INTRODUCTION:
The soil-transmitted helminths are one of the world’s most important causes of physical and intellectual growth retardation. Yet, despite their educational, economic, and public-health importance, they remain largely neglected by the medical and international community (1). Over the past 5 years, however, the worldwide community has begun to recognize the importance of these infections after revised estimates showed that their combined disease burden might be as great as those of malaria, tuberculosis or HIV infection (2).

It is now recognized that STH infection causes significant morbidity worldwide with 39 million disability adjusted life years (DALYs) lost each year-more than those lost to tuberculosis (36 million yearly) and approaching those lost to malaria (46.5 million yearly)(3). Hookworm infection alone causes the loss of 22 million DALYs (3).

Overall, it is believed that, together with schistosomiasis, the soil-transmitted helminth infections account for 40% of the global morbidity caused by all infectious diseases, exclusive of malaria (4). In some of the less developed regions of the world, helminthic intestinal infections may impair ocular, muscle or blood systemic circulation (5). The low cost, good tolerance and broad spectrum of activity of albendazole make it typically the drug of choice for these cases. But albendazole is practically insoluble in water, which limits its oral bioavailability for the treatment of systemic helminthiasis. Therefore, achieving greater albendazole solubility through complexation with HP-β-CD (6, 7) and nanocrystallization technique could increase bioavailability of the drug (8), which would be most advantageous in lengthy therapies such as for hydatid diseases and neurocysticercosis (9). Cyclodextrins are a group of structurally related cyclic oligosaccharides that

ABSTRACT
The aim of the present work was to enhance solubility and dissolution rate of albendazole a class II drug by two different techniques and compare them for improved drug delivery study. These techniques are inclusion complex of albendazole with Hydroxypropyl-β-Cyclodextrin (HP-β-CD) and converting drug into nanocrystal by anti-solvent precipitation technique in the presence of sodium lauryl sulfate as stabilizer. HP-β-CD molecules are cone-shaped with hydrophobic central cavity and hydrophilic outer surface and are capable of forming inclusion complexes with drug by taking up a whole drug molecule or some hydrophobic part of it, into the cavity and there by enhance the drug dissolution and solubility. Nanocrystals are new carrier free colloidal drug delivery system with nano sized particles below 1000 nm, and considered as a great drug delivery technique to enhance the drug dissolution and solubility. In the present work the drug inclusion complex with HP-β -CD were prepared by kneading technique with different ratios of HP-β-CD. All formulations showed marked improvement in dissolution and solubility compared to pure drug. Drug nanocrystals were prepared by anti-solvent precipitation technique. Different concentrations of sodium lauryl sulphate (SLS) as stabilizers were evaluated. All formulations were in the nano size and showed marked improvement in dissolution and solubility compared to pure drug of micron size. Finally it was concluded that formulating poorly soluble drugs in the form of nanocrystals would be a promising approach in delivery of class II drugs by oral route in a simple and effective way.

KEYWORDS: Albendazole, Solubility enhancement, Nanocrystals, Cyclodextrin, Inclusion complex.
are formed by enzymatic cyclization of starch. The three most common naturally occurring cyclodextrins are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin consisting of six, seven and eight (α-1, 4)-linked α-D-glucopyranose units, respectively. The cyclodextrins molecules are cone-shaped with a somewhat hydrophobic central cavity and hydrophilic outer surface. They are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or more frequently, some hydrophobic part of it, into the cavity (10). Increased solubility is obtained when the more commonly substituted cyclodextrins are used instead of non derivatized cyclodextrins (6). This occurs because highly soluble cyclodextrins derivatives are used such as that in hydroxypropyl-β-CD (9). Drug nanocrystals are defined as pure solid drug particles with a mean particle size below 1000 nm. Nanocrystals implies a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous (8). Drug nanocrystals have to be distinguished from polymeric nano particles, which consist of a polymeric matrix and an incorporated drug. Drug nanocrystals do not consist of any matrix material (11). The aim of the present work is to enhance solubility and dissolution rate of albendazole a class II drug by two different techniques and compare them for improved drug delivery study. First method is inclusion complex of albendazole with HP-β-CD and other is to converting it into nanocrystal by anti-solvent precipitation technique in the presence of sodium lauryl sulfate as nanocrystal stabilizer.

MATERIALS AND METHODS:

MATERIALS:

Albendazole was received as gift samples from Maan pharmaceuticals Pvt. Ltd. Gujarat, India. Hydroxypropyl-β-cyclodextrin was received as gift samples from Cadila Pharmaceuticals Pvt. Ltd. Gujarat, India. Sodium lauryl sulfate and Glacial acetic acid were received from central Drug House, New Delhi. All the materials used in this research study comply with the pharmaceutical and analytical standards. Whole research work was carried out at Maharishi Arvind Institute of Pharmacy, Jaipur during year 2011-2012.

METHODS OF PREPARATION:

PREPARATION OF INCLUSION COMPLEX OF ALBENDAZOLE WITH HP-B-CD BY KNEADING TECHNIQUE (KN) (9, 10):

The different batches of kneaded product were prepared by addition of albendazole (200 mg) into the paste of HP-β-cyclodextrin with different drug: polymer ratios of 1:2, 1:4, 1:6, 1:8 and 1:10 w/w followed by trituration the resultant mixture till cracking sound appeared. The resultant mass was dried at room temperature and pass through 80 mesh screen.

PREPARATION OF NANOCRYSTALS OF ALBENDAZOLE (11, 12):

Nanocrystals of albendazole were prepared by anti-solvent precipitation technique. Albendazole (200 mg) was dissolved in glacial acetic acid (10 ml) under constant agitation. The prepared drug solution was injected drop wise into distilled water containing sodium lauryl sulfate (0.1%, 0.2%, 0.3%, 0.4%, 0.5% w/v) under constant stirring at 1000 rpm. Immediately, particles precipitated from the anti-solvent and milk-like suspension was formed which was filtered and dried in hot air oven at 50°C.

CHARACTERIZATION (9, 13, 14):

UV SPECTROSCOPY:

UV spectra were obtained on a UV spectrophotometer 1800-series, Shimadzu Corporation, Japan (Maharishi Arvind Institute of Pharmacy, Jaipur) with a wavelength range of 200 nm- 400 nm.
FOURIER TRANSFORMS INFRARED (FTIR):
Fourier transform infrared (FTIR) spectra were obtained on an IR spectrophotometer (Maharishi Arvind Institute of Pharmacy, Jaipur) from 3500 to 600 cm⁻¹.

PHASE SOLUBILITY STUDY:
ALBEBDAZOLE INCLUSION COMPLEX WITH HP-B-CD (9):
Phase solubility study for albendazole was performed as described by Higuchi and Connors. Excess amount of albendazole was added into 10 ml 0.1 N HCL and shaken for 24 h at room temperature on a flask shaker (Instrument-India, Mumbai). After 24 h the solution was centrifuged (Micro centrifuge, RM-12C, REMI Instruments, India.) followed by filtered through whatmann filter paper (#44). The filtrate was appropriately diluted by 0.1 N HCL and the concentration of the albendazole in the filtrate were determined by UV spectrophotometer (UV-1800 series, Shimadzu corporation, Japan) at 298 nm. Solubility measurements were performed in triplicate. A similar protocol without HP β-CD was used for the direct determination of ABZ solubility in 0.1 N HCL.

ALBENDAZOLE NANOCRYSTALS (9):
Phase solubility study for albendazole nanocrystals was performed as described by Higuchi and Connors. Excess amount of albendazole nanocrystals was added into 10 ml 0.1 N HCL and shaken for 24 h at room temperature on a flask shaker (Instrument-India, Mumbai). After 24 h the solution was centrifuged (Micro centrifuge, RM-12C, REMI Instruments, India.) followed by filtered through whatmann filter paper (#44). The filtrate was appropriately diluted by 0.1 N HCL and the concentration of the albendazole in the filtrate were determined by UV spectrophotometer (UV-1800 series, Shimadzu corporation, Japan) at 298 nm. Solubility measurements were performed in triplicate. A similar protocol for pure drug was used for the direct determination of ABZ solubility in 0.1 N HCL.

PARTICLE SIZE DETERMINATION OF NANOCRYSTALS:
Particle size was measured by light Microscope (Quasmo, India) with stage micrometer and eye-piece. Size of 100 particles of pure albendazole and different batches were determined and averages of all batches were calculated.

MELTING POINT DETERMINATION OF NANOCRYSTALS:
Melting point of pure albendazole and different batches of albendazole nanocrystals were determined using Thiele’s tube filled with liquid paraffin.

X-RAY DIFFRACTION STUDY OF NANOCRYSTALS:
X-ray diffraction analysis was carried out for pure drug and prepared nanocrystals using X-ray diffractometer (Model: D2 phaser Make: Bruker). The powder was scanned from 10 to 80 ° (2 θ).

IN VITRO DISSOLUTION CHARACTERIZATION:
ALBENDAZOLE INCLUSION COMPLEX WITH HP-B-CD (13):
In vitro dissolution studies were carried out in 900 ml of 0.1 N HCL at a temperature of 37±0.5 °C at 50 rpm. Powder sample equivalent to 100 mg of drug was put on muslin cloth and immersed in the dissolution medium. 5ml of dissolution sample was withdrawn at regular time intervals (0, 15, 30, 45, 60, 75, 90, 105 and 120 minutes) was filtered through a whatmann filter (#44). 5ml of 0.1N HCL was replaced to jar. This filtered sample was diluted sufficiently by 0.1 N HCL and absorbance of the resultant solution was measured by U V spectrophotometer (Model: UV- 1800, by Shimadzu corporation, Japan) at 298 nm using 0.1N HCL as a blank.

ALBENDAZOLE NANOCRYSTALS (14):
Crystal powder dissolution study was carried out by using USP apparatus II (Model: TDT-08P, Electrolab, India). Dissolution media was 900 ml of 0.1 N HCL at a temperature of 37±0.5 °C at 50 rpm. Powder sample equivalent to 100 mg of drug was put on muslin cloth and immersed in the dissolution medium. 5ml of dissolution medium was withdrawn at regular time intervals (0, 15, 30, 45, 60, 75, 90, 105 and 120 minutes) was filtered through a whatmann filter (#44). 5ml of 0.1N HCL was replaced to jar. Filtered Sample was diluted with 0.1N HCL. Absorbance of the resultant solution was measured by U V spectrophotometer (Model: UV- 1800, by Shimadzu corporation, Japan) at 298nm using 0.1N HCL as a blank.

RESULTS AND DISCUSSION:

UV SPECTROSCOPY:
Formulation excipients selected on the basis of preliminary tests, which demonstrates no interference of these excipients with the λmax of ABZ. The complex formation with cyclodextrin alters the original UV absorption spectrum of the molecule usually bathochromic shift and or band broadening occurs. The shift of the UV absorption maxima upon complex formation may be explained by a particular shielding of the excitable electrons in the CD cavity.
Figure 1: Photographic image showing $\lambda_{\text{max}}$ of pure albendazole

Figure 2: Photographic image showing $\lambda_{\text{max}}$ of albendazole complexation with HP-\(\beta\)-CD

Figure 3: Photographic image showing $\lambda_{\text{max}}$ of albendazole nanocrystal
FTIR STUDY:
Complex of ABZ and HP β-CD showed superimposed spectra of ABZ and hydroxypropyl β cyclodextrin which proves the compatibility of excipients with the ABZ.

Figure 4: IR spectra of pure albendazole

Figure 5: IR spectra of HP β-CD
Figure 6: IR spectra of albendazole and HP β-CD complex (batch B$_5$)

Figure 7: IR spectra of albendazole nanocrystal (batch B$_{10}$)
PHASE SOLUBILITY STUDY:

The solubility curve of drug- HP-β-CD inclusion with correlation coefficient squared value \(r^2=0.990\) was regarded as a straight line and solubility curve of drug nanocrystals with correlation coefficient squared value \(r^2=0.997\) was regarded as a straight line.

**Figure 8:** Phase solubility study of albendazole with Hydroxypropyl β-Cyclodextrin

**Figure 9:** Phase solubility study of albendazole Nanocrystals

PARTICLE SIZE DETERMINATION OF NANOCRYSTALS:

**Table 2:** Particle size of Albendazole nanocrystals

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Average particle size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-0 (pure drug)</td>
<td>207.0°C</td>
</tr>
<tr>
<td>B-1</td>
<td>207.6°C</td>
</tr>
<tr>
<td>B-2</td>
<td>206.7°C</td>
</tr>
<tr>
<td>B-3</td>
<td>207.7°C</td>
</tr>
<tr>
<td>B-4</td>
<td>205.6°C</td>
</tr>
<tr>
<td>B-5</td>
<td>205.0°C</td>
</tr>
</tbody>
</table>
MELTING POINT DETERMINATION OF NANOCRYSTALS:

Table 3: Melting point of Albendazole nanocrystals

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Average melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-0 (pure drug)</td>
<td>207.0°C</td>
</tr>
<tr>
<td>B-1</td>
<td>207.6°C</td>
</tr>
<tr>
<td>B-2</td>
<td>206.7°C</td>
</tr>
<tr>
<td>B-3</td>
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<tr>
<td>B-4</td>
<td>205.6°C</td>
</tr>
<tr>
<td>B-5</td>
<td>205.0°C</td>
</tr>
</tbody>
</table>

X-RAY DIFFRACTION STUDY OF NANOCRYSTALS:

Comparison of X-Ray diffraction pattern of pure drug and nanocrystals indicate that for nanocrystals reduction in peak intensity takes place but peak position remains the same.
IN VITRO DISSOLUTION STUDY:
Cumulative drug release of pure drug was found 33.52% at the end of 120 min, while highest cumulative drug release of drug-HP-β-CD inclusion was found 49.84% and drug nanocrystals was found 63.43% at the end of 120 min.

Table 4: In vitro % drug release of albendazole from batch B₀-B₁₀

<table>
<thead>
<tr>
<th>Time in min</th>
<th>Pure drug</th>
<th>Complex of drug with HP-β-CD</th>
<th>Nanocrystals of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B₀</td>
<td>B₁</td>
<td>B₂</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>4.09</td>
<td>6.25</td>
<td>7.14</td>
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<td>30</td>
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</tr>
<tr>
<td>60</td>
<td>17.03</td>
<td>20.87</td>
<td>22.68</td>
</tr>
<tr>
<td>75</td>
<td>21.56</td>
<td>24.68</td>
<td>26.95</td>
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<tr>
<td>90</td>
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<td>29.36</td>
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</tr>
<tr>
<td>120</td>
<td>33.52</td>
<td>39.58</td>
<td>43.34</td>
</tr>
</tbody>
</table>

Figure 12: Comparative dissolution profile of batch B₀-B₅

Figure 13: Comparative dissolution profile of batch B₆-B₁₀
CONCLUSION:

The aim of this work was to improve the solubility and the dissolution rate of albendazole which is required for improving the dosage form characteristic and also to reduce fluctuation in dissolution profile as well as for better in vivo characterization. Many techniques are known to improve dissolution rate of poorly soluble drugs amongst these inclusion complex with HP-β-CD by kneading technique and nanocrystallization technique are selected in this research work because of its ease of preparation, ease of optimization, and reproducibility. Amongst these techniques nanocrystalization technique found to be more effective than inclusion complex with HP-β-CD.

ACKNOWLEDGEMENTS:

Heartily thanks to Maan pharmaceuticals pvt. Ltd. Gujarat, for gift sample of albendazole and my college staff for their valuable co-operation and suggestion in this research work.

REFERENCES: