PREPARATION AND EVALUATION OF NANOSUSPENSION OF POORLY SOLUBLE DRUG ALBENDAZOLE

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ABSTRACT

The aim of the present work was to enhance solubility of albendazole a class II drug by nanosuspension technology. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion-solvent diffusion, melt emulsification method and super critical fluid techniques. Nanosuspension is 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 nanosuspension is made by emulsion solvent diffusion (ESD) technique in the presence of sodium lauryl sulfate as stabilizer. All formulations showed marked improvement in dissolution and solubility compared to pure drug. 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 nanosuspension would be a promising approach in delivery of class II drugs by oral route in a simple and effective way.

KEYWORDS: Albendazole, Solubility enhancement, Nanosuspension.

INTRODUCTION:

More than 40% of the new molecules being generated through drug discovery programmes are poorly water-soluble or lipophilic compounds (1). Formulating a poorly water soluble drug has always been a challenging problem to the pharmaceutical scientist. The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and hence partition into gastrointestinal barrier (2). Micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility (3, 4, 5). There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization, solubilisation using co-solvents, salt form, surfactant dispersions, and oily solution. Other techniques are like liposomes, emulsions, microemulsion, solid dispersion and inclusion complexation using cyclodextrins show sensible achiever, but they lack in universal applicability to all drugs. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents. Nanotechnology can be used to solve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanosuspension is favoured for compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses. Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents (6).

NANOSUSPENSIONS:

Nanosuspensions are colloidal dispersions of nano sized drug particles stabilized by surfactants (7). They can also be defined as a biphasic system consisting of pure drug...
particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1μm in size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility (8). The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles. Nanosuspension have disclosed the problems associated with the delivery of poorly water-soluble and poorly water-and lipid soluble drugs and are unequalled because of their simplicity and rewards they confer over other strategies. The top down technologies include (a) media milling (b) high pressure homogenization (c) emulsion diffusion method (d) supercritical fluid method and these are preferred over the precipitation methods (6).

MATERIALS AND METHODS:

MATERIALS:
Albendazole was received as gift samples from Maan pharmaceuticals pvt. Ltd. Gujarat, India. Sodium lauryl sulfate, acetic acid and dichloromethane (DCM) were received from central Drug House, New Delhi. All the materials used in this research study comply with the pharmaceutical and analytical standards, respectively. Whole research work was carried out at Maharishi Arvind Institute of Pharmacy, Jaipur during year 2011-2012.

METHOD:

PREPARATION OF NANOSUSPENSION OF ALBENDAZOLE (9):
Nanosuspensions were prepared with and without stabilizers by emulsion solvent diffusion technique. The stabilizers composition was given in Table 1. Albendazole (2.0 g) was dissolved in good solvent acetic acid (10 mL). The bridging liquid dichloromethane (2.0 mL) was added to it. The resulting solution was then poured dropwise in to the poor solvent distilled water (75 mL) containing different quantity of stabilizers sodium lauryl sulfate (0.1%, 0.2%, 0.3%, 0.4%, 0.5% w/v) with a stirring rate of 800 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature. After agitating the system for 0.5 h, the prepared nanosuspensions were filled in air tight glass bottle and stored at room temperature.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F-0</th>
<th>F-1</th>
<th>F-2</th>
<th>F-3</th>
<th>F-4</th>
<th>F-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid (mL)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>DCM (mL)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SLS (%)</td>
<td>0</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Water (mL)</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Stirring Speed (rpm)</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
</tr>
</tbody>
</table>

FORMULATION CONSIDERATION:

STABILIZER:
The main function of a stabilizer is to wet the drug particles thoroughly, and to prevent ostwald’s ripening and agglomeration of nanosuspension in order to yield a physically stable formulation by providing steric or ionic barrier (6).

ORGANIC SOLVENT:
Organic solvents are used in the formulation of nanosuspension if emulsions or microemulsions are used as a template (6).

CHARACTERIZATION (6, 9, 10):

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 TRANSFORM 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.

SHAPE AND SURFACE MORPHOLOGY (SCANNING ELECTRON MICROSCOPY):
The surface morphology of the particles (crystals) of nanosuspension was accessed by scanning electron microscopy (SEM). Electron photomicrograph was taken at the acceleration voltage of 20 KV, chamber pressure of 0.6 mm Hg, at different magnification.

PARTICLE SIZE DETERMINATION OF NANOSUSPENSION PARTICLES (CRYSTALS):
Particle size was measured by light Microscope (Quasmo, India) with stage micrometer and eye-piece.

**VISCOSITY MEASUREMENT:**
Viscosity of the suspension was measured by Brookfield viscometer with utilization of the “T” spindle.

**SEDIMENTATION VOLUME:**
Sedimentation volume was calculated by following formula after 30 days.
\[
\text{S.V.} = \frac{H_u}{H_0}
\]
Where,
\[
\text{S.V.}: \text{Sedimentation volume}
\]
\[
H_u: \text{ultimate height of sediment}
\]
\[
H_0: \text{initial height of sediment}
\]

**PHASE SOLUBILITY STUDY:**
Nanosuspension was filtered and particles (crystals) were collected. Phase solubility was performed as described by Higuchi and Connors. Excess amount of the collected particles were 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.

**RESULTS AND DISCUSSION:**

**UV SPECTROSCOPY:**
Formulation excipients selected on the basis of preliminary tests, which demonstrates no interference of these excipients with the \( \lambda_{\text{max}} \) of ABZ. Nanosuspension alters the original UV absorption spectrum of the molecule usually bathochromic shift and or band broadening occurs.

![Figure 1: Photographic image showing \( \lambda_{\text{max}} \) of albendazole](image1)

![Figure 2: Photographic image showing \( \lambda_{\text{max}} \) of collected particles of nanosuspension](image2)
FTIR:

ABZ and collected particles from nanosuspension showed superimposed spectra of ABZ which proves the compatibility of excipients with the ABZ.

![Figure 3: FTIR spectra of pure Albendazole](image)

![Figure 4: FTIR spectra of collected particles from nanosuspension](image)

PARTICLE SIZE ANALYSIS:

Particle size distribution of nanosuspension was determined by optical microscope fitted with an ocular micrometer and stage micrometer. The particle sizes of the nanosuspension were found to be 402.70 nm, 400.55 nm, 324.00 nm, 280.02 nm, 249.73 nm, and 234.47 nm for formulations F-0 to F-5 respectively. The particle sizes of all the six formulations were shown in the Table 2.

It was observed that with increase in stabilizer concentration in the nanosuspension from F-1 to F-5, the particle size of the nanosuspension decreases. This was due to the decrease in relative viscosity, which led to decrease in particle size.
Table 2: Particle size distributions of nanosuspension

<table>
<thead>
<tr>
<th>Batch</th>
<th>Average particle size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure drug</td>
<td>1087.85</td>
</tr>
<tr>
<td>F-0</td>
<td>402.70</td>
</tr>
<tr>
<td>F-1</td>
<td>400.55</td>
</tr>
<tr>
<td>F-2</td>
<td>324.00</td>
</tr>
<tr>
<td>F-3</td>
<td>280.02</td>
</tr>
<tr>
<td>F-4</td>
<td>249.73</td>
</tr>
<tr>
<td>F-5</td>
<td>234.47</td>
</tr>
</tbody>
</table>

SHAPE AND SURFACE MORPHOLOGY (SCANNING ELECTRON MICROSCOPY):

Surface morphology of the nanosuspension was investigated with a scanning electron microscope. Different magnifications were used while taking SEM photomicrographs. Particles surface of formulations F-5 was looked like crystal structure with nano sized.

Figure 5: Particles (crystals) collected from nanosuspension (batch F-5)

VISCOSITY AND SEDIMENTATION VOLUME:

Here viscosity of the nanosuspension in the range of inversion required to resuspend the nanosuspension 40-60, so the nanosuspension was easily pourable. The was very less, so the nanosuspension were easily sedimentation volume of the suspension was nearly 1 so resuspend on shaking. Results are shown in the table 3.

Table 3: Viscosity and sedimentation volume

<table>
<thead>
<tr>
<th>Batch</th>
<th>Viscosity (Cp)</th>
<th>Sedimentation volume ratio</th>
<th>No. of inversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-0</td>
<td>58</td>
<td>0.8</td>
<td>8</td>
</tr>
<tr>
<td>F-1</td>
<td>51</td>
<td>0.7</td>
<td>6</td>
</tr>
<tr>
<td>F-2</td>
<td>49</td>
<td>0.7</td>
<td>5</td>
</tr>
<tr>
<td>F-3</td>
<td>48</td>
<td>0.6</td>
<td>5</td>
</tr>
<tr>
<td>F-4</td>
<td>46</td>
<td>0.6</td>
<td>5</td>
</tr>
<tr>
<td>F-5</td>
<td>42</td>
<td>0.6</td>
<td>5</td>
</tr>
</tbody>
</table>

PHASE SOLUBILITY STUDY:

The solubility curve of particles collected from nanosuspension with correlation coefficient squared value ($r^2=0.995$) was regarded as a straight line.
CONCLUSION:
Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Productions technique such as emulsion solvent diffusion is used for large scale production of nanosuspensions. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnology is simple, fewer requirements of excipients, increased aqueous solubility of many poor bioavailability drugs are formulated in nanosuspension form.

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REFERENCES: