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Formulation & Development of nanocomposites for solubility enhancement of BCS Class II model drug using microwave induced diffusion technique

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ABSTRACT

Objective: The oral bioavailability of a specific drug is depends on its solubility and permeability within the Gastro intestinal (GI) tract, which is an aqueous environment. The solubility and bioavailability of BCS Class II drugs can be improved by developing a method reducing the particle size and converting the drug into amorphous state. materials. In the present study nanocomposites (NCs) were formulated using microwave induced diffusion technique (MIND) for solubility enhancement of poorly water soluble (BCS class II) model drug Atorvastatin calcium.

Methods: The nanocomposites of atorvastatin calcium were developed using natural and synthetic carriers such acacia, chitosan, HPMC K4M and avicel 101. Different Physical mixture & nanocomposites formulations were prepared with varying ratios of drug and carriers. The selections of natural & synthetic carriers were based on their surfactant and wetting properties.

Results: In case of developed nanocomposites, the optimum drug-to-carrier ratio was found to be 1:4 with Gum acacia as a carrier which enhanced solubility nearly 15 fold as compared to pure drug. From the dissolution study of the nanocomposites there was evidently a remarkable improvement of the dissolution rate in NCs compared with the pure Atorvastatin calcium was observed. The optimized nanocomposites were characterized by Fourier transform infrared spectroscopy, Differential scanning calorimetry, X-ray diffraction and Scanning electron microscopy.

Conclusion: From Solubility, In vitro drug release and Physical characterization of carriers it is clear that the nanocomposite ATGN4 formulation was found to be optimum in terms of solubility enhancement. The MIND technique employed in this study is green, cost-effective and a promising approach for solubility enhancement.

1. Introduction

The oral route is the major way of dosing both existing and new drug molecules. 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 specific drugs within the GI tract, which have aqueous environment [1]. 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 [2]. The energy-driven step is dissolution of crystalline solid in a process. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for showing pharmacological response [3]. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration[3].

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. A composite consists of two materials of varying natures and combination of those shows improved in their properties greater than that of individual[4]. Microwave induced diffusion technique (MIND) technique is one of the novel techniques for improvement of drug solubility [4,5]. The use of microwave irradiation with the help of microwave oven resulting in to the breakage of internal structure of drug particles resulting in to the formation of *Nanoparticles* which ultimately leads to solubility enhancement [6,7] . Thus the Nanocomposites of poorly soluble drugs using natural and synthetic carriers can be a promising approach for oral delivery of low solubility drug. In the present study Microwave generated nanocomposites were formulated for solubility enhancement of poorly water soluble BCS class II model drug atorvastatin calcium. atorvastatin is a member of the class of drugs known as statins, used for lowering blood cholesterol level. It has very good intestinal permeability and short half-life (T max, 1–2h). However, it has low oral bioavailability (12%) due to low aqueous solubility (less than 0.1mg/mL), crystalline nature and hepatic first pass metabolism. Poor performance of the drug leads to administration in higher doses possibly leading to liver abnormalities, rhabdomyolysis, arthralgia and kidney failure. In the present study nanocomposites of Atorvastatin calcium

were developed by MIND technique using natural and synthetic carriers such acacia, chitosan, HPMC K4M and aAvicel 101.

2. Materials and methods

Materials

Atorvastatin calcium was obtained as a gift sample from Lupin Pharmaceuticals Ltd, Pune, India. Polymers like Gum acacia, chitosan, HPMC K4M and avicel 101 were obtained from Modern Science Apparatus Pvt. Ltd., Nashik, India. All other chemicals used in this study were of analytical grade.

Methods

Determination of solubility

The solubility of Atorvastatin calcium in water and pH 6.8 buffer solution was determined by reported method[8,9]. The examined compound was dissolved in excess in 1-10 ml respective solvent .i.e. water, pH 6.8 phosphate buffer solution, DMSO (di-methyl sulfoxide) in a conical flask. The solutions were stirred for 48 hours in the orbital shaker. The separate phases of the solution were left to sediment under thermostated circumstances. The solution was filtered. Aliquots were taken from clear part of the solution. Aliquots were diluted and the absorption was measured with UV- spectrophotometer (Shimadzu, UV-2450).

Physicalcharacterization of Polymer

a. Swelling Index (SI)

The modified method was used for determination of Swelling index of gums [8,9]. The 1mg of gum acacia, chitosan gum, HPMC K4M and avicel 101 was accurately measured and transferred to 100 ml measuring cylinder. The occupied initial volume by gum was noted. The volume was adjusted to the 100ml with distilled water. The cylinder (open end) is sealed with aluminum foil and kept aside for 24 Hours. After 24 hrs of storage the volume of swelled gum were noted. The swelling index of each polymer was calculated by following formula

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

Where, SI- Swelling index of gum,
H_i - Initial height of powder,
H_f- Final height of powder after 24 hr.

b. Foaming index

The foaming index of gum acacia, chitosan gum, HPMC K4M and avicel 101were calculated to check the surfactant properties of the gum. The 1 gm of gum was accurately weighed and transferred to 250 ml measuring cylinder. The 100ml of distilled water was incorporated in measuring cylinder to make dispersion[8]. The resultant dispersion was shaken vigrasouly for 2min. 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.

c. Viscosity

The Viscosity of gum acacia, chitosan gum, HPMC K4M and avicel 101 were calculated by dissolving one gram of each polymer in 100 ml of water (1% w/v solution).The viscosity of the carrier dispersions of each polymer were measured by Brookfield viscometer using spindle 00 at 200 rpm.

Preparation of physical mixture

Physical mixture of drug (atorvastatin calcium) with polymers like gum acacia, chitosan, HPMC K4M and avicel101were prepared by simple blending of drug with polymer in the ratio 1:1 to 1:4[8-10]. The physical mixture of drug with gum acacia having ratio 1:1, 1:2, 1:3 and 1:4 were formulated & denoted by ATGP1, ATGP2, ATGP3,ATGP4 respectively. The physical mixture of drug with Chitosan having ratio 1:1, 1:2, 1:3 and 1:4 were formulated & denoted by ATCP1, ATCP2, ATCP3, ATCP4 respectively.

Similarly physical mixture of drug with HPMC K4M and Avicel 101having ratio 1:1, 1:2, 1:3 and 1:4 were formulated & denoted by ATHP1, ATHP2, ATHP3,ATHP4 and ATAP1, ATAP2, ATAP3, ATAP4 respectively

Preparation of nanocomposites

The nanocomposites were developed by homogenous mixing of accurately weighed amount of atorvastatin 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.

Briefly, to the mixture of drug and polymer in varying ratio, 4 ml of water was incorporated for each gram of polymer to make homogenous slurry. The constant (fixed) amount of slurry was taken in beaker and was irradiated with microwave radiation at power 556 W with continuous stirring for 5 min(CATA-2R, Catalyst System) [8-10]. The developed Nanocomposites were grounded in mortar & pestle and sieve to achieve the particle size of 80 to 250 µm. The quantity of atorvastatin calcium and polymer for different ratios were taken as shown in Table 1.

Table 1: Formulation of Nanocomposites.

Ratio (For Nanocomposites)	Drug: Polymer 1:1	Drug: Polymer 1:2	Drug: Polymer 1:3	Drug: Polymer 1:4
Formulation Code	**ATGN1**	**ATGN2**	**ATGN3**	**ATGN4**
Atorvastatin calcium (mg)	500	500	500	500
Gum Acacia (mg)	500	1000	1500	2000

Formulation Code	**ATCN1**	**ATCN2**	**ATCN3**	**ATCN4**
Atorvastatin calcium (mg)	500	500	500	500
Chitosan (mg)	500	1000	1500	2000
Formulation Code	**ATHN1**	**ATHN2**	**ATHN3**	**ATHN4**
Atorvastatin calcium (mg)	500	500	500	500
HPMC K4M (mg)	500	1000	1500	2000
Formulation Code	**ATAN1**	**ATAN2**	**ATAN3**	**ATAN4**
Atorvastatin calcium (mg)	500	500	500	500
Avicel 101 (mg)	500	1000	1500	2000

Evaluation of nanocomposites

Solubility study

The solubility study of physical mixtures and nanocomposites (NCs) was determined in pH 6.8 phosphate buffer by reported method [8-10]. The sample solution was analyzed at a wavelength of 246 nm by UV-visible spectrophotometer (Shimadzu, Japan). On the basis of the best solubility results, ratio optimization (drug: carrier) was carried out.

Drug content analysis

The amount of drug incorporated into nanocomposites, drug content analysis was performed[8-10]. The developed nanocomposites were dissolved in 25ml of methanol. The resulting solution was filtered through membrane filter (0.45µ) and analyzed at wavelength 246 nm by UV-visible spectrophotometer against methanol as a blank**.**

In-vitro dissolution test

The i*n-vitro* powder dissolution test was carried out using USP XXIV apparatus II (Paddle) of developed optimised atorvastatin calcium nanocomposites (by using 900ml pH 6.8 phosphate buffers as a dissolution media) by reported method[8-10]. Briefly, powder containing accurate dose of drug was incorporated in the dissolution media drug (equivalent to 10 mg of atorvastatin 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 minute. The sink condition is maintained by replacing 5 ml of pH 6.1.8 phosphate buffer solution in dissolution media. Samples were filtered through membrane filter and analyzed spectrophotometrically at wavelength of 246 nm.

Characterization of nanocomposites (NCs)

Characterizations of BNCs were carried out by FT-IR, differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) to ensure the compatibility of drug and polymer.

Fourier –transform infrared spectroscopy (FTIR)

FTIR study of optimized ratio of nanocomposites was carried out. Nanocomposites were mixed with (KBr) potassium bromide of IR grade in a ratio of 1:100 and compressed using a pellet press. (15 tones pressure) [8-10]. The pellets were scanned using an FTIR spectrophotometer (Shimadzu 8400S). The FTIR spectra of optimized nanocomposites were compared with that of the pure drug.

Differential scanning calorimetry (DSC)

A DSC study of optimized nanocomposites ratio was carried out. Sample was heated from ambient temperature from 50 to 200° in nitrogen atmosphere at the heating rate of 10°C/ min[8-10]. The changes made when nanocomposites were formulated and its effect on solubility of drug was studied.

X-ray diffraction studies (XRD)

The XRD study of atorvastatin calcium and optimized nanocomposites were carried out to assess the changes in crystallinity when drug was mixed with polymer[8-10].. The XRD pattern was recorded using with Cu-kα radiation. The scanning angle is ranged from 10° to 80° of 2θ. The XRD Study was carried out to assess the changes in the crystallinity made when the drug was mixed with carriers.

Scanning electron microscopy (SEM)

External surface morphology was examined by Scanning electron microscopy. The detailed particle structural characterizations and morphologies of pure drug and nanocomposites were studied by scanning electron microscope. Samples were developed by mounting powder onto a brass stub using graphite glue, then coated with gold under vacuum before use. Images were recorded at an acceleration voltage of 10 KV at the required magnification using a scanning electron microscope[8-10].

Particle size analysis

The 0.5 gm of nanocomposite sample was diluted by 10ml of double distilled water and the particle size and zeta potential were determined by laser scattering particle size analyzer (Malvern Particle Analyser) [8,9]..

Stability study of optimized nanocomposites

Accelerated stability study was carried out as per ICH guidelines [11-13]. The sample of optimized nanocomposites was placed at 40 ±2°C for 3 month in stability chamber and 75 ±5% RH. Various parameters such as drug content,

appearance and *in-vitro* drug release were measured after 1, 2 and 3 month of stability study.

3. Results and discussion

Solubility of atorvastatin calcium :

Atorvastatin calcium was found to be poorly soluble in water. The solubility of pure drug in water was observed to be 0.028 mg/ml.

Physical characterization of carriers

The percentage swelling, viscosity, and foaming index are shown in Table 2. From this data, it can be concluded that the swelling characteristics and viscosity of gum acacia and chitosan is low while HPMC K4M and avicel 101 shows very high swelling properties. The past results revealed that, because of less swelling and low solution viscosity, they are playing crucial role in dissolution enhancement. They are very less prone to the formation of the tough matrix therefore assist rapid liberation of the nanocrystals from the nanocomposites. From the foaming index it is observed that foaming ability of acacia and Chitosan is higher among the various carriers. Hence, acacia and Chitosan can enhance the solubility more efficiently than the other carriers.

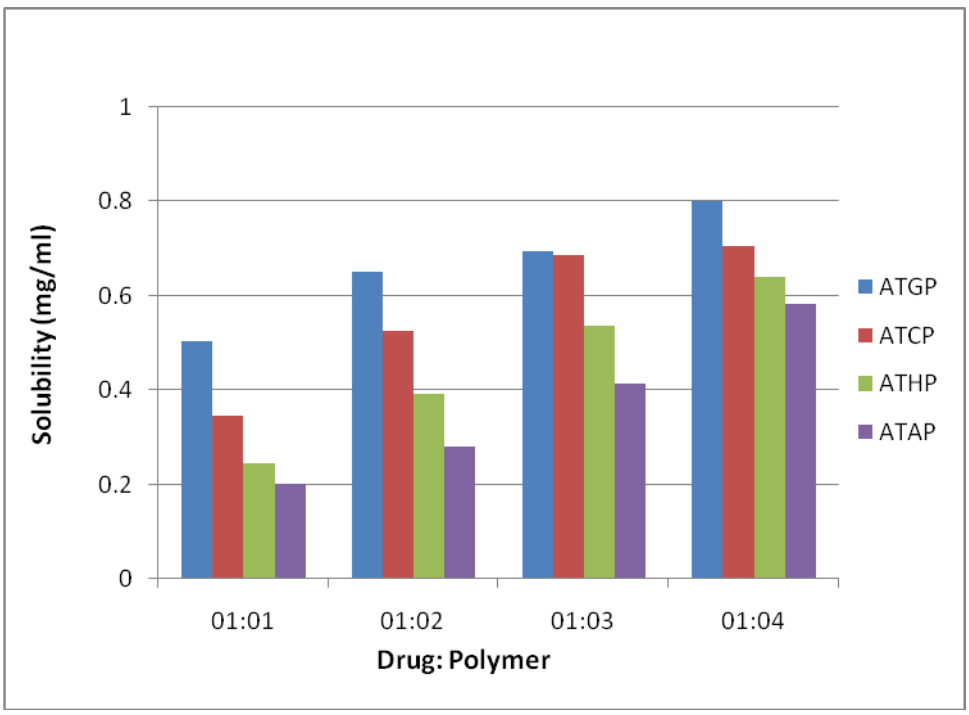
Table 2: Physical characterization of polymer

Polymer	% Swelling*	Viscosity* (cp)	Foaming Index*
Gum Acacia	63.26 ± 1.21	2.93 ± 0.83	11 ± 0.59
Chitosan	71.87 ± 1.09	3.74 ± 0.62	10 ± 0.89
HPMC K4M	90.23 ± 1.40	7.87 ± 0.89	8 ± 0.65
Avicel 101	92.05 ± 1.27	6.45 ± 1.05	6 ± 0.92

Each value represents the mean±SD (n = 3)

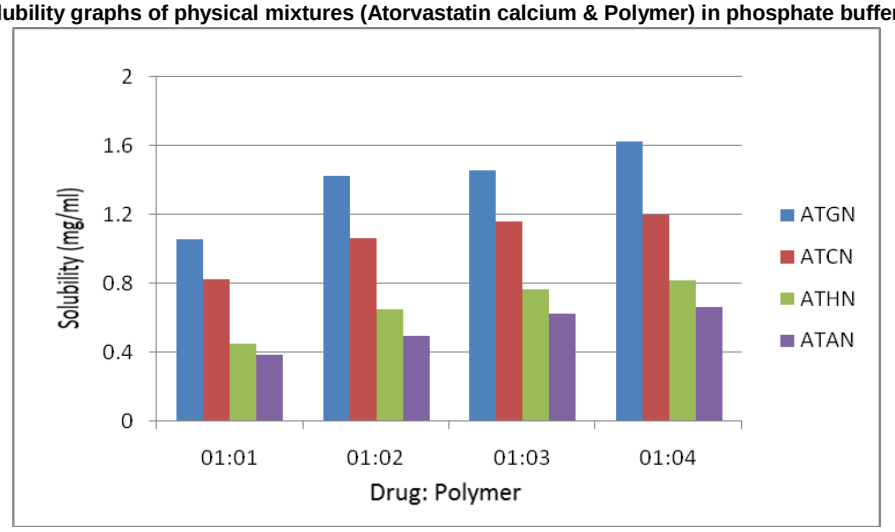
Solubility study

Solubility studies were performed to analyze the solubility enhancing properties. Solubility studies provided the basis for selection of optimised ratio that is selected for formulation. The solubility of atorvastatin calcium 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 study of physical mixture and developed nanocomposites were shown in following Figure 1 & Figure 2 respectively. Solubility studies clearly indicate that physical mixtures improve the solubility of atorvastatin calcium significantly compared with pure drug. This effect can be attributed to the surfactant and wetting property of chitosan & gum acacia. Solubility studies of physical mixtures clearly indicated that the ratio of drug to polymer increases solubility. When compared to previous study it is observed that nanocomposites developed with gum acacia are showing best results in terms of solubility than nanocomposites developed with chitosan and other polymers. The ATGN4 showing best solubility result at 1:4 ratio, therefore it was considered optimal. The solubility of ATGN4 was found to be 1.627 mg/ml (i.e.15 fold increase in solubility). In case of developed nanocomposites solubility data indicates a good rise in solubility compared with pure drug; this effect may be due to reduction of crystal size of the atorvastatin calcium into a nanocrystalline form. It was also observed that the more increase in solubility was shown by nanocomposites prepared by using gum acacia in all formulations.



Each value represents the mean±SD (n = 3)

Figure 1: Solubility graphs of physical mixtures (Atorvastatin calcium & Polymer) in phosphate buffer pH 6.8



Each value represents the mean±SD (n = 3)

Figure 2: Solubility graphs of Nanocomposites (Atorvastatin calcium & Polymer) in phosphate buffer pH 6.8

Drug content analysis of nanocomposites

The uniform dispersion of drug in the nanocomposites can be determined by drug content analysis. It was observed that around 58 to 91 % drug can be incorporated in the nanocomposites. ATGN4 (1:4) showing uniform dispersion of drug in the nanocomposites. Drug content analysis are shown in Table 3.

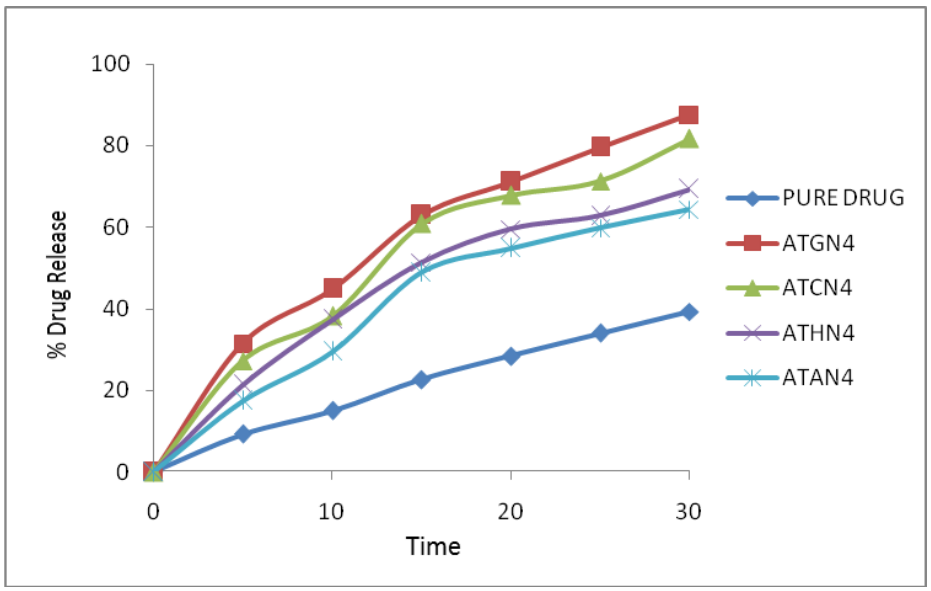
Table 3: Drug content analysis of nanocomposites

Nanocomposites Code	ATGN4	ATCN4	ATHN4	ATAN4
Drug content	91.12 ± 0.54%	85.83 ± 0.50 %	69.42 ± 0.66%	58.37 ± 0.66%

Each value represents the mean±SD (n = 3)

***In vitro* drug release:**

A powder dissolution test (*In vitro* drug release) was performed as solubility studies are not always a predictable means to study the solubility enhancing properties of any material. The dissolution studies of drug and developed nanocomposites give more specific information about the solubility and dissolution of drug. The dissolution profile of pure drug and nanocomposites is shown in Figure 3. From the dissolution study of the nanocomposites there was evidently a remarkable improvement of the dissolution rates in all NCs compared with the pure drug. Among all of the nanocomposites the best result was shown by ATGN4 which show 87.59% drug released in comparison to pure Atorvastatin which shows only 39.32% drug release. When compared to previous study it is observed that nanocomposites developed with gum acacia are showing best results in *In vitro* drug release than nanocomposites developed with chitosan and other polymers.



Each value represents the mean±SD (n = 3)

Figure 3: Dissolution profile of pure drug and optimised nanocomposites

Characterization of optimized nanocomposite

Fourier transform infrared spectroscopy (FTIR)

From the various batches developed, nanocomposites prepared by using Gum acacia were found to be best in terms of various evaluation parameters. The formulation containing more amount of polymer i.e. 1:4 ratio is the best optimized ratio i.e. ATGN4 (1:4). The optimized ratio ATGN4 further characterized by different parameters**.**

In FTIR spectra of nanocomposites, if any physicochemical interaction was taking place like formation of hydrogen bond between carrier & drug, then it will be automatically reflected in the spectrum such as frequency shifts or splitting in peaks of absorption. In FTIR spectra of atorvastatin no such peak were observed. The FTIR spectra clearly indicate only secondary interaction between carrier (gum acacia) & drug within nanocomposites. Generally as reported in literature these interactions occur at hydroxyl groups only. The spectrum of optimised nanocomposites was found to be similar to pure atorvastatin calcium. Further no shift of absorbance of carbonyl (C=O) was observed. The major difference observed in the spectrum of nanocomposites (Figure 5) is the reduction in intensity of the characteristic peak of hydroxyl group (3623 cm-1) indicating reduction in crystal size. From this it can be concluded that major peak values of the Atorvastatin calcium remain unchanged in the microwave-treated nanocomposites. Thus, it can be concluded that, no major chemical interaction is taking place between the drug and carrier.

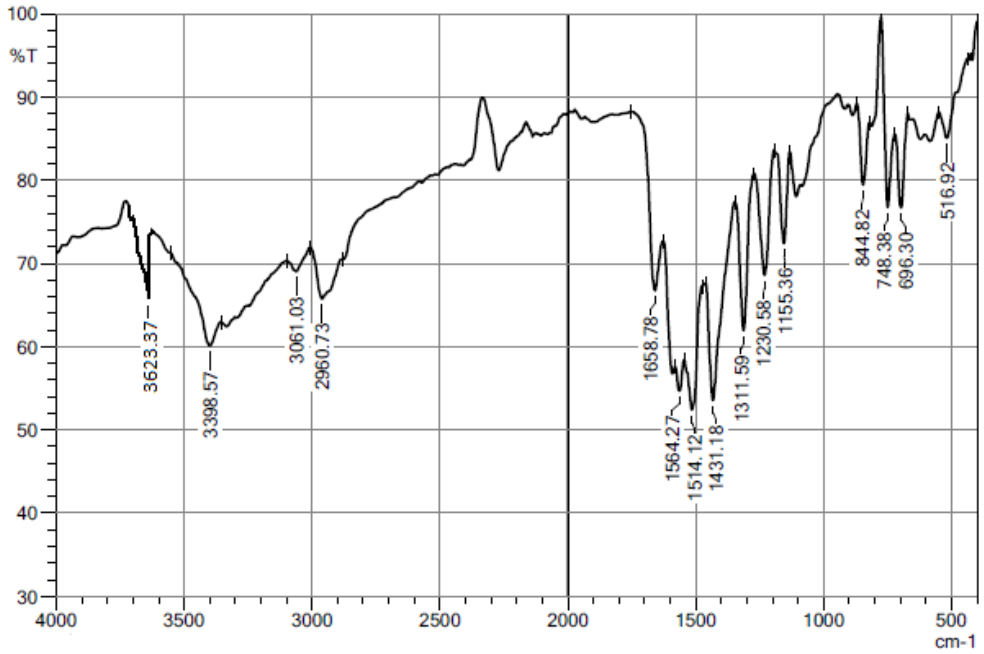


Figure 4:FTIR Spectra of Atorvastatin calcium

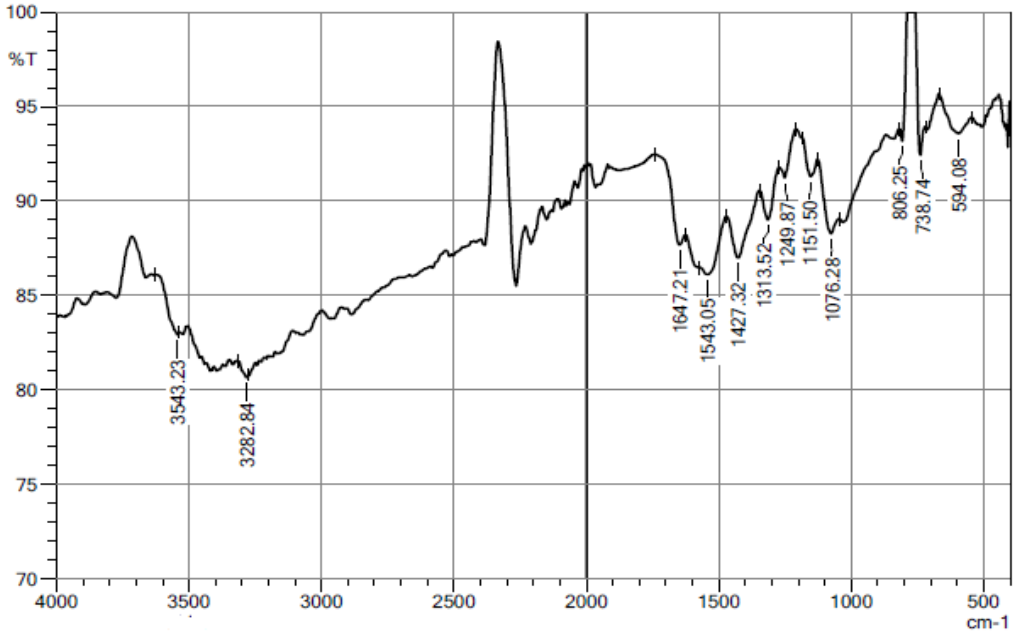


Figure 5: FTIR spectra of optimized Atorvastatin calcium nanocomposites

Differential Scanning Calorimetry (DSC)

DSC was performed to check interaction between drug and polymer. The DSC thermogram of pure drug shows a endothermic peak(sharp peak) which corresponds to the melting point of crystalline drug at 159.45°C (Figure 6). The DSC spectra of optimized nanocomposites ATGN4 (1:4) shows slight variation in endothermic peak as that of pure drug while the intensity of peak is slightly reduced (Figure 7). This effect may be due to the decrease in the crystalline size of the drug. The DSC thermogram of ATGN4 at 144.15^{0}C shown a broad endothermic peak. The peak broadening in the spectra indicated that most of the drug is embedded in nanocomposites in the nanocrystalline form. The little shift in melting point was noted due to reduction of drug to the nanocrystalline form. It is also reported that as the crystal size of crystalline nanoparticle reduces its melting point also gets reduced. Similar kinds of results were obtained in the DSC study of optimisied nanocomposites. This phenomenon is attributed for the solubility enhancement of drug as the crystallinity has been reduced to the nanocrystalline form therefore solubility get enhanced.

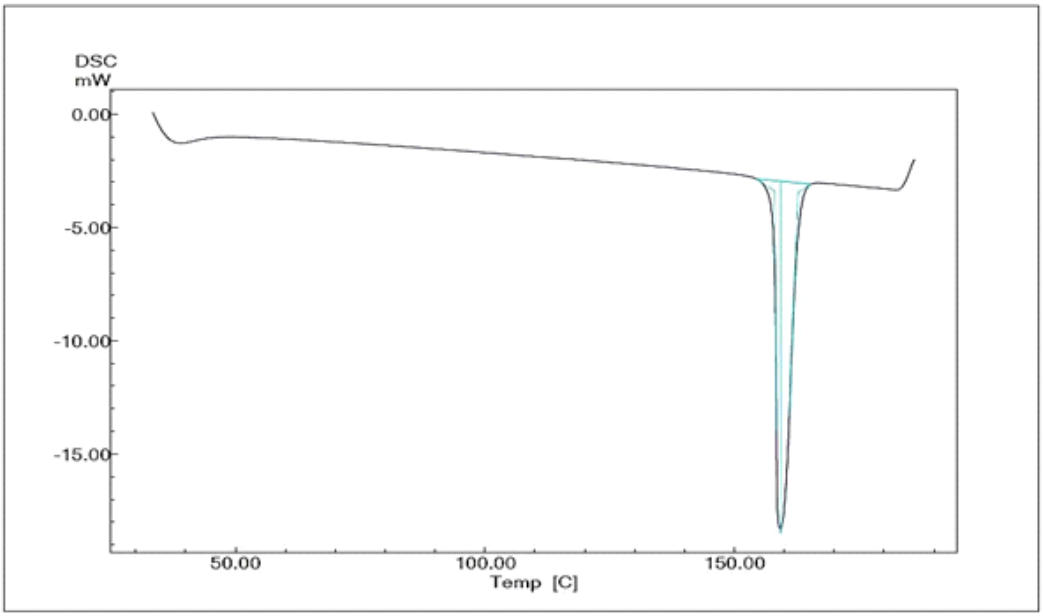


Figure 6 :DSCthermogram of Atorvastatin calcium

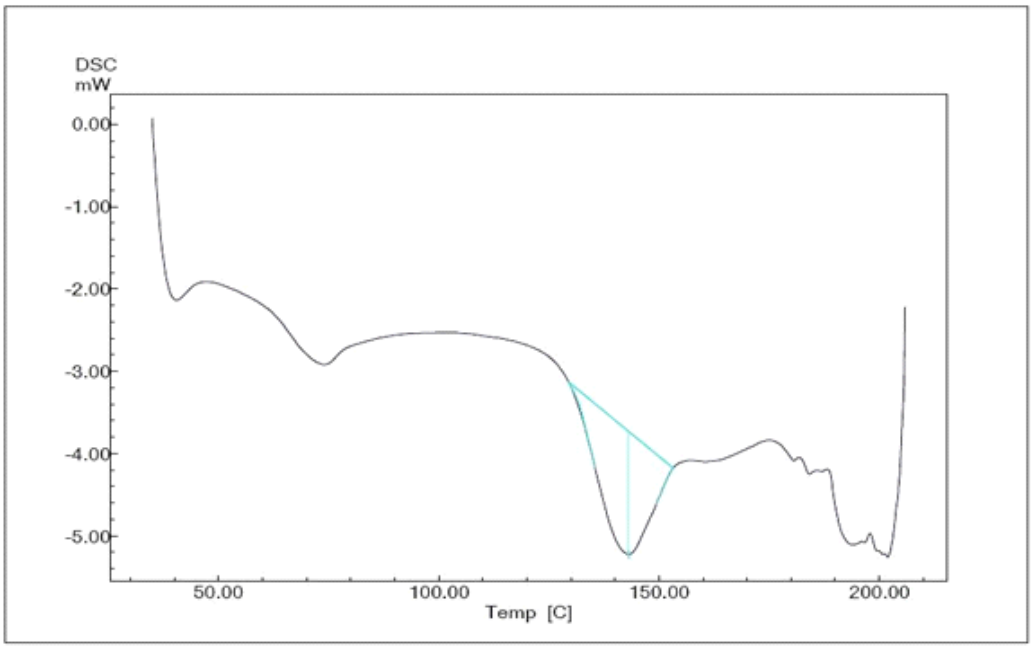


Figure 7:DSC thermo gram of optimized nanocomposites

X-Ray diffraction studies (XRD)

The X-ray diffraction studies of atorvastatin calcium and optimized nanocomposites ATGN4 are shown in figurer respectively. The pure drug exhibit intense crystalline peak between 10° and 50° and the characteristic diffraction peaks were observed at 16.12°,17.31°, 18.24°, 19.53°, 23.76°,

25.48°, 26.39°, 31.72° and 34.56 °.Also intense peak observed with at 16.34° indicating the crystalline nature of Atorvastatin calcium. While in the other spectra of optimised NC's ATGN4 it is observed that the peak intensity is reduced indicating reduction in crystallinity. This phenomenon is responsible for enhancement in solubility of drug.

The XRD pattern of pure drug and nanocomposites were showed in Figure 8 and Figure 9espectively.

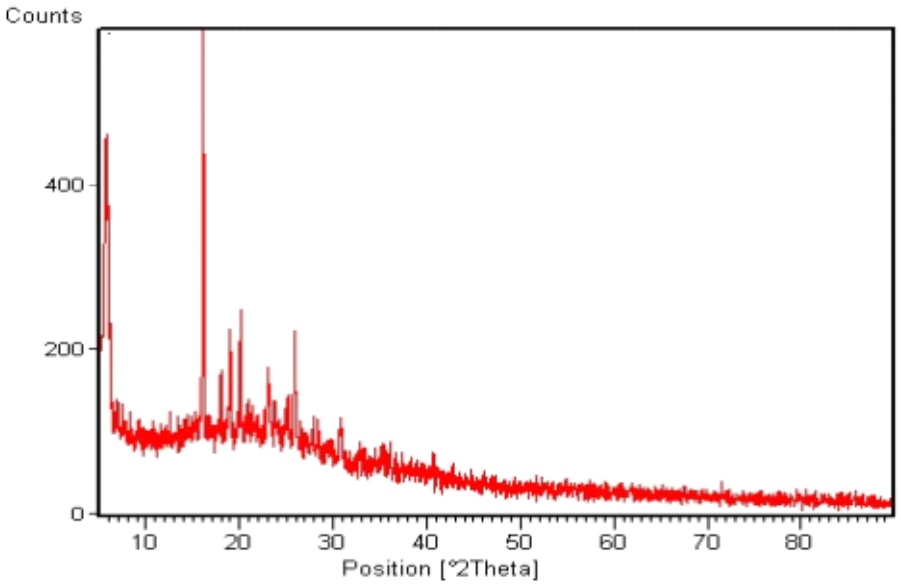


Figure 8:XRD Pattern of (plain drug)Atorvastatin calcium

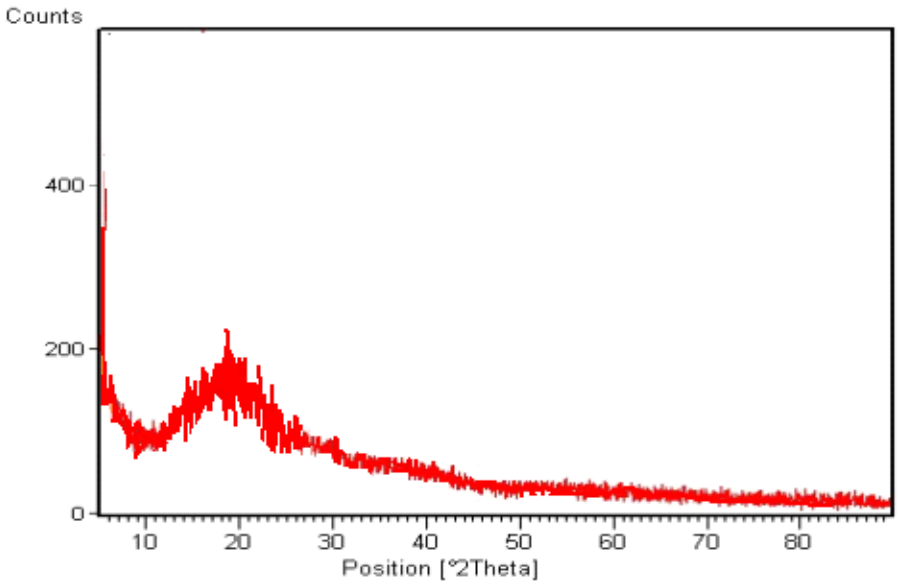
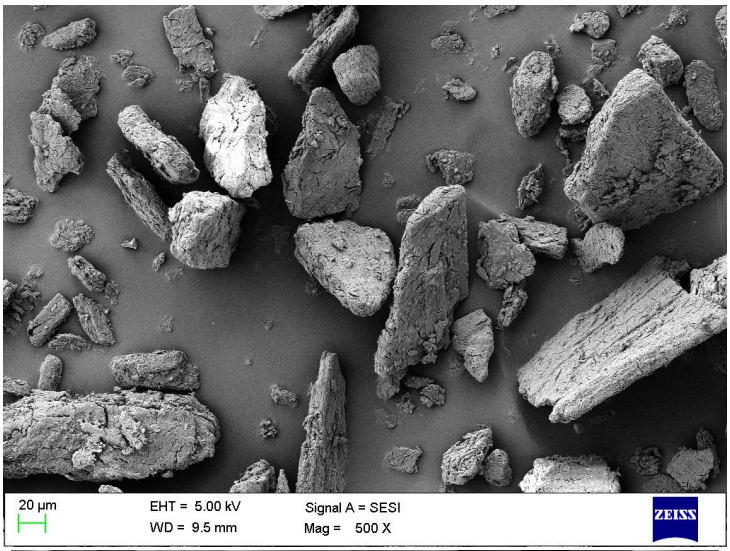
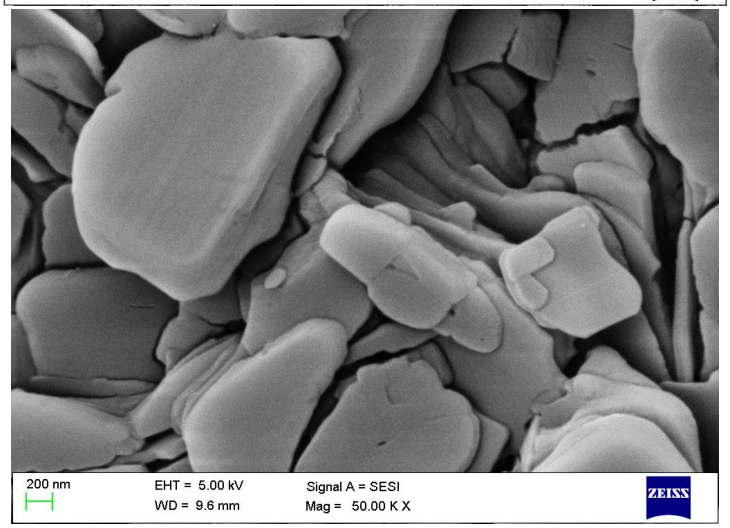


Figure 9:XRD Pattern of developed Atorvastatin calcium Nanocomposites

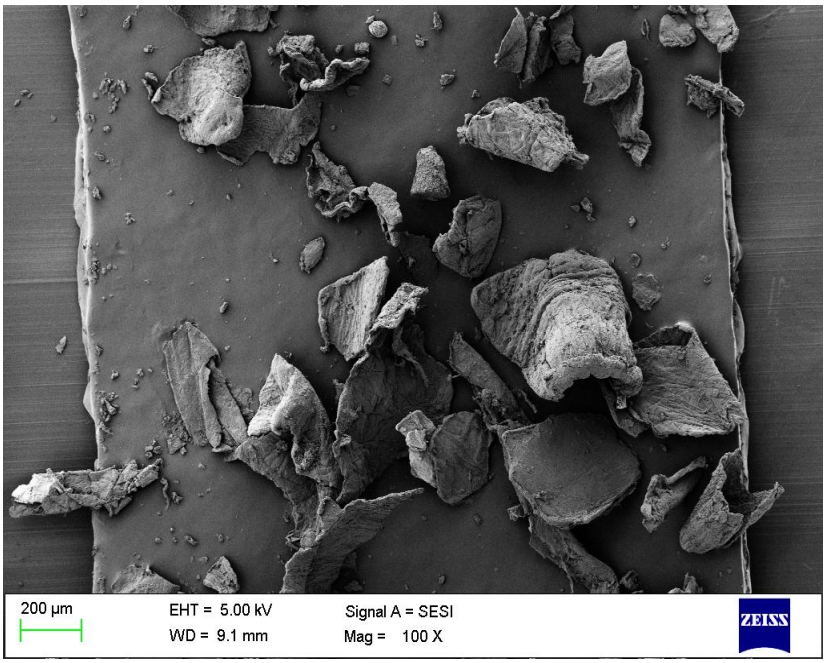
Scanning electron microscopy (SEM)

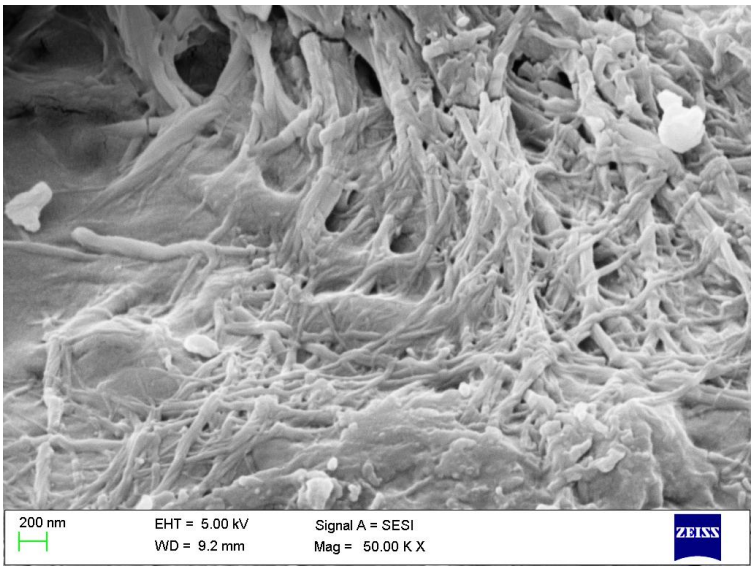
By scanning electron microscopy, the surface morphology of drug particles can be studied. The storvastatin calcium and optimized ATGN4 were characterized by SEM. From the Figure 10, it is concluded that that pure atorvastatin calcium drug showed plate shaped crystals having smooth surface while in case of ATGN4 it was observed that they were of irregular shape and size. It is observed that microwave irradiation created a finer dispersion of drug in the polymeric matrix. It is clearly concluded that plated crystal shape of atorvastatin calcium completely changed in nanocomposites i.e. embedded drug crystals in the matrix of polymer (acacia). The similar results were reported in previous studies, which is responsible for solubility enhancement.





(A)





(B)

Figure 10:SEM images of(A) Atorvastatin calcium (B) Optimised Atorvastatin calcium Nanocomposites.

Particle size analysis

The optimised batch was subjected to Particle size analysis using laser scattering particle size analyser. The average particle size was found to be 187.4 nm. Graph was observed (Figure 11), in which the particle size ranges from 100 to 300 nm. The nanocomposites produced in this study are well within the nano-size range, the particle size the atorvastatin calcium loaded NCs was higher than the particle size of drug-free NCs. As given in the literature the result suggest that the drug incorporation has a significant influence on the particle size is indicative of drug incorporation in the NCs matrix. The results indicates that the SP srea ratio of NCs produced in this study less than 1.5 indicative of narrow distribution of particles in the dispersion.

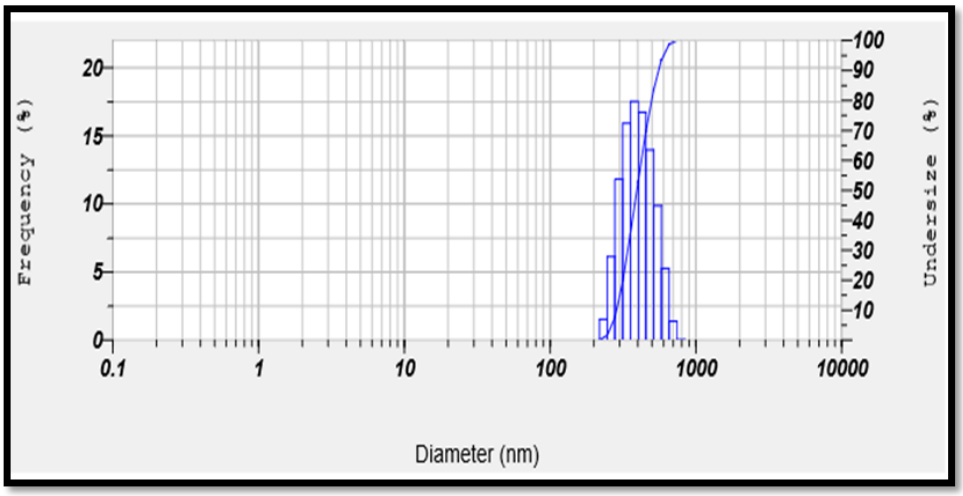


Figure 11: Particle size graph of optimised Nanocomposites of Atorvastatin calcium

Stability Study

Stability study of optimized ratio of powder nanocomposites of atorvastatin calcium (ATGN4) was done to see the effect of temperature and humidity on powder nanocomposites during the storage time. Nanocomposites were evaluated periodically 0 and 1, 2, 3 months for appearance, drug content and *in-vitro* drug release. Stability study results shown that there was no significant change in appearance, drug content and *in-vitro* drug release of the formulation shown in Table 3.

Table 3: Results of Stability study.

Duration (Months)	Appearance	Drug content(%)	*In vitro* 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

Each value represents the mean±SD (n = 3)

4. Conclusion

The present study revealed use of microwave induced diffusion technique for the solubility enhancement of BCS Class II drugs. From the developed nanocomposites of Atorvastatin, the optimum drug-to-carrier ratio was found to be 1:4 (atorvastatin drug with acacia as a carrier) which enhanced solubility nearly 15 fold (ATGN4) as compared to pure drug. The key feature of this study includes the uniform distribution of drug in carrier in a nanocrystalline form in optimized nanocomposites, which is sufficiently stable and easy to prepare. It can be concluded that, microwave-generated NCs can be successfully used for the enhancement of solubility and dissolution of poorly soluble drug.

***Conflict of interest statement*:**

All authors have none to declare.

Author Contribution:

All authors contributed equally.

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