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Development of microwave generated Nanocomposites for solubility enhancement of BCS class II drug

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Abstract
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. The Nanocomposites (NCs) 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 nanocomposites were formulated using microwave induced diffusion technique (MIND) for solubility enhancement of poorly water soluble (BCS class II) model drug Miconazole Nitrate. Its oral bioavailability is very low due to low aqueous solubility. The nanocomposites of Miconazole Nitrate 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. In case of developed nanocomposites, the optimum drug-to-carrier ratio was found to be 1:4 with Chitosan as a carrier which enhanced solubility nearly 16 fold as compared to pure drug. From the dissolution study of the nanocomposites there was evidently a remarkable improvement of the dissolution rates in NCs compared with the pure Miconazole nitrate (*In vitro* drug release of 88.43% as compared to 44.31%. of pure drug). The optimized nanocomposites were characterized by Fourier transform infrared spectroscopy, Differential scanning calorimetry, X-ray diffraction and Scanning electron microscopy. From Solubility, *In vitro* drug release and Physical characterization of carriers it is clear that the nanocomposites MCN4 formulation was found to be optimum in terms of solubility enhancement of a drug by microwave assisted synthesis. The MIND technique employed in this study is green, cost-effective and a promising approach for solubility enhancement.

Keywords: nanocomposites, solubility, BCS class II, microwave induced diffusion technique

Introduction
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. 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 [1]. According to US pharmacopoeia more than 40% of the drugs are poorly soluble or insoluble in aqueous environments. 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 [1]. 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 [2]. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration [3]. A nanocomposites 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 (MW) irradiation 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 Miconazole Nitrate. Miconazole nitrate is an imidazole antifungal drug used for the treatment of orophyrangeal candidiasis, Tineapedis, and vulvovaginal

candidiasis caused by mainly Candida albicans. It is applied to skin or vagina as a cream or ointment. It has very good skin permeability. However, it's oral bioavailability is very low (4-5%) due to low aqueous solubility. Poor performance of drugs leads to administration in higher doses possibly leading to Allergic, contact dermatitis, Burning, Maceration, itching, Irritation. In the present a nanocomposites of Miconazole Nitrate were developed using natural and synthetic carriers such acacia, Chitosan, HPMC K4M and Avicel 101.

Materials and Methods

Materials

Miconazole Nitrate was obtained as a gift sample from GlaxoSmithKline Pharmaceuticals Ltd, Nashik, 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 [8, 9]

The solubility of Miconazole nitrate in water and pH 6.8 buffer solution was determined by reported method. 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).

Physical Characterization of Polymer [8, 9]

a. Swelling Index (SI)

The modified method was used for determination of Swelling index of gums. The 1mg of Gum acacia, Chitosan gum, HPMC K4M and Avicel 101 was accurately measured and transferred to 100ml 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. 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 weremeasured by Brookfield viscometer using spindle 00 at 200 rpm.

Preparation of Physical Mixture [8-10]

Physical mixture of drug (Miconazole nitrate) 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. Different physical mixtures of Miconazole nitrate and various polymers were developed. The physical mixture of drug with Gum acacia having ratio 1:1, 1:2, 1:3 and 1:4 were formulated & denoted by MGP1, MGP2, MGP3, MGP4 respectively. The physical mixture of drug with Chitosan having ratio 1:1, 1:2, 1:3 and 1:4 were formulated & denotedbyMCP1, MCP2, MCP3, MCP4 respectively. Similarly physical mixture of drug with HPMC K4M and Avicel 101 having ratio 1:1, 1:2, 1:3 and 1:4 were formulated & denoted by MHP1, MHP2, MHP3, MHP4 and MAP1, MAP2, MAP3, MAP4 respectively.

Preparation of Nanocomposites [8-10]

The nanocomposites were developed by homogenous mixing of accurately weighed amount of Miconazole nitrate with individual polymer. In preparation the 1:1 to 1:4ratio 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 560 W with continuous stirring for 5 min (CATA-2R, Catalyst System). The developed Nanocomposites were grounded in mortar & pestle and sieve to achieve the particle size of 80 to 250 µm. The quantity of Miconazole nitrate and polymer for different ratios were taken as shown in Table 1.

Table 1: Preparation of Nanocomposites

Ratio (For Nanocomposites)	Drug: Polymer 1:1	Drug: Polymer 1:2	Drug: Polymer 1:3	Drug: Polymer 1:4
Formulation code	MGN1	MGN2	MGN3	MGN4
Miconazole Nitrate (mg)	500	500	500	500
Gum Acacia (mg)	500	1000	1500	2000
Formulation code	MCN1	MCN2	MCN3	MCN4
Miconazole Nitrate (mg)	500	500	500	500
Chitosan (mg)	500	1000	1500	2000
Formulation code	MHN1	MHN2	MHN3	AHN4
Miconazole Nitrate (mg)	500	500	500	500

HPMC (mg)	500	1000	1500	2000
Formulation Code	MAN1	MAN2	MAN3	MAN4
Miconazole Nitrate (mg)	500	500	500	500
Avicel 101 (mg)	500	1000	1500	2000

Evaluation of Nanocomposites [8-10]

Solubility Study

The solubility study of Physical mixtures and Nanocomposites (NCs) was determined in pH 6.8 phosphate buffer by reported method. 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. The developed nanocomposites were dissolved in 25ml of methanol. The resulting solution was filtered through membrane filter (0.45µ) and analyzed at wavelength 272 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 Miconazole nitrate nanocomposites (by using 900ml pH 6.8 phosphate buffers as a dissolution media) by reported method.

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). 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. 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 Miconazole nitrate and optimized nanocomposites were carried out to assess the changes in crystallinity when drug was mixed with polymer. 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.

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).

Stability study of optimized nanocomposites [11]

Accelerated stability study was carried out as per ICH guidelines. 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.

Results and Discussion

Solubility of Miconazole nitrate

Miconazole nitrate was found to be poorly soluble in water. The solubility of pure drug was was observed to be 0.0081mg/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

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 Miconazole nitrate was found to be 0.0081mg/ml in water and 1.14 mg/ml in phosphate buffer (pH 6.8). The results of solubility study of physical mixture and developed nanocomposites are shown in following Figure 1 & Figure 2 respectively. Solubility studies clearly indicate that physical mixtures improve the solubility of Miconazole nitrate 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 Chitosan are showing best results in terms of solubility than nanocomposites developed with Gum acacia and other polymers. The MCN4 showing best solubility result at 1:4 ratio, therefore it was considered optimal. The solubility of MCN4 was found to be 18.59 mg/ml. 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 Miconazole nitrate into a nanocrystalline form. It was also observed that the more increase in solubility was shown by nanocomposites prepared by using Chitosan.

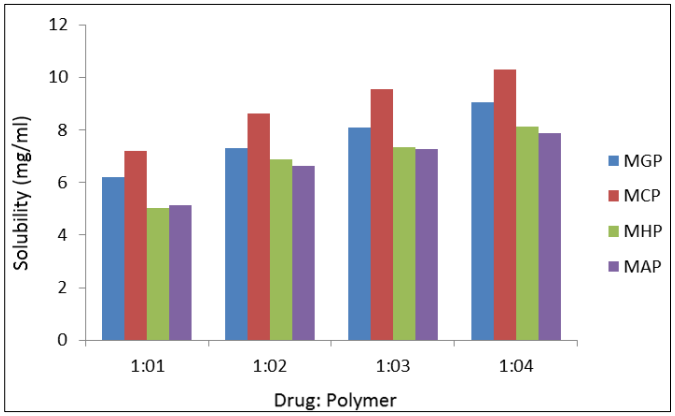

Fig 1: Solubility graphs of physical mixtures inphosphate buffer pH 6.8

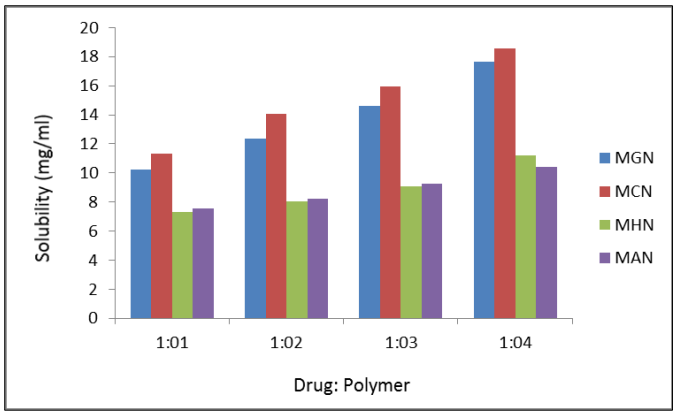

Fig 2: Solubility graphs of Nanocomposites in phosphate buffer pH 6.8

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 62 to 87 % drug can be incorporated in the nanocomposites. The MCN4 (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	MGN4	MCN4	MHN4	MAN4
Drug content	86.61 ± 0.54%	88.10 ± 0.50 %	71.45 ± 0.66%	62.22± 0.66%

***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 Miconazole itrate. Among all of the nanocomposites the best result was shown by MCN4which show 88.43% drug released in comparison to pure Miconazole nitrate which released 44.31%. When compared to previous study it is observed that nanocomposites developed with Chitosan are showing best results in *In vitro* Drug release than nanocomposites developed with Gum acacia.

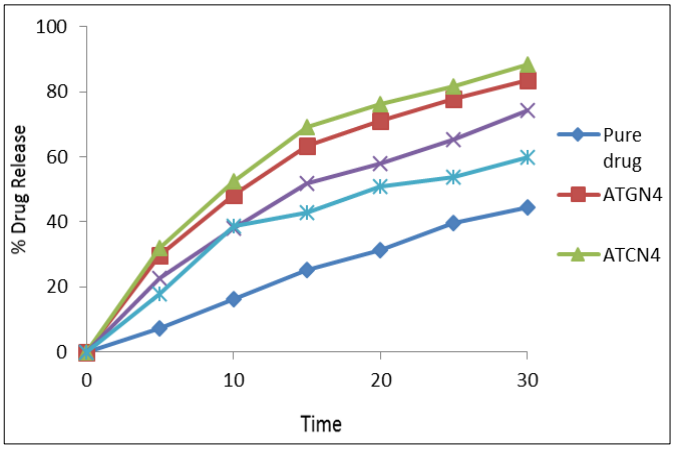

Fig 3: Dissolution profile of pure drug and optimised nanocomposites

Characterization of optimized nanocomposites

Fourier transform infrared spectroscopy (FTIR)

From the various batches developed, nanocomposites prepared by using Chitosan 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. MCN4 (1:4). The optimized ratio MCN4 further characterized by following 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 Miconazole nitrate no such peak were observed (Figure 4). The FTIR spectra clearly indicate only secondary interaction between carrier (Chitosan) & drug within nanocomposites. The spectrum of optimised nanocomposites was found to be similar to pure Miconazole nitrate. Further no shift of absorbance of carbonyl (C=O) (1581cm-1) was observed. The major difference observed in the spectrum of nanocomposites (Figure 5) is the reduction in intensity of the Aromatic &Aliphatic C-H stretching group (2889cm-1, 3102 cm-1 respectively) indicating reduction in crystal size. From this it can be concluded that major peak values of the Miconazole nitrate remain unchanged in the microwave-treated nanocomposites. Thus, it can be concluded that, no chemical interaction is taking place between the drug and carrier.

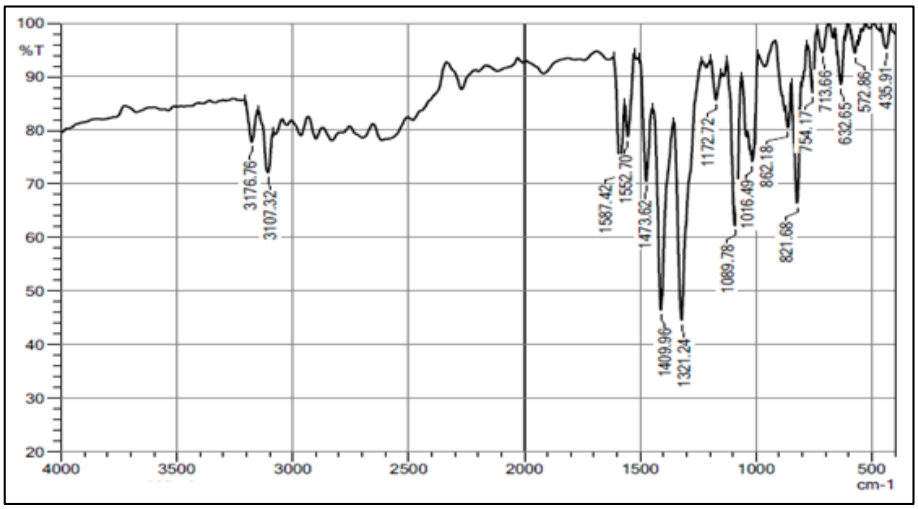

Fig 4: FTIR Spectra of Miconazole nitrate

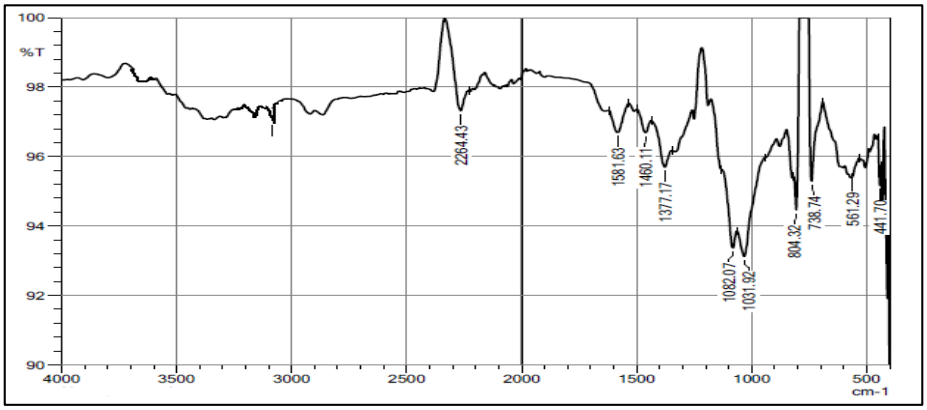

Fig 5: FTIR spectra of optimized Miconazole nitrate nanocomposites

Differential scanning calorimetry (DSC)

DSC was performed to check any 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 174.25 °C (Figure 6). The DSC spectra of optimized nanocomposites MGN4 (1:4) shows slight variation in endothermic peak as that of pure drug while the intensity of peak is slightly reduced. This effect may be due to the decrease in the crystalline size of the drug. The DSC thermogram of MCN4 at 160.12ºC showed 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. DSC thermogramof nanocomposites are shown in Figure 7.

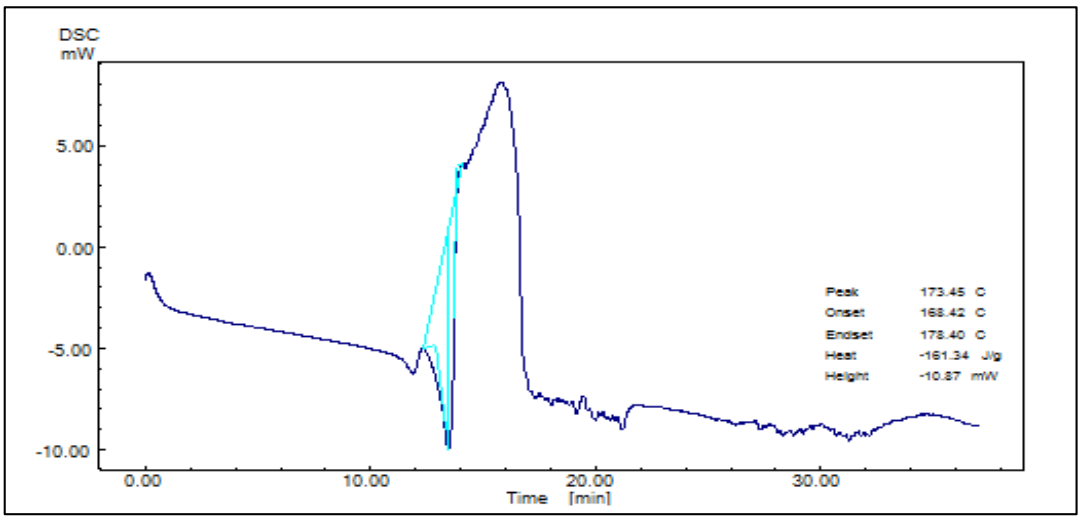

Fig 6: DSC thermogram of Miconazole nitrate

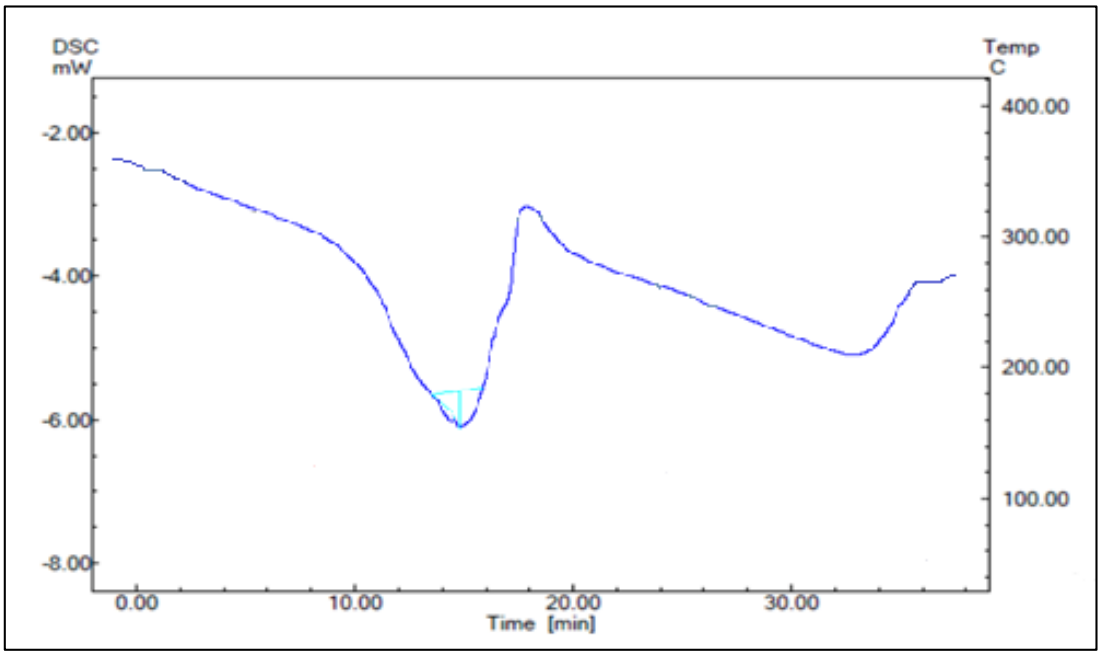

Fig 7: DSC thermo gram of optimized nanocomposites

X-Ray diffraction studies (XRD)

The X-ray diffraction studies of Miconazole nitrate and optimized nanocomposites MCN4 are shown in figurer respectively. The pure drug exhibit intense crystalline peak between 10° and 60° and the characteristic diffraction peaks were observed at 11.71°, 16.23°, 19.65°, 23.54°, 25.12°, 28.83º, 30.47ºand 38.25 °. Also intense peak observed with at 21.57° indicating the crystalline nature of ATR. While in the other spectra of optimised NC's ATGN4 it's 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 9 espectively.

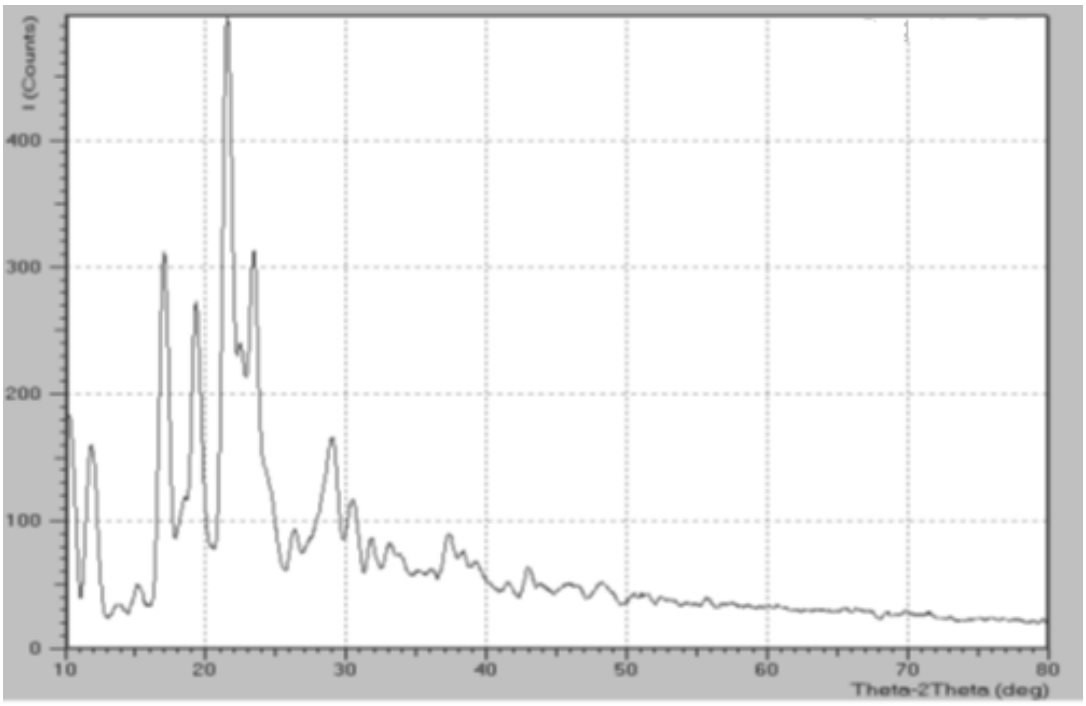

Fig 8: XRD Pattern of (plain drug) Miconazole nitrate

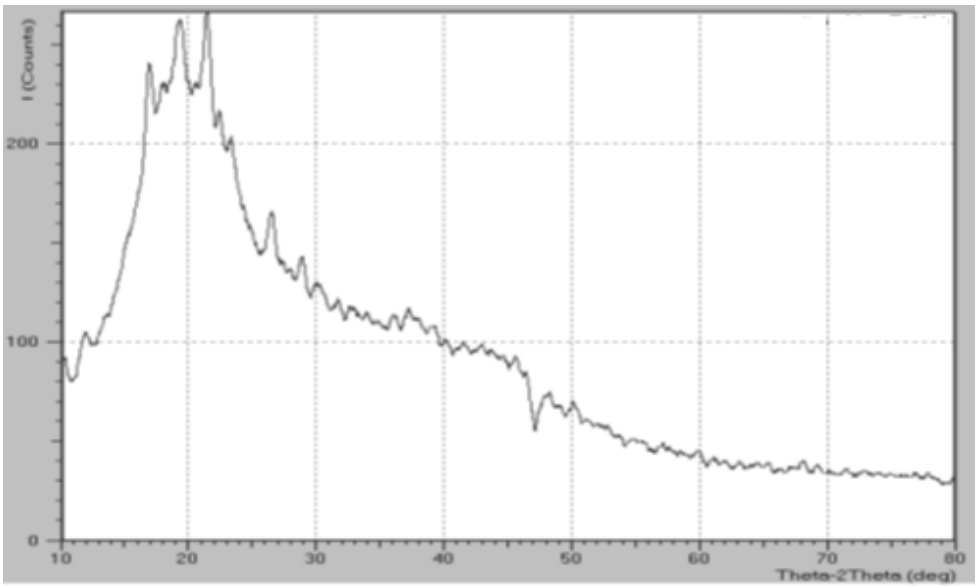

Fig 9: XRD Pattern of Miconazole nitrate Nanocomposites

Scanning electron microscopy (SEM)

By Scanning electron microscopy SEM the surface morphology of drug particles can be studied. The Miconazole nitrate and optimized MGN4were characterized by SEM. From the Figure 10, is concluded that pure Miconazole nitrate drug showed acicular crystals with smooth surface while in case of nanocomposites it was observed that they were irregular shape and size. It is observed that microwave irradiation created a finer dispersion of drug in the polymeric matrix. The shaped of Miconazole nitrate completely changed in nanocomposites i.e. embedded drug crystals in the Miconazole nitrate of polymer (chitosan). The similar results were reported in previous studies, which is responsible for solubility enhancement.

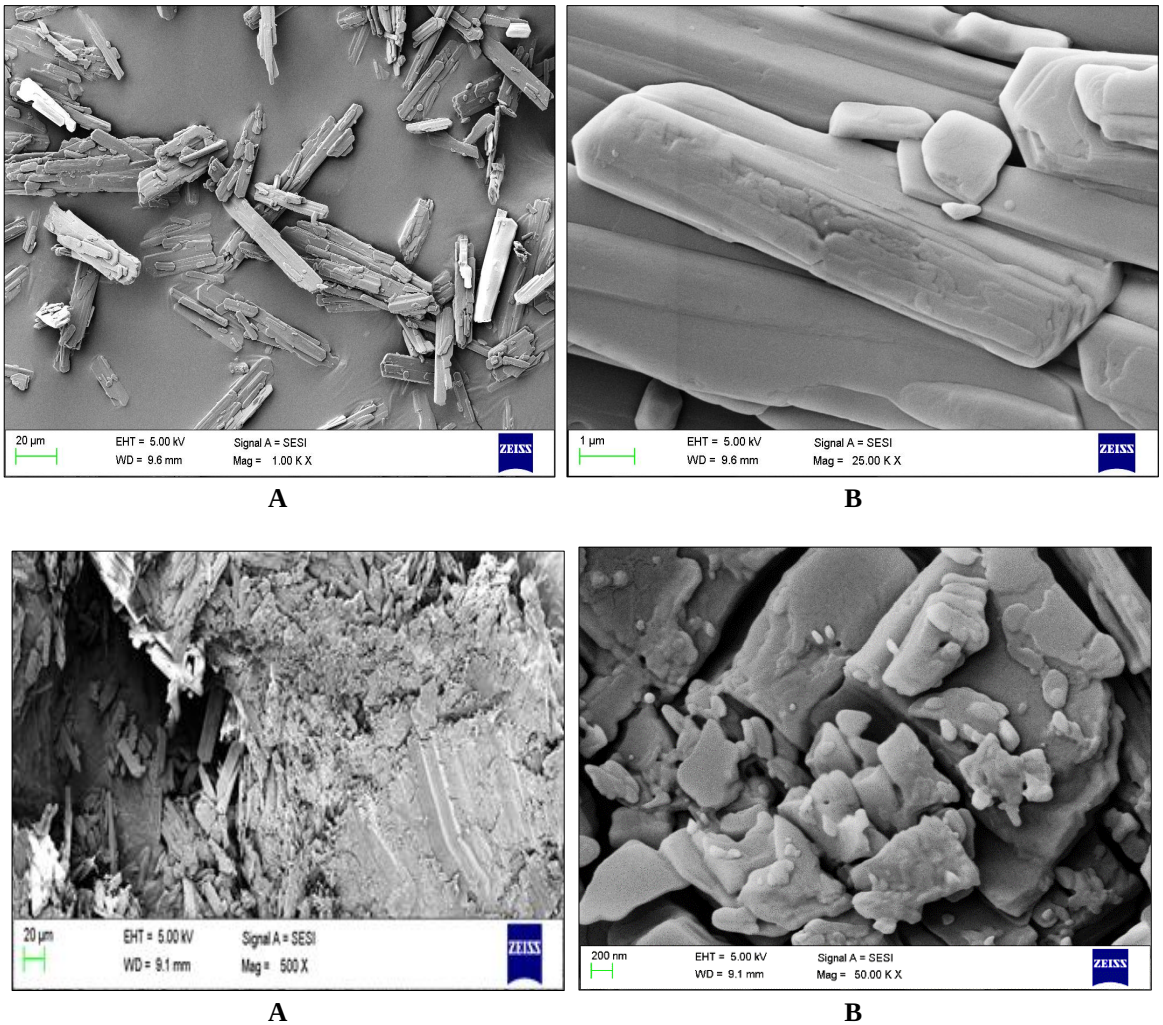

Fig 10: SEM images of (A) Miconazole nitrate (B) Optimised Miconazole nitrate Nanocomposites

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 183.6 nm. Graph was observed, in which the particle size ranges from 100 to 250 nm (Figure 11). The nanocomposites produced in this study are well within the nano-size range, the particle size the Miconazole 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 Area Ratio of NCs produced in this study less than 1.5 indicative of narrow distribution of particles in the dispersion

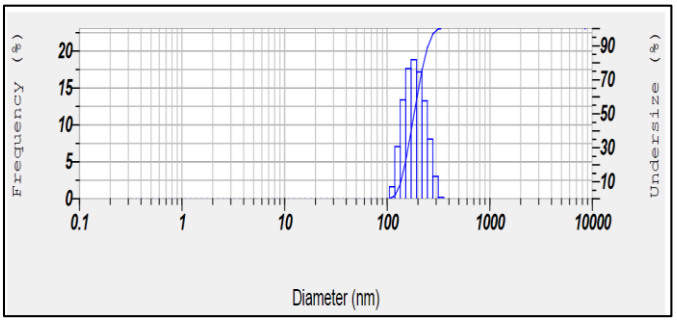

Fig 11: Particle size graph of optimised Nanocomposites of Miconazole nitrate

Stability Study

Stability study of optimized ratio of powder nanocomposites of Miconazole (MCN4) 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 4.

Table 4: Results of stability study

Duration (Months)	Appearance	Drug content (%)	*In vitro* release (%)
0	Yellowish brown fine powder	88.10 ± 0.50	88.43±1.28
1	No change	87.69 ± 0.62	87.90± 1.39
2	No change	87.43 ± 0.71	87.67± 1.65
3	No change	87.38 ± 0.88	87.32± 1.29

Conclusion

The present study revealed the employability of natural carriers such as Chitosan in the microwave-generated NCs for the enhancement of solubility and therefore dissolution of drug substance. From the various batches developed, nanocomposites prepared by using Chitosan (MCN4) were found to be best in terms of various evaluation parameters. The solubility of drug was increased 16 fold along with significant improvement in dissolution performance of formulation. The key feature of this study includes the uniform distribution of drug in carrier in a nano crystalline 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, dissolution and thus bioavailability of poorly soluble BCS class II drugs.

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