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Research Article

### FORMULATION AND EVALUATION OF MICONAZOLE NITRATE LOADED NANOSPONGES FOR VAGINAL DRUG DELIVERY

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#### Abstract:

*The aim of this work is to enhance the solubility of Miconazole nitrate and to control the drug release for a prolonged period.  $\beta$ -Cyclodextrin based nanosponges were prepared by cross-linking  $\beta$ -Cyclodextrin with carbonate bonds of di phenyl carbonate in different proportions, which are porous as well as nanosized. Drug was incorporated by solvent evaporation method by dissolving the drug in various solvents like ethanol, acetone and chloroform. The formulated nanosponges were incorporated into carbopol gel. From the encapsulation efficiency of the drug loaded nanosponges formulations, it was inferred that as the crosslinking ratio increased the encapsulation efficiency was found to be enhanced. It is also found that the encapsulation efficiency of drug loaded nanosponges are influenced by the solvent used for drug loading by solvent evaporation technique. Based on the drug encapsulation efficiency, drug content and extent of sustained nature, the gel prepared with polymer and crosslinking agent in 1:1 ratio, chloroform as a solvent and carbopol as a gelling agent (F12 formulation) was concluded to be the best formulation. All the formulations followed zero order release kinetics and mechanism of drug release was governed by Peppas model. The diffusion exponential coefficient(n) values were found to be in between 0.9402 to 1.1864 indicating non fickian diffusion mechanism. The optimized formulation has good spreadability, extrudability and mucoadhesive nature. The  $P^H$  and viscosity of the formulation were appropriate for the vaginal drug delivery and nanosponges technique was a better choice for sustained release with very fewer chances for the burst effect.*

**Key Words:** Miconazole,  $\beta$ -cyclodextrin, nanosponges, diffusion rate

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**INTRODUCTION:**

Nanosponges are the advancement in nano technology, which are the conspicuous answers for the various formulation challenges like low aqueous solubility, controlled release and targeted release. As compared to nano particles these are less prone to bursting and release the drug in a controlled and predictable manner throughout the intended period of application or administration [1]. Nanosponges are a novel class of nanoparticles with nanostructured hyper branched polymers and few nanometres wide cavities, in which a large variety of substances can be encapsulated. Nanosponges could be a perfect solution for resolving the scalability issues of various nano approaches in the pharmaceutical industry, paving the way for a nano revolution.

Miconazole Nitrate is a broad-spectrum antifungal agent that has been widely used for the treatment of vaginal candidiasis. It acts by means of a combination of two mechanisms: ergosterol biosynthesis inhibition, which causes lysis of fungal cell membranes because of the changes in both membrane integrity and fluidity, and direct membrane damage of the fungal cells. The limited solubility of miconazole nitrate and the drug intensive hepatic transformation that results in poor oral drug bioavailability (25-30%) of the drug and hinders its use for systemic treatment via gastro intestinal tract<sup>5</sup>. Miconazole nitrate's poor skin penetration capability causes a problem in the treatment of cutaneous diseases by topical application. For effective treatment, the drug must be delivered in sufficient concentration to the site of infection [2]. The conventional topical dosage cannot reside at the site of application for longer times and does not release the drug in sustained manner. Various methods are available to sustain the release of the drug. Among them the nanosponges have some unique advantages, which are three dimensional sponges like nanostructure encapsulating the drug. The nanostructure has potential for decreased skin irritation and stabilization of sensitive activities. Moreover nanosponges have good penetration into stratum corneum by overcoming the skin barrier effect and maintaining the good physical and chemical stability [3].

**MATERIALS AND METHODS:**

Miconazole nitrate was the generous gift from Natco Pharmaceuticals, Hyderabad. Carbapol 934 P was procured from SD Fine chemicals, Mumbai.  $\beta$ -cyclodextrins and Di phenyl carbonate were purchased from Sigma Aldrich (Milan, Italy). All other ingredients used were of analytical grade.

**Synthesis of  $\beta$ - Cyclodextrin Nanosponges:**

$\beta$ -cyclodextrin based nanosponges were prepared using Di phenyl carbonate as a cross-linker. Nanosponges were prepared using different ratios of  $\beta$ -cyclodextrin and Di phenyl carbonate [1:0.25, 1:0.5, 1:0.75 and 1:1]. Finely homogenized anhydrous  $\beta$ -cyclodextrin and Di phenyl carbonate were placed in a 100 ml conical flask. The system was gradually heated to 100 °C under magnetic stirring, and left to react for 5 h. During the reaction crystals of phenol appeared at the neck of the flask. The reaction mixture was left to cool and product obtained was broken up roughly. The solid was repeatedly washed with distilled water to remove unreacted  $\beta$ -cyclodextrin and then with acetone, to remove the unreacted Di phenyl carbonate and the phenol present as by-product of the reaction. After purification, nanosponges were stored at 25 °C until further use [4].

**Preparation of Miconazole Nitrate Loaded Nanosponges:**

The Miconazole nitrate loading into  $\beta$ -cyclodextrin nanosponges was carried out by solvent evaporation technique. In this various solvents like chloroform, acetone and ethanol were used. . In 100 ml of each solvent 4000 mg of Miconazole was dissolved separately to form solutions. To the each solution, prepared nanosponges were added and triturated until the solvent evaporated. While triturating the clumps of nanosponges will be segregated and absorbs the drug solubilised solvent. The solid dispersions were dried in an oven overnight (at 50 °C at atmospheric pressure) to remove any traces of solvents and were sieved through 60 # and used for further work [5].

**Preparation of Miconazole Nitrate Nanosuspension:**

The dried drug encapsulated nanosponges were collected and required quantities of drug equivalent nanosponges were transferred into 250ml volumetric flask containing 100ml methanol in order to remove the free unencapsulated drug by solubilising in the methanol. The drug encapsulated nanosponges were separated from the free drug by membrane filtration by using 0.22 $\mu$  membrane filter. The residual drug loaded nanosponges were collected and dispersed in distilled water by using ultra sonication to form a nanosuspension [6].

**Formulation Of Carbopol Gel Containing Miconazole Nitrate Loaded Nanosponges:**

500 mg of carbopol 934 was dispersed in 5 ml of distilled water and allowed for swelling over night.

The swelled carbopol was stirred for 60 minutes at 800 rpm. The previously prepared required drug (Miconazole Nitrate) equivalent nanosuspensions, methylparaben and propylparaben were incorporated into the polymer dispersion with stirring at 500 rpm, by a magnetic stirrer for 1 h. The P<sup>H</sup> of above mixture was adjusted to 4.5 with tri ethanolamine (0.5%). The gel was transferred in to a measuring cylinder and the volume was made up to 10ml with distilled water [7].

### Evaluation Studies

#### Fourier Transform Infrared (FTIR) Spectroscopy

To confirm the formation of nanosponges, Fourier Transform Infrared (FTIR) spectroscopy studies were used. Potassium Bromide pellet method was used in the study. The spectra were studied for the conformational changes of optimized drug when compared with the pure drug and pure excipients spectrums [8]. The spectra were recorded in the wave number region of 4000-500cm<sup>-1</sup>.

#### Encapsulation Efficiency:

The encapsulation efficiency of nanosponges was determined spectrophotometrically ( $\lambda_{max} = 272 \text{ nm}$ ). A sample of Miconazole nitratenanosponges (100 mg) was dissolved in 100 ml of methanol and kept it for overnight. 1 ml of the supernatant was taken and diluted to 10 ml with a solution containing 4.5 pH phosphate buffer and was analyzed at 272 nm using UV-visible spectrophotometer. From the absorbance the free drug content was calculated. The methanol dispersion containing Miconazole nitratenanosponges was then ultra sonicated to release the encapsulated drug from the nanosponges structure [9]. Then the solution was filtered by using 0.22 $\mu$  filter paper and the filtrate was analysed at 272 nm using UV visible spectrophotometer for the total drug content. The encapsulation efficiency (%) of the nanosponges will be calculated according to the following equation,

$$\text{Encapsulation efficiency} = \frac{\text{Encapsulated drug content in nanosponges}}{\text{Total drug content}} \times 100$$

All measurements were performed in triplicate. The results of the best polymer and cross linking agent ratio were analyzed statistically for their significance of difference.

#### Determination of Particle Size Distribution

The particle size distribution was determined by using Dynamic Light Scattering (DLS) technique. The equipment used for the particle size distribution is HORIBA particle size analyzer. In this technique the particle sizes of a batch of the nanosponges were

observed and from the standard deviation and mean particle size of nanosponges, the Poly Dispersity Index (PDI) was calculated. The poly dispersity index is the indication for the nature of dispersity [10].

#### Determination of Zeta Potential

Zeta potential is a measure of surface charge of dispersed particles in relation to dispersion medium. It was determined by using HORIBA zeta sizer having the capability of determination of zeta potential [11].

#### Evaluation of Drug Loaded Nanosponges Containing Gels:

The drug loaded Nano sponges containing gels were evaluated for p<sup>H</sup>, Viscosity Spreadability, Extrudability and mucoadhesive time [12].

#### Drug Content in the DLNS Containing Gel Formulations:

The sample of 1 gram of gel formulation containing 100 mg of Miconazole nitrate was dissolved in methanol, filtered and the volume will be made to 20 ml with methanol. The drug content will be determined by diluting the resulting solution for 10 times with a solution containing 4.5 P<sup>H</sup> phosphate buffer and methanol in 6:4 ratio and the absorbance was measured at 272nm using UV Visible spectrophotometer [13].

#### In-vitro Drug Diffusion Study:

Modified Franz diffusion cell was used for these studies. Cellophane membrane was used as the simulation for the skin. Cellophane membrane was mounted in a modified Franz diffusion cell. The known quantity (1g of gel containing 100 mg of the drug equivalent DLNS) was spread uniformly on the cellophane membrane on donor side. The solution containing 4.5 P<sup>H</sup> phosphate buffer solution was used as the acceptor medium, from which 1ml of samples were collected for every hour and the same amount of fresh medium was replaced to maintain sink conditions for 12 hrs. While taking the samples from the acceptor medium, precautions were taken that no air bubbles were formed in the acceptor medium [14]. The fresh samples were analyzed at 272nm by UV-spectrophotometer and the amount of drug diffused for each hour was calculated. All the samples were analysed in triplicate.

### RESULTS AND DISCUSSION:

The FTIR structure of formed nano sponges were studied by comparing with unreacted  $\beta$ -cyclo dextrin and diphenyl carbonate FTIR spectra. In all the ratio of nanosponges, the major peaks were observed at 940 cm<sup>-1</sup> which represents the  $\alpha$ -1,4 glycoside bond

which is the indication that there was no change in the cyclodextrin linkages. The absence of peaks responsible for carbonyl group of the diphenyl carbonate at  $1768\text{cm}^{-1}$  in the nanosponges is the indication of the removal of C=O from diphenyl carbonate. The absence of peaks responsible for  $\text{C}=\text{C}$  at  $1591$  and  $1497\text{cm}^{-1}$  in the IR spectra of nanosponges is indication of absence of phenol rings which were present in the unreacted diphenyl carbonate. Similarly absence of an intense peak responsible for  $\text{C}=\text{O}$  group at  $1157\text{cm}^{-1}$  in the IR spectra of nanosponges is the indication of removal of C=O group from the diphenyl carbonate which might be attached to the primary or secondary hydroxyl groups of  $\beta$ -cyclodextrin by leaving phenol as by product. All these changes infer that the formation of nanosponges by reacting of primary/secondary hydroxyl groups of  $\beta$ -cyclodextrin with the carbonyl groups of diphenyl carbonate. From the encapsulation efficiency of the drug loaded nanosponges formulations it was inferred that, as the crosslinking ratio increased the encapsulation efficiency was found to be enhanced. The order of encapsulation efficiency in the nanosponges is  $1:1 > 1:0.75 > 1:0.5 > 1:0.25$ . It is also found that the encapsulation efficiency of drug loaded nanosponges is influenced by the solvent used for drug loading by solvent evaporation technique. Chloroform  $>$  Acetone  $>$  Ethanol

The change in the encapsulation efficiency with respect to solvent might be due to the solubility of Miconazole nitrate in the particular solvent. The extended sustained release was observed in all the 12 formulations. But the extent of sustained nature was varied from one ratio to other. The order of sustained action was as follows  $1:1 > 1:0.75 > 1:0.5 > 1:0.25$

Based on the drug encapsulation efficiency, drug content and extent of sustained nature F12 formulation was concluded to be the best formulation. The results of the present investigation overlay the path and provide substantial information for the utilization of Beta cyclodextrin in the development of drug delivery systems. The optimized formulation (F12) was evaluated for their particle size and zeta potential. The particle size (334 nm) and zeta potential (-26.7 mV) was found to be good enough to maintain the physical stability of the nanosponges.

Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in different ratios and by using ethanol as a solvent shown drug release for a period of 7 hours, 7.5 hours, 8 hours and 9.5 hours respectively. Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di

phenyl carbonate in different ratios and by using acetone as a solvent shown drug release for a period of 8 hours, 8.5 hours, 9 hours and 10 hours respectively. Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in different ratios and by using chloroform as a solvent shown drug release for a period of 8.5 hours, 9 hours, 9.5 hours and 11 hours respectively. Based on the drug encapsulation efficiency, drug content and extent of sustained nature, the gel prepared with polymer and crosslinking agent in 1:1 ratio, chloroform as a solvent and carbopol as a gelling agent (F12 formulation) was concluded to be the best formulation. The initial burst release decrease with increase in concentration of crosslinking agent. To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) and diffusion kinetics values were shown in table 4. Amount of drug diffused versus time curves exhibited straight line for the formulations and confirmed that the diffusion rate followed zero order release kinetics. Percentage of drug release versus square root of time curves shows linearity and proves that all the formulations followed Peppas model.

The diffusion exponential coefficient (n) values were found to be in between 0.9402 to 1.1864 indicating super case-II transport diffusion mechanisms. These results indicated that the diffusion rate was found to be decrease with increase in concentration of cross linking agent.

### CONCLUSION:

The optimized formulation has good Spreadability, extrudability and mucoadhesive nature. The  $P^H$  and viscosity of the formulation were appropriate for the topical and vaginal drug delivery and nanosponge's technique was a better choice for sustained release with very fewer chances for the burst effect.

### REFERENCES:

1. Cavalli R., Trotta F., Tumiatti W., Cyclodextrin-based Nanosponges for Drug Delivery. J of Inclusion Phenomena and Macro Chemistry 2006;56(1-2):209-213.
2. Tripathi K D. Antifungal drugs. Tripathi K D (Ed). Essentials of Pharmacology, 6<sup>th</sup> edition, New Delhi: Jaypee Publication; 2008. p. 762-763.
3. Patricia V A., Formulation Development Forum: Nanosponges, pharmaceutical technology, 2013; 35(5):56-60.

4.Monica Rao., Amrita Bajaj., Ishwar Khole., Ghanshyam Munjapara., Francesco Trotta., In vitro and in vivo evaluation of Beta cyclodextrin-based nanosponges of telmisartan. *J Incl Phenom Macrocycl Chem* 2012; 1-11

5. Shankar Swaminathan., PR Vavia., Francesco Trotta., Satyen Torne., Formulation of Beta cyclodextrin based nanosponges of itraconazole. *J Incl Phenom Macrocycl Chem* 2007; 57:89–94.

6.Rakesh P Patel., Hardik H patel., Ashok H baria., Formulation and Evaluation of Carbopol Gel Containing Liposomes of Ketoconazole (Part-II). *International Journal of Drug Delivery Technology* 2009; 1(2): 42 – 45.

7.Shankar Swaminathan., Pradeep R Vavia., Francesco Trotta., Roberta Cavalli., Simonetta Tumbiolo.,Luca Bertinetti., Structural evidence of differential forms of nanosponges of Beta-cyclodextrin and its effect on solubilization of a model drug. *J Incl Phenom Macrocycl Chem* 2013; 76(1-2): 201-11.

8.Bhupendra G Prajapati., Madhabhai M Patel.,Crosslinked chitosan gel for local drug delivery

of Clotrimazole. *e -Journal of Science & Technology* 2010; 5(6): 43-52.

9.Elisabetta Esposito., Laura Ravani., Catia Contado., Andrea Costenaro., Markus Drechsler and Damiano Rossi. Clotrimazole nanoparticle gel for mucosal administration. *Materials Science and Engineering* 2013; C33: 411–8.

10.Cavalli R., Trotta F .,Tumiatti W.,Cyclodextrin-based Nanosponges for Drug Delivery. *J of Inclusion Phenomena and Macro Chemistry*;2006: 56 (1-2);209-213.

11. Jilsha G., Vidya Viswanad., Nanosponges: A Novel Approach of Drug Delivery System *Int. J. Pharm. Sci. Rev. Res.*,2013; 19(2); 119-123.

12. Gursalkar Tejashri, Bajaj Amrita ., cyclodextrin Based Nanosponges For Pharmaceutical Use: A Review *Acta Pharm.* 2013;63;335–358.

13. Honey Tiwari.,Alok Mahor.,Manjoo Kushwaha.,A Review On Nanosponges World *Journal Of Pharmacy And Pharmaceutical Sciences* ,2014 :3(11); 219-233.

14.Prathima Srinivas., Sreeja K., Formulation and Evaluation of Voriconazole Loaded Nanosponges for Oral and Topical Delivery *Int. J. Drug Dev. & Res.*, 2013, 5(1): 55-69.

**Table1: Composition of Miconazole Nitrate Loaded Nanosponges Using Different Solvents**

| S. No | Batch code | Polymer : cross linking agent | Drug (mg) | Solvent    |
|-------|------------|-------------------------------|-----------|------------|
| 1     | MNLNS1     | 4000:1000                     | 4000      | Ethanol    |
| 2     | MNLNS2     | 4000:2000                     | 4000      | Ethanol    |
| 3     | MNLNS3     | 4000:3000                     | 4000      | Ethanol    |
| 4     | MNLNS4     | 4000:4000                     | 4000      | Ethanol    |
| 5     | MNLNS5     | 4000:1000                     | 4000      | Acetone    |
| 6     | MNLNS6     | 4000:2000                     | 4000      | Acetone    |
| 7     | MNLNS7     | 4000:3000                     | 4000      | Acetone    |
| 8     | MNLNS8     | 4000:4000                     | 4000      | Acetone    |
| 9     | MNLNS9     | 4000:1000                     | 4000      | Chloroform |
| 10    | MNLNS10    | 4000:2000                     | 4000      | Chloroform |
| 11    | MNLNS11    | 4000:3000                     | 4000      | Chloroform |
| 12    | MNLNS12    | 4000:4000                     | 4000      | Chloroform |

**Table 2: Encapsulation Efficiency of Miconazole Nitrate Loaded Nanosponges**

| S. No | Batch code | % Encapsulation efficiency (n=3) |
|-------|------------|----------------------------------|
| 1     | MNLNS1     | 71.29 ± 1.07                     |
| 2     | MNLNS2     | 74.34± 1.03                      |
| 3     | MNLNS3     | 78.47 ± 2.57                     |
| 4     | MNLNS4     | 81.59 ± 1.37                     |
| 5     | MNLNS5     | 76.36 ± 1.05                     |
| 6     | MNLNS6     | 80.52 ± 1.91                     |
| 7     | MNLNS7     | 84.68 ± 2.20                     |
| 8     | MNLNS8     | 88.77 ± 2.09                     |
| 9     | MNLNS9     | 78.15 ± 2.06                     |
| 10    | MNLNS10    | 82.26 ± 2.2                      |
| 11    | MNLNS11    | 86.33 ± 2.84                     |
| 12    | MNLNS12    | 90.44 ± 2.29                     |

**Table 3: Percentage of Drug Content in the Miconazole Nitrate Loaded Nanosponges Containing Gel Formulations**

| S. No | Batch code | % Drug content |
|-------|------------|----------------|
| 1     | F1         | 99.34±0.85     |
| 2     | F2         | 99.41±0.21     |
| 3     | F3         | 99.23±0.47     |
| 4     | F4         | 99.64±0.60     |
| 5     | F5         | 99.22±0.89     |
| 6     | F6         | 99.30±0.40     |
| 7     | F7         | 99.41±0.30     |
| 8     | F8         | 99.52±0.40     |
| 9     | F9         | 99.53±0.89     |
| 10    | F10        | 99.64±0.40     |
| 11    | F11        | 99.13±0.21     |
| 12    | F12        | 99.48±0.41     |

**Table 4: *In Vitro* Drug Release Kinetic Data of Carbopol Gels Containing Nanosponges Prepared With B - Cyclodextrin and Di Phenyl Carbonate in Different Ratios and By Using Different Solvents**

| Formulation     | Correlation coefficient |             |         |        | Diffusion Rate Constant (mg/hr) $K_0$ | $T_{50}$ (hr) | $T_{90}$ (hr) | Diffusion Exponent (n) |
|-----------------|-------------------------|-------------|---------|--------|---------------------------------------|---------------|---------------|------------------------|
|                 | Zero order              | First order | Higuchi | Peppas |                                       |               |               |                        |
| F <sub>1</sub>  | 0.9702                  | 0.8290      | 0.9741  | 0.9971 | 14.8                                  | 3.3           | 6.0           | 0.6162                 |
| F <sub>2</sub>  | 0.9939                  | 0.8168      | 0.9496  | 0.9946 | 13.4                                  | 3.7           | 6.6           | 0.7970                 |
| F <sub>3</sub>  | 0.9971                  | 0.8138      | 0.9427  | 0.9947 | 12.4                                  | 4.0           | 7.2           | 0.8301                 |
| F <sub>4</sub>  | 0.9994                  | 0.8085      | 0.9271  | 0.9971 | 10.4                                  | 4.8           | 8.6           | 0.9290                 |
| F <sub>5</sub>  | 0.9963                  | 0.8175      | 0.9457  | 0.9972 | 12.4                                  | 4.03          | 7.25          | 0.8162                 |
| F <sub>6</sub>  | 0.9928                  | 0.8020      | 0.9236  | 0.9997 | 11.4                                  | 4.3           | 7.1           | 0.9650                 |
| F <sub>7</sub>  | 0.9993                  | 0.7977      | 0.9136  | 0.9999 | 11                                    | 4.5           | 8.2           | 1.0618                 |
| F <sub>8</sub>  | 0.9991                  | 0.7984      | 0.9147  | 0.9993 | 9.8                                   | 5.1           | 9.2           | 1.0840                 |
| F <sub>9</sub>  | 0.9976                  | 0.7964      | 0.9404  | 0.9975 | 12.5                                  | 4.0           | 7.2           | 0.8418                 |
| F <sub>10</sub> | 0.9998                  | 0.8044      | 0.9268  | 0.9995 | 11.62                                 | 4.3           | 7.8           | 0.9427                 |
| F <sub>11</sub> | 0.9994                  | 0.8068      | 0.9228  | 0.9928 | 10.20                                 | 4.9           | 8.7           | 1.0301                 |
| F <sub>12</sub> | 0.9998                  | 0.7640      | 0.9261  | 0.9993 | 9.09                                  | 5.5           | 10.0          | 1.1035                 |

**Table 5: Physical Properties of Optimized Gel**

| Formulation | Viscosity (cps) | Extrudability (N) | Spreadability (g.cm/sec.) | pH          | Muco adhesive time |
|-------------|-----------------|-------------------|---------------------------|-------------|--------------------|
| <b>F12</b>  | <b>3918±26</b>  | <b>33.48±1.87</b> | <b>91.79±0.09</b>         | <b>4.46</b> | <b>&gt;12 hrs</b>  |

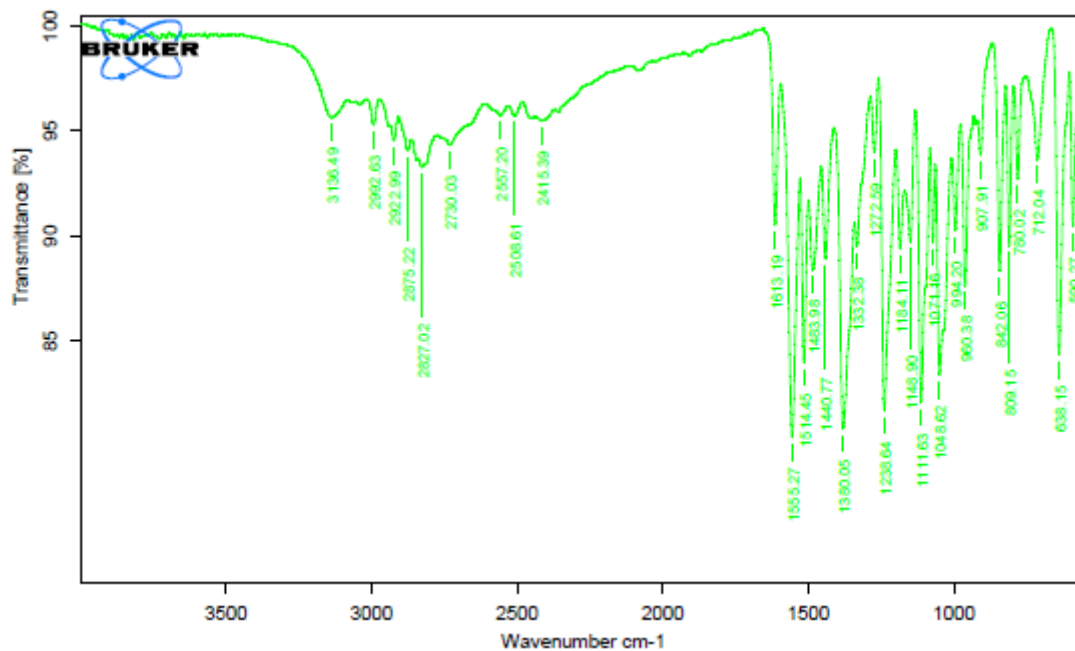


Figure 1: FT-IR Spectra of Miconazole Nitrate

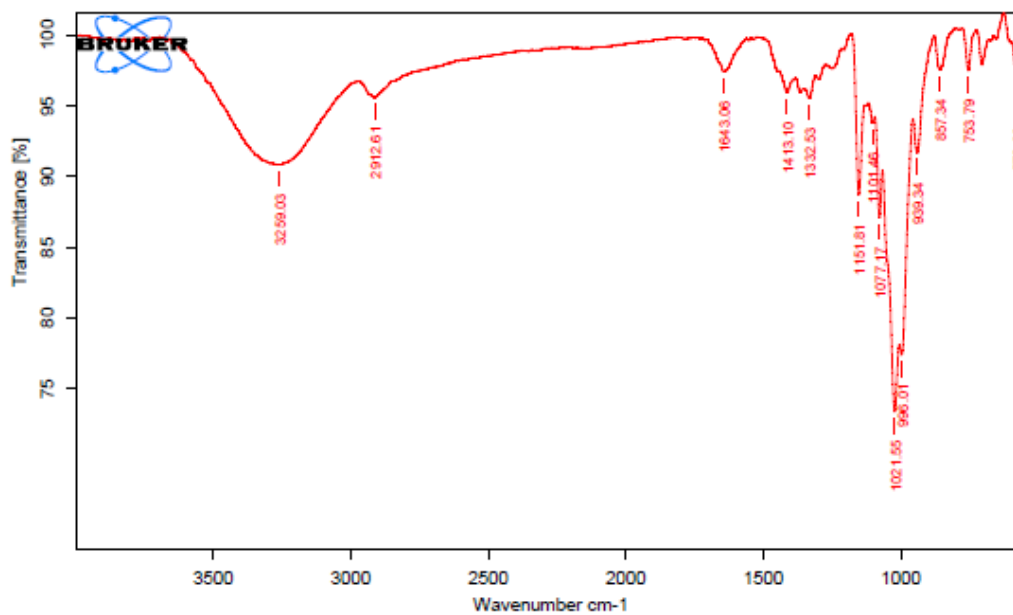


Figure 2: FT-IR Spectra of B-Cyclodextrin



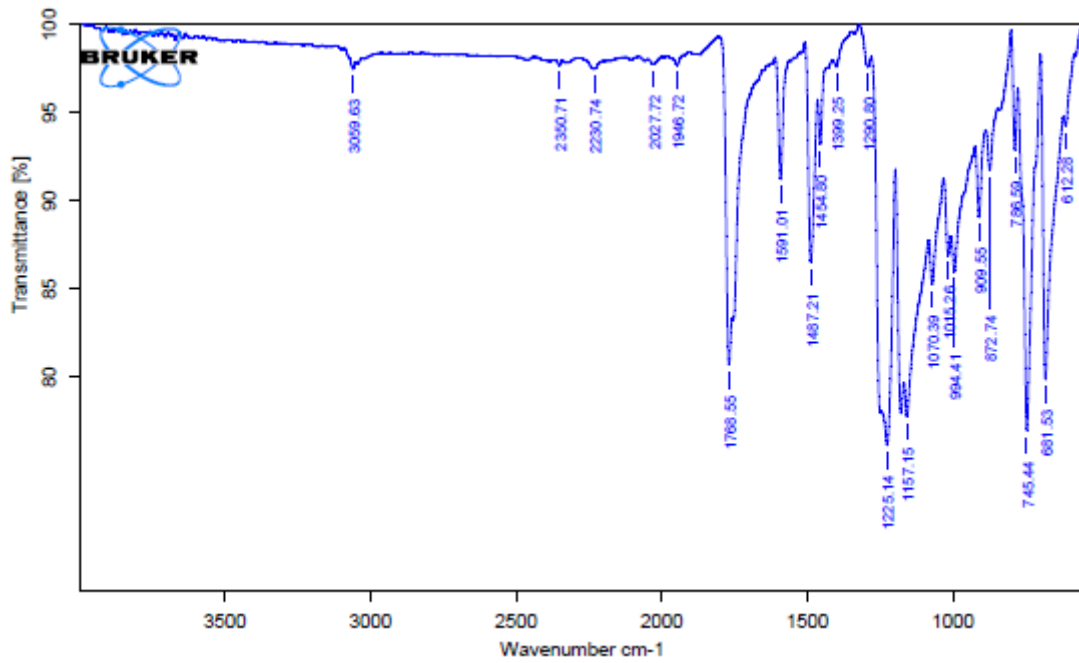


Figure 3: FT-IR Spectra of Diphenyl Carbonate

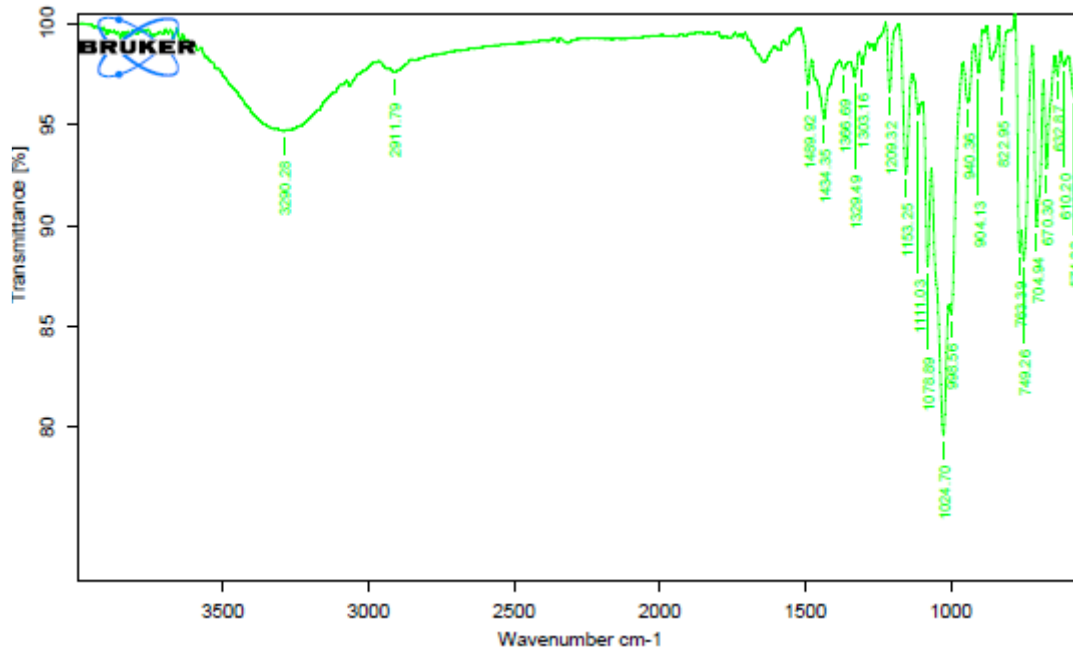
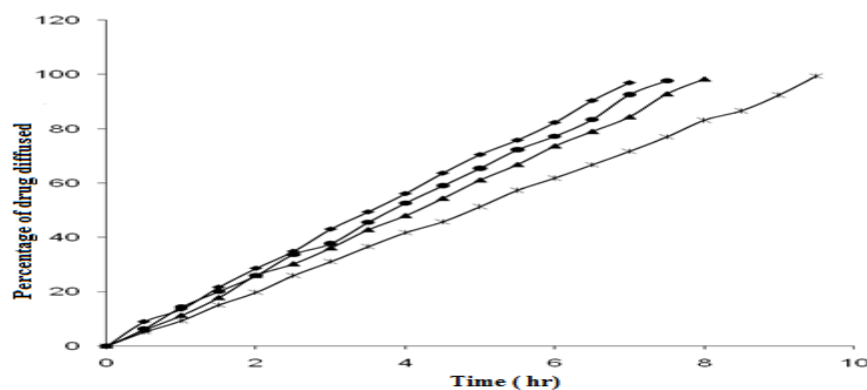
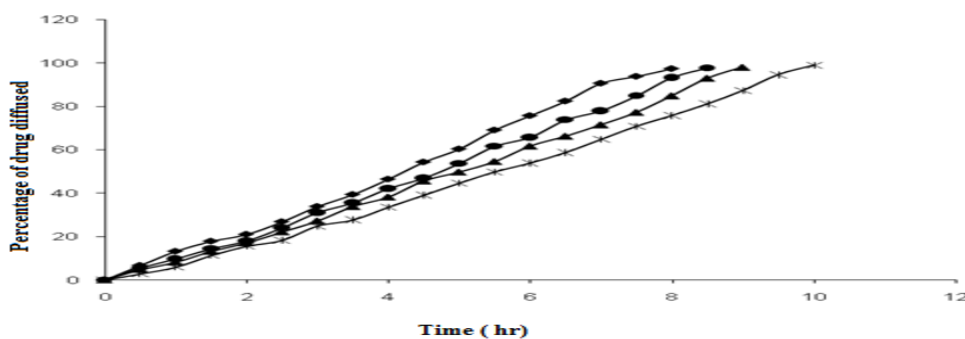


Figure 4: FT-IR Spectra of Optimized Formulation



- (-■-)  $F_1$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:0.25 ratio and by using ethanol as a solvent  
 (-●-)  $F_2$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:0.5 ratio and by using ethanol as a solvent  
 (-▲-)  $F_3$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:0.75 ratio and by using ethanol as a solvent  
 (-×-)  $F_4$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:1 ratio and by using ethanol as a solvent

**Figure 5: Comparative *in vitro* Drug Diffusion Profile of Carbopol Gels Containing Nanosponges Prepared With B-Cyclodextrin and Di Phenyl Carbonate in Different Ratios and By Using Ethanol as A Solvent**



**Figure 6: Comparative *in Vitro* Drug Diffusion Profile of Carbopol Gels Containing Nanosponges Prepared With B-Cyclodextrin and Di Phenyl Carbonate In Different Ratios and By Using Acetone as A Solvent**

- (-■-)  $F_5$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:0.25 ratio and by using acetone as a solvent  
 (-●-)  $F_6$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:0.5 ratio and by using acetone as a solvent  
 (-▲-)  $F_7$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:0.75 ratio and by using acetone as a solvent  
 (-×-)  $F_8$ . Carbopol gels containing nanosponges prepared with  $\beta$ -cyclodextrin and Di phenyl carbonate in 1:1 ratio and by using acetone as a solvent