to US pharmacopoeia more than 40% of the drugs are poorly soluble or insoluble in aqueous environments. The enhancement oral bioavailability of poorly water-soluble drugs represent an actual challenge for pharmaceutical research, with the aims of improving drug therapeutic effectiveness as well as creating new market opportunities. The BCS class II drugs are water-insoluble (solubility equal or less than 100 µg of solute per 1 ml of solvent) but have high membrane permeability is only limited by dissolution. The energy-driven step is dissolution of crystalline solid in an process. In general, the kinetics of the process depends on solute, solvent chemical nature, microstructure and on the system conditions. It is possible to show that the dissolution rate of a crystalline drug in a given dissolution environment can be increased by forcing it to assume a microstructure by the theories of dissolution and non-electrolytes solubility characterized in nanoscale (short range) periodicity. The latest and most effective approaches to water-insoluble drugs solubilization are based on generating a drug dispersion (at molecular and/or nanoscale level) in a stabilizing media, preferably in solid-state form. Our main approach is that the enhancing effects of Microwave (MW) heating on mass transport might provide a green, effective

instrument for generating such dispersions [1]. Rosuvastatin Calcium have an class of drugs which is statins and it used for lowering blood cholesterol level. It has very good intestinal permeability and short half-life(Tmax,19h).However, the factors like low aqueous solubility(0.1mg/mL), crystalline nature and hepatic first pass metabolism responsible for low oral bioavailability (20%) of Rosuvastatin[2]. Due to the poor performance, drug have to administrated in higher doses which can causes liver abnormalities, rhabdomyolysis, arthralgia and kidney failure [3].To avoid such side effects, salt formation[4] and inclusion complexes with b-cyclodextrin[5] has been tried. A snanocomposites 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. A composite consists of two materials of varying natures and combination of those shows improved in their properties greater than that of individual [6]. The melting or fusion technique is one of the simple and efficient technique in the preparation of nanohybrids or/and bionanocomposites for the solubility and dissolution enhancement. Particle size reduction provides more surface area for absorption and rapid dissolution[7].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 heatin a sample at any point at a given time [8-9].The first and unique attempt was proposed by Kerk et al in the direction of bioavailability enhancement[10].prevent re-crystallization of the drug. The cross-linked polyvinylpirrolidone (Crospovidone) is first chosen matrix which constrains the drug into stable molecular clusters and/or nanocrystals by its 3D network [11-13].

The other matrix like cyclodextrin, is a torus-shaped molecule that forms molecular complexes with the drug[14]. In the present work, we developed a nanohybrids of rosuvastatin calcium using natural carriers such as gum acacia, guar gum and synthetic polymer like pvp k-30.The rosuvastatin nanohybrids 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(PM) were also formulated and compared with nanohybrids and plain drug for solubility analysis . Optimized nanohybrids were followed by DSC, XRD, SEM and TEM studies for confirmation of formation of nanohybrids. Finally in-vivo studies were carried out to elucidate the anti-hyperlipidemic potential of optimized nanohybrids with comparison to pure drug.

MATERIALS AND METHOD

Materials

Rosuvastatin calcium was generous gift from Mylan lab, Nashik, Maharashtra (India). Gum acacia, guar gum and PVP K-30 were purchased from Modern science, Nashik, Maharashtra(India). All the materials were of analytical grade. The materials were used as received without any further purification.

Selection of natural gum

Gum acacia and guar gum , PVP K-30 were studied for swelling index, foaming index, viscosity method which described by Murali M. B GV et al.

Swelling Index (SI)

Swelling index of gums was determined by modified method reported. 1gm of acacia,pvp k-30 and gaur gum was accurately measured and transferred to 100 ml measuring cylinder. The initial volume which occupied by gum was noted. Made up the volume upto the 100ml with distilled water. The open end of cylinder was sealed with aluminum foil and kept aside for 24 hrs. After 24 hrs volume of swelled gum was noted. The swelling index of gum was calculated by the following formula.

Foaming Index

The foaming index of gum was calculated to check the surfactant properties of the gum. Accurately weighed 1 g of gum and transferred it in 250 ml measuring cylinder. 100 ml distilled water was added in measuring cylinder to make dispersion. Resultant dispersion was vigorously shaken for 2 minutes. The foaming index of gum calculated by the following equation,

Foaming index = Hf – Hi

Where, Hf = Height of solution of gum after shaking; Hi = Height of solution of gum before shaking.

Viscosity

Viscosity of gums was calculated by dissolving one gram of each acacia, PVP K-30,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 mixture [7, 15, 16, 18]

Physical mixture of drug with polymer acacia (AC), guar gum, PVP K-30 were prepared by simple blending of drug with polymer in the ratio 1:1 to 1:6 .The quantity of pure drug and respected polymers were mentioned in Table 1. The physical mixture prepared to check the solubility enhancing property of nanohybrids as compared with physical mixture.

Table 1: Formulation of physical mixture

Ratios (for physical mixture)	Quantity (mg)			
	Rosuvastatin Calcium (drug)	Gum acacia	Guar gum	PVP K-30
1:1	500	500	500	500
1:2	500	1000	1000	1000
1:3	500	1500	1500	1500
1:4	500	2000	2000	2000
1:5	500	2500	2500	2500
1:6	500	3000	3000	3000

The resultant physical mixtures of rosuvastatin calcium with carriers acacia gum, guar gum and pvp k-30 are denoted by AAp, AGp and APp, respectively. Data are means ± SD, n = 3.

Preparation of nanohybrid

For each sample, a physical mixture of rosuvastatin calcium and individual carrier (acacia gum, guar gum, PVP K-30) was made by homogeneous mixing. The weight-to weight (w/w) ratio of drug to the carrier was taken from 1 to 6 keeping amount of mixture constant. To this mixture, 4 ml of water was added for each gram of the drug–carrier mixture to make homogeneous slurry (the water was added for hydration of the carrier). A fixed amount of the slurry (5 g) was placed in a glass beaker with a Teflon stirrer (transparent to microwaves) and treated with microwave irradiation for different times at power of 560 W . The temperature of the mixture at the end of treatment was recorded using an inbuilt temperature measurement probe. The samples were then ground in a glass mortar and sieved to achieve a particle size of 80–250 mm. The nanohybrid of drug with the carrier (acacia gum, guar gum, PVP K-30) was respectively designated as follows: RSVACCM (1–6), RSVGGM (1–6), and GPZPVPM (1–6).

Evaluation of nanohybrids

Drug content analysis

To study the amount of drug incorporated in the Nanohybrid, rosuvastatin calcium was extracted from the nanohybrid by dissolving them in 25 ml methanol. The resulting solution was filtered through a 0.2-micron membrane filter. The rosuvastatin calcium content in the methanolic extracts was analysed spectrophotometrically by using UV-Visible spectrophotometer (UV 1601; Shimadzu, Tokyo, Japan) at a wavelength of 241 nm, against the methanol as blank

Solubility study

The solubility of rosuvastatin calcium, RSVACCP, RSVGGP, RSVPVPP, RSVACCM, RSVGGM, RSVPVPM was determined in pH 6.8 phosphate buffer. The solubility of drug, physical mixtures and nanohybrid was determined by taking an excess amount of drug (30 mg) and nanohybrid (equivalent to 30 mg of drug) and adding them to 10 ml of solvent (pH 6.8 buffer), in Teflon-facing screw-capped vials. The samples were kept at equilibrium for a period of 48 h on an orbital shaking incubator (CIS-24; Remi Instruments, Mumbai, India) at 37 0.5°C and 50 rpm. The supernatant fraction collected from the vials was filtered through a 0.2- micron membrane filter and analysed by UV-Visible spectrophotometer (UV 1601; Shimadzu) at a wavelength of 241 nm. Ratio optimisation (drug: carrier) was done on the basis of the best solubility results obtained.

Powder dissolution test

The powder dissolution test was carried out on rosuvastatin calcium nanohybrid following the USP XXIV Apparatus 2 (paddle) method in 900 ml of pH 6.8 phosphate buffer as dissolution media maintained at 37 0.5 0C at 50 rpm. Powder containing 5 mg (or equivalent to 5 mg of) rouvastatin calcium was added to dissolution media. At predetermined times (5, 10, 15, 30 and 45) 5-ml samples were collected periodically and replaced with fresh dissolution medium. After filtration through a 0.2-micron membrane filter samples were analysed spectrophotometrically at 241 nm. A cumulative correction was made for the removed samples while determining the total amount of drug dissolved. All experiments were run in triplicate. Dissolution profiles of rosuvastatin calcium nanohybrid were compared with that of the pure drug rosuvastatin calcium at the same experimental conditions.

Fourier –transform infrared spectroscopy (FTIR)

FTIR study of drug and optimized ratio of nanohybrid (APN 1:4) was carried out. Nanohybrid were mixed with potassium bromide (KBr) of IR grade in a ratio of 1:100 and compressed using a pellet pressed at 15 tones pressure. Then pellets were scanned using an FTIR spectrophotometer (Shimadzu, 8400S). The FTIR spectra of optimized nanohybrids were compared with that of the pure drug to assess any change in the principal peaks of spectra of optimized nanohybrid.

Differential Scanning calorimetry (DSC)

A DCS study of optimized nanocomposites ratio (APN 1:4) was employed to access what changes had actually made when nanohybrid were formulated and by what fact these enhances the solubility of drug. The DSC curves were obtained by Differential Scanning Calorimeter (Shimadzu, DSC 60, Japan) at the heating rate of 10°C/ min from 50 to 200° in nitrogen atmosphere.

X-ray diffraction studies (XRD)

XRD studies of drug rosuvastatin calcium and optimized nanohybrid (APN 1:4) were carried out to investigate the change in crystallinity when drug was mixed with polymer. XRD pattern were recorded using with Cu-kα radiation (D500, Siemens Diffractometer). The scanning angle ranged from 10° to 80° of 2θ. XRD Study was carried out to assess the changes in the crystalline made when the drug was mixed with carriers.

Scanning electron microscopy (SEM)

Scanning electron microscopy was used to examine external surface morphology. The morphologies and detailed particle structural characterizations of pure drug and nanohybrid (APN 1:4) were observed by scanning electron microscope (JEOL JSM-630 J, Scanning Electron Microscope). Nanohybrid that showed the best results in the solubility and dissolution studies were subjected to scanning electron microscopy (SEM) studies to confirm the changes made during the formation of nanohybrid. Samples were prepared by mounting powder onto a brass stub using graphite glue and coated with gold under vacuum before use. Images were recorded at the required magnification at an acceleration voltage of 10 KV using a scanning electron microscope.

Transmission electron microscopy (TEM)

The drug rosuvastatin calcium and optimized ratio of nanohybrid (APN 1:4) showing the best results in the solubility and dissolution studies was subjected to transmission electron microscopy (TEM) studies to confirm the formation of nanocrystals embedded in composites. The particle size and shape of pure drug crystal dispersed in polymer were analyzed with trmission electron microscopy. The morphology of the nanohybrid was obtained by transmission electron microscope (PHILIPS CM200, Transmission Electron Microscope).

Preparation of sustained-release tablets

The ratios of nanohybrids that showed the best results in solubility and dissolution studies were selected for formulating the sustained-release tablets. The composition of tablets was as shown in Table 2. All the components of the tablets were sieved through a #60 sieve, weighed, mixed and compressed by direct compression into tablets using a 7-mm punch for RSVAPNM tablets on rotary tablet minipress .

Evaluation of sustained-release tablet

Pre-compression evaluation

Pre-compression evaluation included measurement of angle of repose, Carr's index (compressibility) and Hausner's ratio of optimised BNC and various formulation mixtures, following the procedures given in USP 30 (2007).

Post-compression evaluation

Post-compression evaluation included measurement of weight variation, hardness, friability, drug content of prepared formulations, following the procedures given in USP 30 (2007).

Assay of the total drug content

Drug content analysis was performed to study the amount of drug incorporated in tablets. Rosuvastatin Calcium from powdered tablets was extracted by dissolving the tablets in 25 ml methanol. The resulting solution was filtered by using a 0.2- micron membrane filter. Rosuvastatin Calcium content in the methanolic extract was analysed spectrophotometrically at 241 nm against the methanol as blank.

In-Vitro Dissolution Test

The dissolution test was carried out in USP apparatus type II (paddle) with Phosphate buffer p^H 6.8 as the dissolution medium of 500ml quantity at 50 rmp. The samples were drawn at 0,1,2,3,4 and 24 hours.fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed by using UV-Visible spectrophotometer at 241 nm for assessing the percentage of drug released.

Dissolution apparatus:

USP apparatus type ll(paddle)

Dissolution medium: Phosphate Buffer p^H6.8

Volume: 500 ml

Temperature: 37+ 2c

Rpm: 50

Sampling intervals (min) : 1,2 ,3,4,5 hours

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

Stability study

Optimised formulation was subjected to stability studies according to ICH guidelines. Various variables, such as drug content, disintegration time and in-vitro drug release, were measured before and after 30, 60 and 90 days of storage. There was no significant change in the above-mentioned variables following the elevated temperature and humidity conditions imposed during the stability study. Thus, it can be concluded that the prepared formulation is stable and not much affected by elevated humidity and temperature.

RESULTS AND DISCUSSION

Preliminary Investigation of Rosuvastatin Calcium

Saturation solubility of pure Rosuvastatin calcium in water, methanol and phosphate buffer pH 6.8 were determined. The results suggest that Atorvastatin calcium has very less solubility (0.028 mg/ ml) in water. The melting point was observed 158-160°C.

Selection of Natural Gum

Swelling characteristics and viscosity of the gums are presented in Table19. From this data, it can be concluded that the swelling characteristics and viscosity of acacia gum, guar gum,PVP k-30 were low. The High viscosity and toughness of the carrier may affect its dissolution enhancement property. According to past results it known that less swelling and low solution viscosity, they are more prone to dissolution enhancement. They are less prone to the formation of the tough matrix which will assist rapid liberation of the nanocrystals from the nanohybrid. The foaming index clearly indicates the greater foaming ability of PVP K-30 from other carriers. Hence, PVP K-30 enhances the solubility more efficiently than the other carriers.

Table 2:Physical characterization of polymer

Material	% Swelling	Viscosity (cp)	Foaming Index
Acacia	65.66± 1.20	2.22±0.13	7 ±0.45
Guar gum	72.12± 1.02	2.21±0.11	5±0.60
PVP K-30	75.13± 1.03	2.20± 0.14	8±0.40

Data are means ± SD, n = 3.

Evaluation of nanohybrid

In-vitro Solubility studies

Solubility studies were performed to find out the solubility enhancing properties of nanohybrid. Solubility studies provided the basis for selection of the best ratio that was to be forwarded for formulation. Pure drug Rosuvastatin calcium and physical mixtures of Rosuvastatin with individual carriers in varying ratios, as well as nanohybrid of Rosuvastatin with individual carrier in varying ratios were analyzed for solubility determination. The solubility of pure drug was found to be 0.028 mg/ml in water and 0.112 mg/ml in phosphate buffer pH 6.8. The results of solubility studies of a various ratios of physical mixture and nanohybrid are presented in Table 20 . Solubility studies reveals that physical mixtures improves the solubility of RSV significantly compared with pure drug .This may be due to the surfactant and wetting property of acacia gum, guar gum,PVP K-30. In case of nanohybrid solubility data indicates a tremendous rise in solubility compared with pure drug; this may be due to reduction of crystal size of the drug to a nanocrystalline form. This aspect is to be investigated by performing SEM and X-ray diffraction analyses.

Table 3 : Solubility of Physical mixture and Nanohybrid of Rosuvastatin Calcium

Drug polymer Ratio	AA_P mg/ml	AG_p mg/ml	AP_p mg/ml	AA_N mg/ml	AG_N mg/ml	AP_N mg/ml
1:1	0.204±0.01	0.347±0.07	0.501±0.04	0.255±0.02	0.829±0.03	1.046±0.05
1:2	0.650±0.06	0.526±0.09	0.680±0.09	1.424±0.04	1.066±0.08	1.392±0.08
1:3	0.695±0.07	0.617±0.06	0.614±0.04	1.547±0.04	1.164±0.12	1.538±0.03
1:4	0.501±0.04	**0.695±0.05**	**0.883±0.08**	1.627±0.08	**1.200±0.02**	**1.639±0.09**
1:5	**0.739±0.06**	0.549±0.19	0.628±0.10	**1.402±0.05**	0.661±0.10	0.740±0.03
1:6	0.481±0.14	0.448±0.11	0.402±0.01	0.897±0.06	0.436±0.06	0.515±0.06

Data are means ± SD, n = 3.

Solubility studies of physical mixtures and nanohybrid clearly indicated that as the ratio of drug to carrier increases solubility up to specified ratio. It was also found that the high solubility was shown by nanohybrid formulation and nanohybrid prepared by using PVP K-30 (APN) showing best solubility result at 1:4 ratio was considered optimal. The solubility of APN was found to be 1.639 mg/ml. AA_N (1:5), AK_N (1:4), AP_N(1:4) are the best ratios from different drug: polymers nanohybrids formulations, which were showing high solubility, hence those were subjected to invitro drug release study with pure drug and drug content analysis.

In-vitro Drug release

A powder dissolution test was performed because the solubility studies are not always a predictable parameter to determining the solubility enhancing properties of any material.

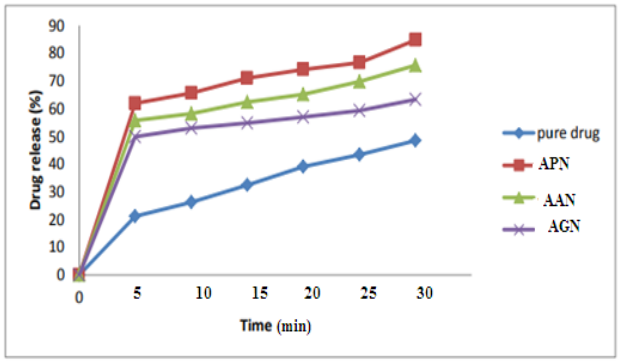

Fig 1 . Dissolution Profile of Pure Drug AA_n, AG_n, AP_n

The dissolution studies of Rosuvastatin and Rosuvastatin (NBs) give more specific information about the solubility and dissolution of drug. The dissolution profile of pure drug and NBs is presented in fig. . From the dissolution profiles of the NBs, there was evidently a remarkable improvement of the dissolution rates in all NBs compared with the pure Rosuvastatin. All Of the NBs, the best result was shown by AP_N which show the drug released 84.72% in comparison to pure Rosuvastatin which released 48.47%. From the solubilition and dissolution studies the AP_N was selected for formulating the dosage form.

Drug content analysis

Uniform dispersion of drug in the nanohybrid can be determined by drug content analysis. It was found that 85-92% drug was incorporated in the nanohybrod. APN (1:4) showing uniform dispersion of drug in the nanohybrid. Drug content analyses are presented in Table

Table 4 : Drug Content analysis of nanohybrids

Nanohybrids	AA_N	AG_N	AP_N
Drug Incorporated	89.42±0.54%	85.82±0.50 %	91.42±0.66 %

Solid state studies of optimized nanohybrids

The optimized ratio AP_N 1:4 further characterized by following parameters.

Fourier –transform infrared spectroscopy (FTIR)

FT-IR of A) Pure Drug B) Optimized Nanohybrids

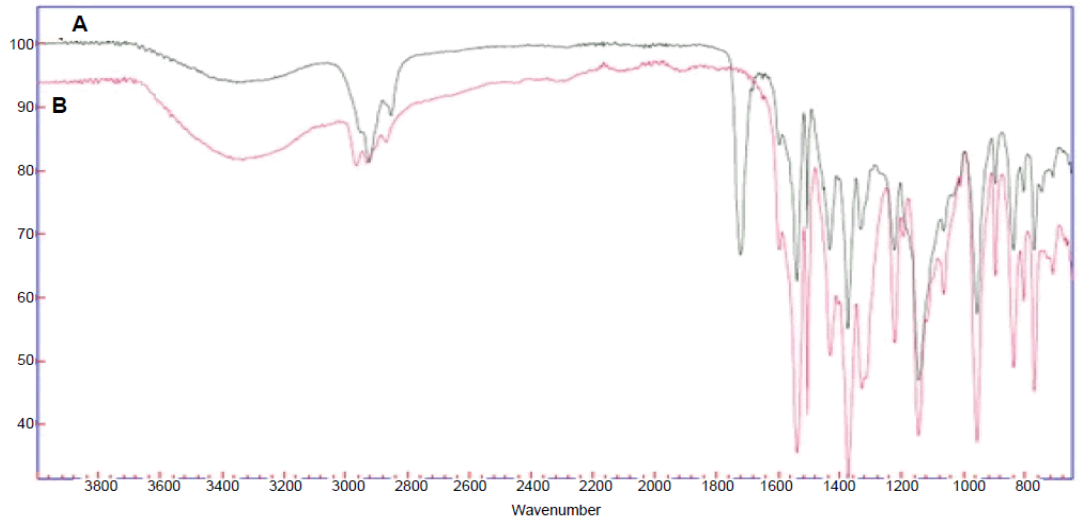

Fig 2 : FT-IR of A) Pure drug B) Optimized Nanohybrids

Differential Scanning calorimetry (DSC)

DSC was performed to detect the interaction between Rosuvastatin calcium and polymer. The DSC thermogram of pure drug shows a sharp endothermic peak corresponding to the melting point of crystalline drug was found to at 159.03°C. DSC of optimized nanohybrids APN 1:4 shows slight variation in endothermic peak as that of pure drug and intensity of peak is reduced this may be due to the decrease in the crystalline size of the drug. The DSC thermogram of APN at 143.050C had shown a broad endothermic peak. The peak broadening indicated that most of the drug is embedded in NBs in the nanocrystalline form. Little shift in melting point was observed due to reduction of drug to the nanocrystalline form. This phenomenon is responsible for the solubility enhancement as the crystallinity has been reduced to the nanocrystalline form solubility get enhanced. DSC thermogram of pure drug and nanohybrids are shown in fig.

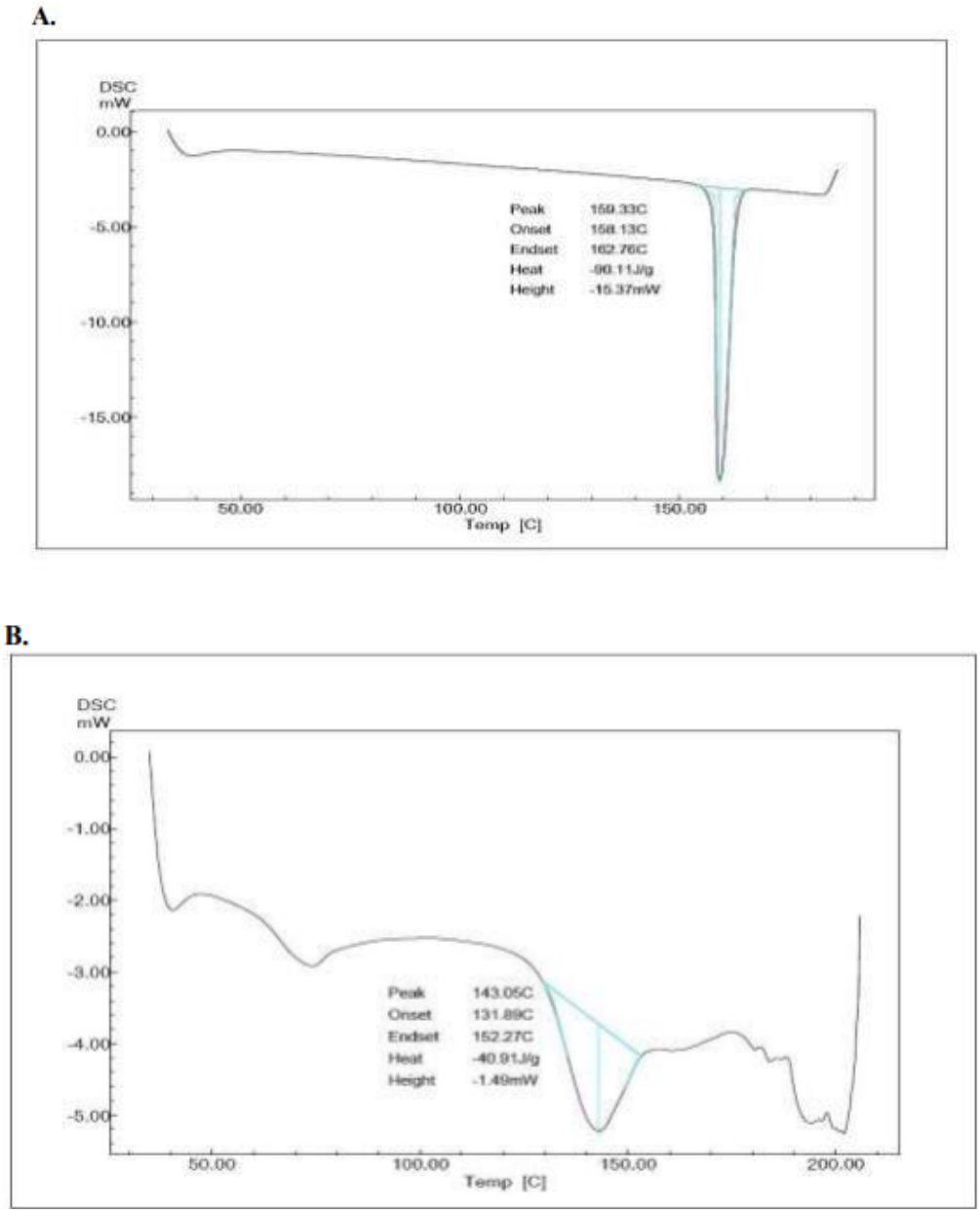

Fig 3 :DSC Thermo gram of A) Rosuvastatin Calcium B) Optimized nanohybrid

X -Ray Diffraction Studies (XRD)

The X-ray diffraction studies (XRD) of Rosuvastatin calcium (ATR) and optimized nanohybrid APN 1:4 are shown in figure. The pure (ATR) exhibit intense crystalline peak between 10° and 50°, characteristic diffraction peaks at 10.44°, 11.90 °, 17.04°, 19.33°, 23.40°, 24.82°, 28.83o , 30.43o and 37.33 ° were observed with intense peak at 21.58° indicating the crystalline nature of RSV. On the other hand APN it's observed that the peak intensity is reduced indicating reduction in crystallinity. This phenomenon is also responsible for enhancement of solubility. XRD pattern of pure drug and nanohybrids were showed in fig

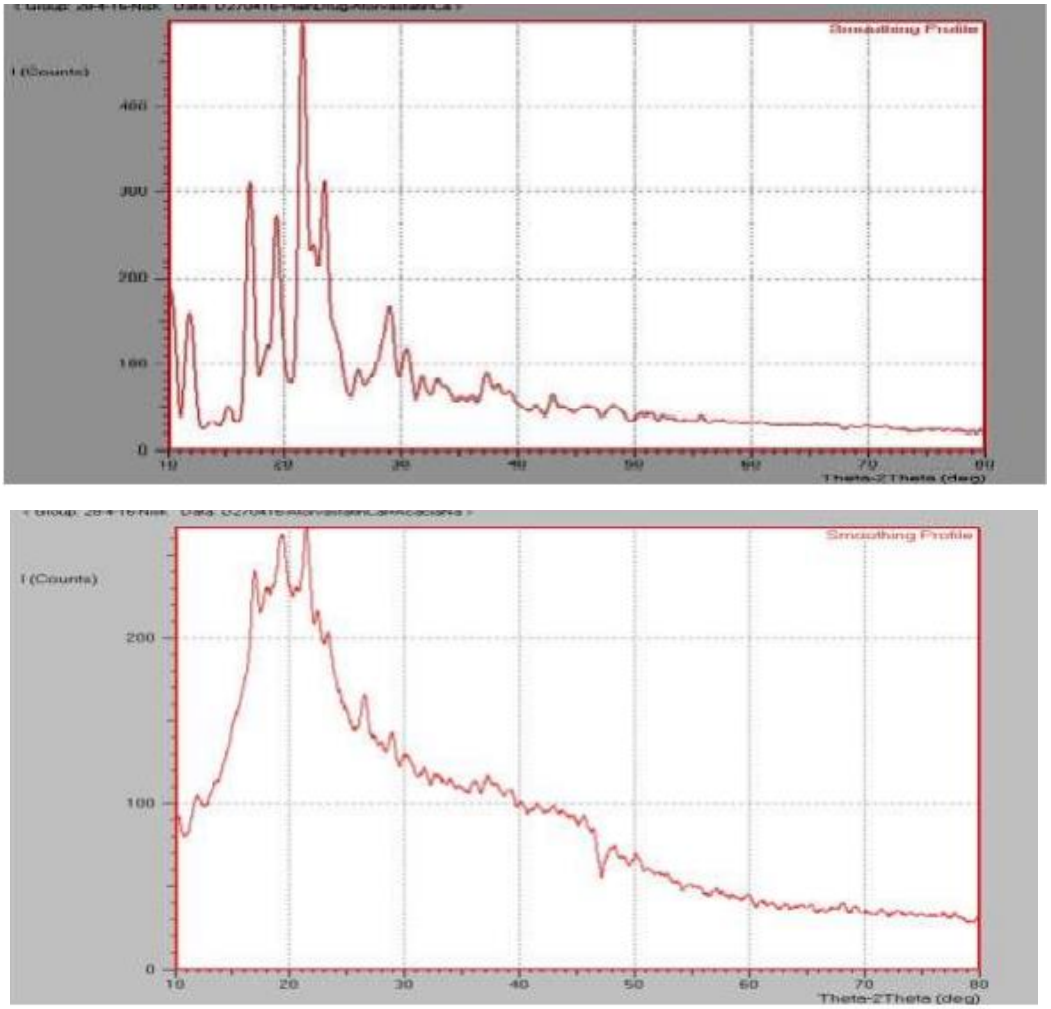

Fig 4 . : XRD Pattern of (A) Rosuvastatin Calcium and (B) optimized nanohybrids

Scanning electron microscopy (SEM)

SEM studies are usually done to study the surface morphology of drug particles. Rosuvastatin calcium and optimized nanohybrid APN 1:4 were characterized by SEM. From the fig19, it is concluded that pure Rosuvastatin calcium drug showed needle and plate shaped with smooth surface while in case of APN it was observed that they were irregular shape and size. Figure clearly shown that crystal shaped of Rosuvastatin calcium completely changes in nanohybrid which showing embedded Rosuvastatin crystal in the matrix of polymer (PVP K-30).

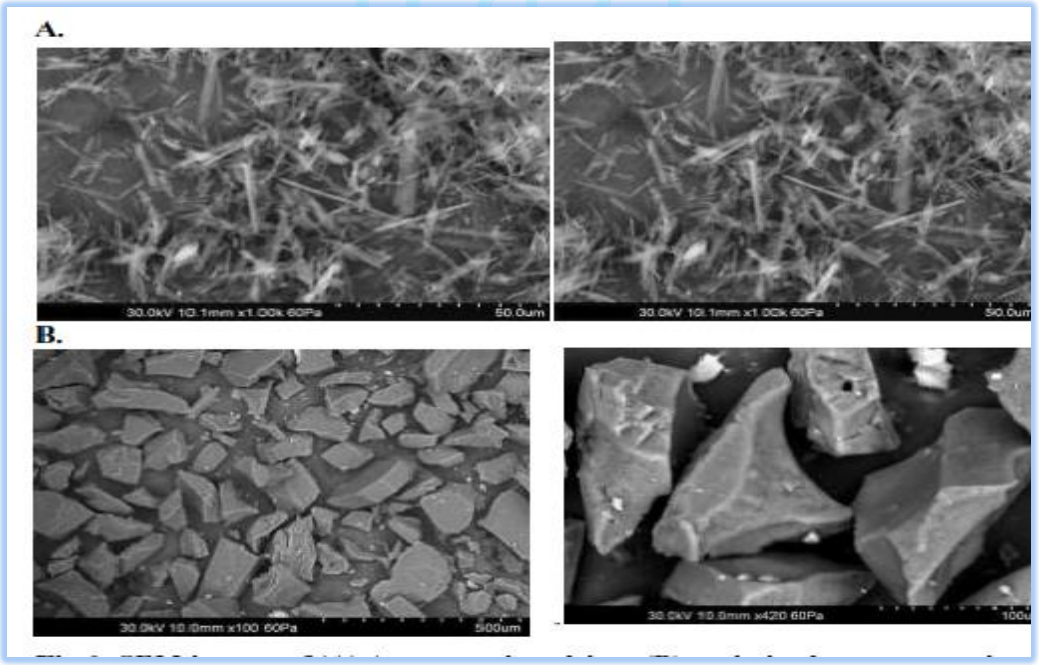

Fig5 : SEM images of (A) Rosuvastatin Calcium (B) optimized nanohybrids

Transmission electron microscopy (TEM)

The TEM of pure drug and optimized nanohybrid APN 1:4 are shown in the following fig20. . The TEM image of drug was observed first at 200 nm. In that image the drug is showing dark colour particles and pure drug image of TEM at 100 nm had shown the large free particles can be observed in somewhat cubic and rod shaped structure. After preparation of nanohybrid (APN) those were shown drug and polymer is mostly mixed looking flowery and most of the drug has transformed with the polymer. The polymer background which has more brightens and therefore drug is looking on the surface of polymer at 50 nm. When this preparation is observed at 20 nm the polymer is in background and the rod shaped structure of drug has converted into somewhat square shaped which shows that there is reduction of particle size of drug when it was treated with MIND method and all drug and polymer are finely embedded in each other.

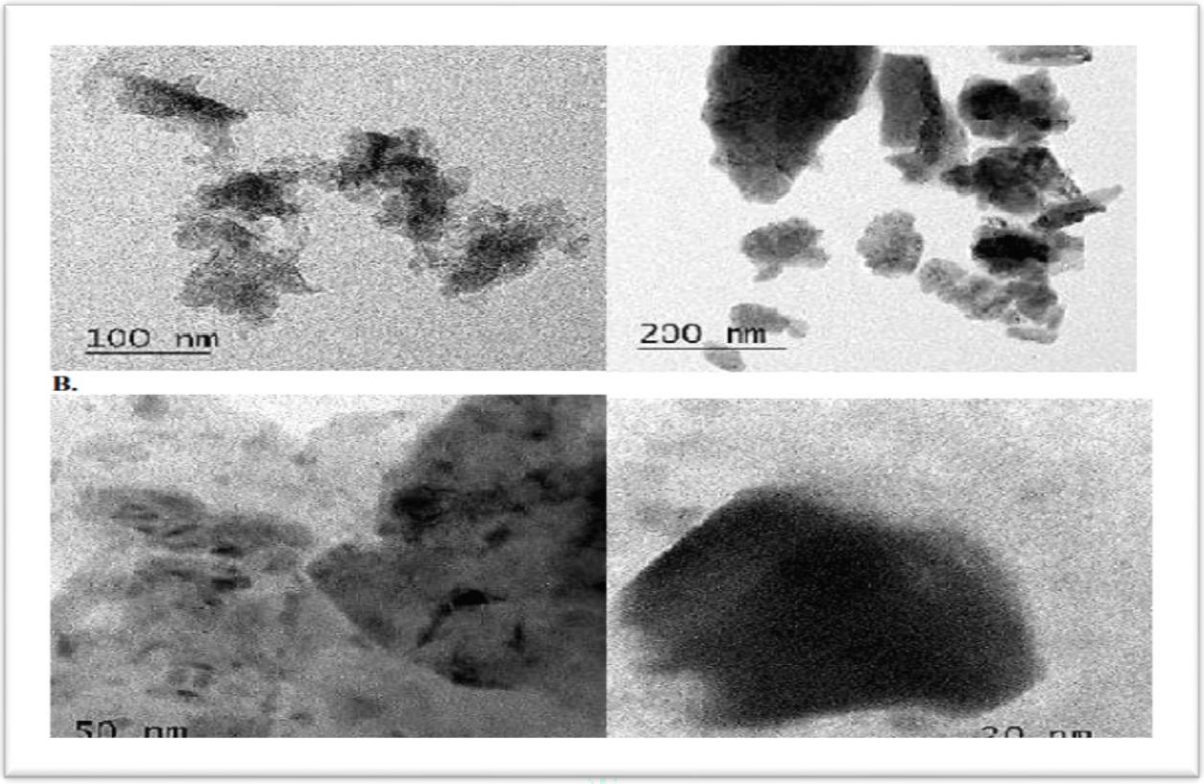

Fig 6. : TEM images of (A) Rosuvastatin calcium (B) optimized nanohybrids

Evaluation of sustained-release tablets

Pre-compression evaluation

All the formulation mixtures were subjected to measurement of angle of repose, Carr's index and Hausner's ratio. The results are shown in Table . From the angle of repose, Carr's index and Hausner's ratio data, it can be clearly concluded that RSVAPN and its mixture with different formulation components have excellent flow properties and fairto-good compressibility, which allows these formulation mixtures to be directly compressed into tablets and good flow of the mixture from the hopper with good content uniformity in the final tablets.

Post-compression evaluation

Prepared formulations were subjected to various compendial tests for post-compression evaluations such as hardness, friability, content uniformity of prepared tablets, DT. The results are shown in Table . All the parameters were within the limits given in the USP 30 (2007).

Table5 : Pre- compression evaluation of RSVAP$_M$

Formulation	Bulk Density G/CC	Tapped Density G/CC	Hausner Ratio	Compressibility Index %	Angle of Repose
F_1	0.51±0.05	0.56±0.02	1.15±0.05	2.72±0.02	26.21±0.01
F_2	0.50±0.03	0.58±0.03	1.17±0.02	12.24±0.03	20.48±0.04
F_3	0.53±0.01	0.57±0.02	1.16±0.03	13.11±0.03	24.38±0.01
F_4	0.55±0.04	0.59±0.01	1.18±0.01	13.85±0.06	27.40±0.05

Table 6 : Physical evaluation of matrix tablets

Formula Code	Hardness (kg/cm2)	Thickness (mm)	Weight variation (mg)	Friabiity (%)	Assay *%)
F_1	4.7±0.12	4.28±0.13	316.3±0.15	0.18±0.12	90.15±0.12
F_2	4.5±0.13	4.22±0.12	313.7±0.12	0.14±0.12	99.53±0.14
F_3	4.2±0.11	4.10±0.13	313.5±0.13	0.21±0.14	99.15±0.13
F_4	5.1±0.14	4.42±0.15	316.5±0.13	0.22±0.16	100.24±0.12

In-Vitro Drug Release Studies

The in-vitro dissolution studies were performed using the USP-I1 (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900ml of phosphate buffer pH 6.8, maintained at 37±0.5 C. An aliquot (5ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer at 241 nm.

Table 7: in-vitro drug release data of Rosuvastatin Calcium from formulations F1 to F4 and comparative with Marketed product

Time in Hrs	**0**	**1**	**4**	**8**	**12**	**16**	**20**
% Drug release inF_1	0	11.40±1.1 2	24.50±1.2	40.10±2.2	54.05±1.4	60.05±2.3	64.05±1.4
% Drug release in F_2	0	10.70±0.2	24.62±1.3	44.31±2.3	58.31±2.2	54.1±1.2	69.31±2.2
%Drug release in F_3	0	9.63±0.3	26.81±1.6	46.94±1.9	59.35±2.4	71.1±2.1	79.35±2.4
%Drug release in F_4	**0**	**15.6±0.4**	**35.6±1.1**	**53.5±0.2**	**68.09±2.6**	**73.0±1.2**	**95.09±2.6**
% Drug release in marketed product	**0**	**13.3**	**33.8**	**51.5**	**68.02**	**`73.0**	**80.02**

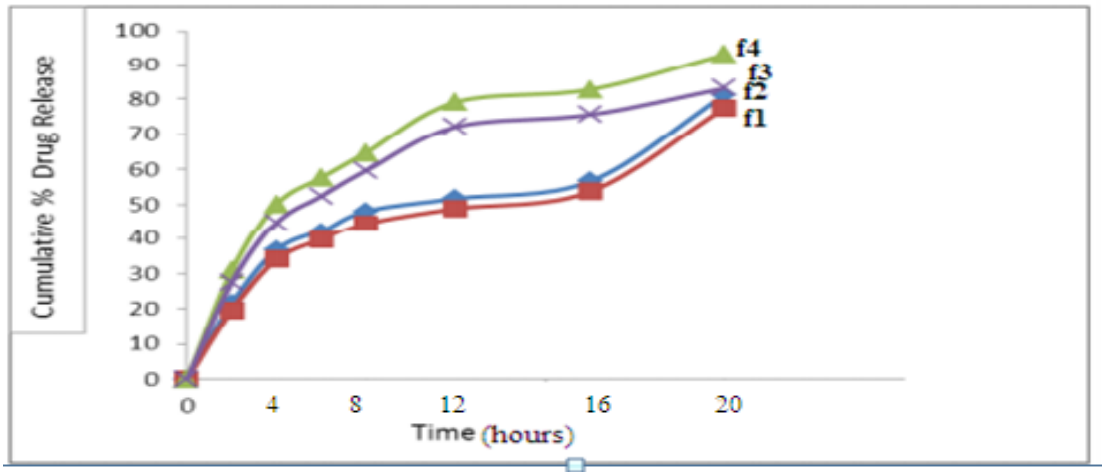

Fig.7 : In-vitro drug release profiles of Rosuvastatin Calcium from F1 to F4

CONCLUSION

This study successfully demonstrated the use acacia gum, guar gum and pvp k-30 as carriers for the formation of microwave-generated nanohybrids in the solubility and dissolution enhancement of rosuvastatin calcium. Solubility and dissolution studies confirmed the use of these materials for solubility enhancement. This demonstrates the possibility of using BNCs as drug delivery systems, particularly using the MIND technique. The RSVPVPM nanohybrids showed the best results regarding solubility and dissolution enhancement. From the FTIR, DSC, XRD, SEM and TEM characterization it can be concluded that rosuvastatin had been converted to nanocrystals in the composites and this was responsible for the solubility enhancement. Characterisation confirmed that there was no interaction between the drug and polymers. In-vitro assessment of optimised formulations further confirmed the use of nanohybrids for enhancing solubility and dissolution by use of natural carriers. The stability studies showed that the nanohybrids-containing formulations were stable. Here we have demonstrated that it is indeed possible to prepare nanohybrids using rosuvastatin as a model drug. Key feature of this study include the uniform distribution of drug in carrier in a nanocrystalline form, which is sufficiently stable and easy to prepare. Finally from these studies overall we can conclude that microwave-generated nanohybrids can be successfully used for the enhancement of solubility, dissolution and bioavailability.

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