**Screening of Stabilizers in Azithromycin Nanosuspensions**

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**ABSTRACT**

In this study, an attempt was made to formulate nanosuspensions of azithromycin dihydrate, a BCS class-II antibiotic by nanoprecipitation method, with three different stabilizers like Poloxamer 188, Poloxamer 407 and PVP in different ratios. The objective of the study was to investigate role of stabilizers in the formulation of nanosuspensions and thereby improve the bioavailability of azithromycin. The prepared nanosuspensions were characterized by Differential Scanning Calorimetry, X-ray diffractionmetry, Fourier transform infra-red spectroscopy, Scanning Electron Microscopy, In-vitro dissolution profile. FTIR and DSC studies confirmed that there was no distinguishable interaction between drug and excipients used. SEM images showed the surface morphology of the nanosuspensions to be accurate and size to be in nanometers. XRD data confirmed the crystallinity of the drug and slight changes in the crystallinity of azithromycin dihydrate in the formulations. Nanosuspensions containing azithromycin dihydrate and Poloxamer 407 in ratios of 1:5 were selected to be the best based on their drug release profiles. All the formulations showed more than 60 % drug release within 180 minutes, which was far better when compared to pure drug. By this study, it can be concluded that Poloxamers can be used as good stabilizers in the formulation of nanosuspensions.

**Keywords:** Nanosuspensions, stabilizers, azithromycin, Poloxamer 188, Poloxamer 407, PVP.

**INTRODUCTION**

High thorough put screening approaches to drug development have led to an increasing number of lipophilic water-insoluble drug candidates or drugs whose clinical usefulness is hampered by their insolubility in water. These drugs are classified as Class II (i.e., poorly soluble/highly permeable) or Class IV (i.e., poorly soluble/poorly permeable) drugs according to the Biopharmaceutics Classification System1. In general, formulation techniques that increase the apparent aqueous solubility of Class II and Class IV drugs without decreasing their lipophilicity will enhance their absorption through biological membranes. These techniques include particle size reduction, salt formation, and solid dispersion, melt extrusion, spray drying, and complexation, as well as drug solutions in microemulsions, liposomes, and nonaqueous solvents.

**Nanosuspensions**

Nanosuspension technology has been developed in the recent times as a promising technique for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oil5. 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 1 μm in size5. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Various methods utilized for preparation of nanosuspensions include precipitation technique, media milling, high-pressure homogenization in water, high pressure homogenization in nonaqueous media, and combination of Precipitation and high-Pressure homogenization.

A Nano suspension of pure drug offers a method to formulate poorly soluble drugs and enhance the bioavailability of such drugs. It has many formulation and therapeutic advantages such as simple method of preparation, less requirement of excipients, increased dissolution velocity and saturation solubility, improved adhesion, increased bioavailability leading to a decrease in the dose and fast-fed variability and ease of large-scale manufacturing. Nanosuspensions can be formulated for various routes of administration such as oral, parenterals, ocular, topical and pulmonary routes. This technology is gaining significance as the number of molecules with solubility and bioavailability related problems are increasing day by day. Thus, nanotechnology can play a vital role in drug discovery programs to increase aqueous solubility as well as bioavailability of poorly soluble drugs.

As a result of this technique, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g., after oral or intravenous administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without blockade of the blood capillaries. The
nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a nanosuspension can also be incorporated in a solid matrix\(^4\).

**Preparation techniques**

Preparation of nanosuspensions can be achieved using either top-down approaches or bottom-up approaches: In top-down methods, large particles are broken down to small ones (e.g. wet milling and high pressure homogenization (HPH)), while bottom-up methods rely on a process of dissolved drug molecules building up to nano-sized particles (e.g. precipitation)\(^5\).

**Bottom-up techniques**

The term “Bottom-up technology” means that one starts from the molecular level, and goes through a process of molecular association to the formation of a solid particle. Precipitation techniques by reducing the solvent quality, for example, by pouring the solvent into a nonsolvent or changing the temperature or a combination of both can be used as a classical technique in pharmaceutical chemistry and technology. Higher saturation solubility is the advantage for precipitation compared to other methods of nano suspension preparation\(^6\). The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and in organic media), Miscibility of solvents and non solvents, removal of solvent residues, preservation of particle character are few disadvantages.

In general, it is recommended that a second consecutive process has to be performed for particle preservation that is spray drying or lyophilisation\(^7\).

**Nanoprecipitation technique**

Nanoprecipitation is a simple and reproducible technique that produces particles with narrow size distribution. It requires two miscible phases: an organic/oil phase and an aqueous phase\(^8\).

The oil/organic phase consist of an organic solvent which is miscible with water such as ethanol or acetone. It was observed from review of literature that most commonly used organic solvent in nanoprecipitation was acetone. The organic phase contains also the polymer and the hydrophobic drug. The aqueous phase is usually water with other excipients such as hydrophilic surfactants, which are added to avoid particles’ aggregation and thereby stabilize the formulation. The technique is based on the addition of one phase to the other under moderate magnetic stirring. The subsequently obtained suspension of nanoparticles is subjected to evaporation of the organic solvent by a rotavapor or at ambient temperature. The next step consists of the removing of the aqueous phase either by ultracentrifugation or freeze drying. The obtained nanoparticles are characterized by the measurement of size, zeta potential, and by transmission electron microscopy (TEM) or scanning electron microscopy (SEM).

![Figure 1: Nanoprecipitation technique](image)

**Top-down techniques**

The top down technologies include media milling and high pressure homogenization\(^9\)

**Stability of Nanosuspensions**

Stability is a very important parameter when it comes to research on poorly soluble drugs. Since nanosizing results in increased surface area and a positive Gibbs free energy change, nanosuspensions can be categorized into thermodynamically unstable systems with high chances of agglomeration and crystal growth. Despite extensive research on nanosuspension technology, stability remains a limitation for pharmaceutical or industrial applications of nanosuspensions. Furthermore, the empirical relationship between stabilizer efficacy and nanosuspension stability has not been well characterized. Aggregation of the nanoscopic particles is the main stability issue which can occur during preparation process or storage and it is due to the Ostwald ripening phenomenon. Most commonly used stabilizers to stabilize nanosuspensions are either polymer like (e.g., polyvinyl pyrrolidone (PVP), crystalline cellulose,\(8\) amphiphilic amino acid, hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), and d-\(\alpha\)-tocopherol polyethylene glycol 1000 succinate (TPGS 1000), where as surfactant such as ionic are (e.g., sodium dodecyl sulphate (SDS), sodium lauryl sulphate (SLS), poly(ethyleneimine) (PEI), chitosan and non-ionic surfactant (e.g., polysorbate (tween 80), block co-polymer like pluronic) and some food protein are also used as stabilizers such as soya bean protein isolate, whey protein isolate and \(\beta\)-lactoglobuline\(^10\).

**MATERIALS AND METHODS**

Materials used for the research were of analytical grade and of highest purity. Azithromycin dihydrate was a kind gift from Aurobindo Pharma Ltd. Poloxamer 188(Pluronic\(\nsim F\)-188), Poloxamer 407(Pluronic\(\nsim F\)-407) were obtained as gift samples from BASF India ltd., Hydroxyl propyl methyl cellulose was obtained from ALDRICH chemicals. Acetone, methanol, ethanol, PVP used in this work were obtained from Qualichems, Fischer scientific, Changshu yangyuan chemical, Oxford laboratory respectively. Distilled water was used to
prepare aqueous solutions and was obtained by a suitable process.

Determination of Λ Max

The wavelength at which the drug absorbs to its maximum is called as Λ max. Λ max of a substance is characteristic feature of the drug and cannot be changed easily. To find out the Λ max of azithromycin, a stock solution of 1 mg/ml was prepared by dissolving 100 mg of drug in small quantity of methanol and diluted with 100 ml of phosphate buffer (pH 6.8). The stock solution was serially diluted to get solutions in the range of 2-12 µg/ml and Λ max of the solution was found out by scanning from 200 - 400 nm.

Determination of Calibration Curve

A stock solution of 1 mg/ml of Azithromycin was prepared by dissolving 100 mg of drug in small quantity of methanol and diluted with 100 ml of phosphate buffer (pH 6.8). The stock solution was serially diluted to get solutions in the range of 2-20 µg/ml. The absorbances of the different diluted solutions were measured in a UV-Visible spectrophotometer at 210 nm. A calibration curve was plotted by taking concentration of solution in X axis and absorbance in Y axis and correlation coefficient ‘r’ was calculated.

Determination of melting point:

Melting point of the drug was determined by taking a small amount of the drug in a capillary tube that was closed at one end. The capillary tube was placed in thermionic melting point apparatus and the temperature at which the drug melt was noted. Average of three readings was taken.

Drug excipients interaction study by FTIR

FTIR emission spectrometer (Shimadzu, Japan) was used to record the FTIR spectrum of the drugs from 400 to 4000 cm−1 to confirm compatibility between the excipients used and pure drug in the formulation. FTIR spectra of pure drug, along with physical mixture of polymers and drug were taken separately. The sample was grounded with KBr and pressed to a suitable size disk for measurement.

Preparation of drug nanosuspensions by nanoprecipitation technique

The nanoparticles were prepared by nanoprecipitaion method by using different stabilizers as shown in table 1. Accurately weighed quantities of HPMC and drug were dissolved in 5 mL of acetone. This organic phase was injected drop wise (using a syringe) into three beakers containing 20 mL of distilled water along with varied concentrations of stabilizer like Poloxamer 188 with moderate magnetic stirring at room temperature. Nanoparticles were spontaneously formed and turned the solution slightly turbid. Then, acetone was removed by continuing stirring for 4 hrs. The prepared suspension was centrifuged at 5,000 rpm at for 2 hours. The supernatant liquid was removed and the sediment nanosuspension was dried for 48 hrs and used for further analysis. The same was repeated using different concentrations of stabilizers like poloxamer 407 and PVP, for preparation of nanosuspensions.

Formulation of nanosuspensions

**Table 1: Formulation Table of nanosuspensions**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Ingredients (gm)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
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<tbody>
<tr>
<td>AZITHROMYCIN</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
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<tr>
<td>HPMC</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>POLOXAMER 188</td>
<td>0.12</td>
<td>0.18</td>
<td>0.24</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>POLOXAMER 407</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.12</td>
<td>0.18</td>
<td>0.24</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>PVP</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.12</td>
<td>0.18</td>
<td>0.24</td>
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<tr>
<td>ACETONE</td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
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<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
<td>5ml</td>
</tr>
<tr>
<td>DISTILLED WATER (q.s)</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
<td>25ml</td>
</tr>
</tbody>
</table>

Differential Scanning Calorimetry (DSC)

The amount of product to be analyzed shall range from 3 to 5 mg and be placed in perforated aluminium sealed 50 µl pans. Heat runs for each sample were set from 5 °C to 300°C using nitrogen as purging gas and the samples were analyzed.

Scanning electron microscopy

Particle morphology and shape was observed using scanning electron microscopy. The samples were fixed on an SEM stub using double-sided adhesive tape and coated with platinum at 50 mA for 6 min through a sputter-coater. A scanning electron microscope with a secondary electron detector was used to obtain digital images of the samples at an accelerating voltage of 20 kV.
In Vitro Dissolution Studies

Dissolution tests were performed using a rotating paddle apparatus with an Electro lab dissolution system at 37°C and rotating speed of 50 rpm in 900 ml of phosphate buffer pH 6.4. Nanosuspensions equivalent to 100 mg of azithromycin was hand filled into a capsule and placed in each dissolution vessel. At predetermined time intervals, 5 ml of dissolution medium was withdrawn and the same volume of pre-thermostated fresh medium was added to maintain sink conditions. The amount of azithromycin released was calculated using calibration curve and plotted against time and compared with pure drug.

X-ray diffraction studies (XRD)

XRD diffractograms of the raw drug and the processed drug formulations were recorded using a Siemens Diffractometer D5000 (Siemens, Germany) with Ni-filtered Cu Kα radiation. The 2θ scan range was 5–600 with a step size of 0.020 and the scan speed was 30 min\(^{-1}\).

DISCUSSION

\(\lambda_{\text{max}}\) of azithromycin dihydrate at 210 nm in pH 6.8 phosphate buffer

From the stock solution, 1 mg/ml azithromycin dihydrate in pH 6.4 phosphate buffer, suitable dilutions were made with distilled water to get a concentration 12 μg/ml and scanned for maximum absorbance using UV - visible spectrophotometer in the range from 200 - 400 nm. The absorption maximum was found to be 210 nm and hence the same was used as \(\lambda_{\text{max}}\) for the estimation of azithromycin dihydrate (Figure 2).

Calibration curve of azithromycin dihydrate

The stock solution of azithromycin dihydrate in pH 6.4 phosphate buffer and further dilution in distilled water showed good linearity (r\(^2\) = 0.999) over the concentration range of 4- 20 μg/ml at \(\lambda_{\text{max}}\) 210 nm. (Table 2 and Figure 3).

Melting point determination

The melting point of azithromycin dihydrate was determined by capillary method. The melting point of azithromycin dihydrate was found to be 114 °C (Table 3). It complies with standards thus indicating the purity of the drug sample.

FTIR studies

FTIR was performed for the pure drug, HPMC, PVP, Poloxamer 188, Poloxamer 407 and physical mixture of drug and polymers to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic peaks of the compound.

The IR spectra of the pure azithromycin dihydrate (figure 4) had shown characteristic peaks at 3083.38 due to CH aromatic stretch, 3335.62 due to NH secondary stretch, 1718.26 cm\(^{-1}\) due to C=O stretch and 1248.86 cm\(^{-1}\) due to C-N stretch and CH\(_3\) rock.

The IR spectra of the physical mixtures of pure drug along with Poloxamer 188, Poloxamer 407 and PVP, HPMC (Figure 4 overlay) were also recorded and the spectra showed the presence of characteristic peaks of both pure azithromycin dihydrate and polymers, thereby confirming the compatibility between them.

The IR spectra showed neither shift nor disappearance of characteristic peaks suggesting that there was no interaction between drug and excipients used for preparation of nanosuspensions.

Differential scanning calorimetric analysis

Figure 5 reveals the thermal behaviors of the pure components together with the thermal behavior of the excipients.

Evidence of interactions between pure drug and excipients used in the solid state can be obtained using thermal analysis. Azithromycin dihydrate peaks are clear in its DSC thermogram (Figure 4) demonstrating a sharp characteristic endothermic peak at 115 °C, which is within its melting temperature range(Tm); such endothermic peak signifies that azithromycin dihydrate used was in pure crystalline state.

DSC thermogram of the physical mixture of azithromycin dihydrate with PVP, Poloxamer 188, Poloxamer 407 and other excipients demonstrated the presence of endothermic peaks, at their respective melting ranges of azithromycin dihydrate and excipients indicating not much interaction between them.

SEM Studies

Morphology of precipitated drug particles in the nanosuspension after drying is shown in Figure 6. The drug particles precipitated with the Poloxamer 407 as stabilizer are spherical in shape and the size ranges from 150 to 500 nm. The particles are discrete and uniform in size and there is no sign of agglomerations. The drug particles precipitated with the PVP and poloxamer 108 as stabilizer are slightly bigger and spherical and somewhat cuboidal and the size ranges from 300 to 600 nm.

In-vitro drug release profile

In vitro release studies were carried out using USP type II tablet dissolution test apparatus paddle method at 37±0.5 °C, taking 900 ml of pH 6.4 phosphate buffer as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 5 ml were withdrawn at a regular interval of 15 minutes and analyzed spectrophotometrically at 210 nm. The in vitro dissolution profiles of all the 9 formulations using three different concentrations of stabilizers like poloxamer 188, poloxamer 407 and PVP prepared by nanoprecipitation technique in three molar ratios of 1:1, 1:3 and 1:5 of azithromycin dehydrate and poloxamer 188, poloxamer 407 and PVP (Figure 7) indicated faster drug release from
all the formulations and the maximum drug release was from formulations F6. Formulation F6 prepared by nanoprecipitation method including pure drug and poloxamer 407 in ratios of 1:5 showed 79.29% drug release at the end of 180 min when compared to nanosuspensions prepared using stabilizers like poloxamer 188 and PVP (Figure 8).

XRD Data
The XRD results were in good agreement with the thermal analysis data. X-ray diffraction patterns in Figure 9, revealed that pure azithromycin dihydrate was clearly in crystalline state as it showed sharp distinct peaks notably at 2θ diffraction angles of 9.97°, 17.04°, 18.74°, 19.40°, 21.63°, 23.94°, 25.16°, 27.96° and 29.28°. X-ray diffraction pattern of nanosuspensions prepared by nanoprecipitation technique using three different stabilizers like poloxamer 188, poloxamer 407 and PVP showed sharp distinct peaks at 2θ diffraction angles of 12.4º, 19.0º, 17.04°, 18.74°, 19.40° for azithromycin dihydrate and stabilisers (Figure 9). The complex formation led to the sharpening of the existing peaks, appearance of a few new peaks and shifting of certain peaks, which could mean changes in the peaks of pure drug lead to improvement in solubility.

TABLES AND FIGURES

λmax of azithromycin dihydrate at 210 nm in pH 6.8 phosphate buffer

![UV Spectrum of azithromycin dihydrate](image2)

**Figure 2:** UV Spectrum of azithromycin dihydrate

Standard calibration curve of azithromycin dihydrate in pH 6.8 phosphate buffer at λmax of 210 nm

**Table 2:** Standard calibration curve of drug

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Concentration(μg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0.148</td>
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<tr>
<td>2</td>
<td>8</td>
<td>0.379</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>0.582</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>0.797</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>0.951</td>
</tr>
</tbody>
</table>

![Standard calibration curve of drug](image3)

**Figure 3:** Standard calibration curve of drug

Table 3: Melting point determination of azithromycin dihydrate

**Melting point determination of azithromycin dihydrate**

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Melting point(°C)</th>
<th>Average of three readings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>118</td>
<td>114</td>
</tr>
</tbody>
</table>
FTIR Studies

Figure 4: FTIR overlay showing FTIR studies on pure drug, pure drug + HPMC, Pure drug + Poloxamer 188, Pure drug + Poloxamer 407, Pure drug + PVP from bottom to top

Differential scanning calorimetric analysis

Figure 5: Differential scanning calorimeters of Pure drug formulation f3, formulation f6 and formulation f9 from bottom to top
**Scanning Electron Microscopic studies**

*Figure 6:* Scanning Electron Microscopic studies showing SEM photographs of formulation F3, formulation F6 and formulation F9 from top to bottom

**In-vitro dissolution studies**

*Figure 7:* Comparative In Vitro Dissolution profile

*Figure 9:* XRD Diffractograms of Pure drug, Formulation F3, Formulation F6 and Formulation F9

**CONCLUSION**

Any drug from a given dosage form to be absorbed must be present in the form of solution at the site of absorption. Low aqueous solubility is one of the major problems encountered during formulation development of new chemical entities especially in the process of generic product development. More than 40% new chemical entities developed in pharmaceutical industry are practically insoluble in water. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug like particle size reduction, crystal engineering, and salt formation, and solid dispersion, use of surfactant, complexation, and so forth.

Therefore, in this present study, an attempt was made to formulate nanosuspensions of azithromycin dihydrate, a...
poorly water soluble BCS class-II macrolide antibiotic by nanoprecipitation method with three different stabilisers in three different concentrations like 1:1, 1:3 and 1:5 of poloxamer 188, poloxamer 407 and PVP and objective of the study was to evaluate activity and role of stabilisers in the formulation of nanosuspensions. Thus, by formation of nanosuspension using different stabilisers, the bioavailability of azithromycin dehydrate can be greatly improved. The prepared nanosuspensions were characterized by Differential Scanning Calorimetry (DSC), X-ray diffractometry (XRD), Fourier transform infra-red (FT-IR) spectroscopy, Scanning Electron Microscopy (SEM) images, In – Vitro dissolution profile. FTIR studies and DSC studies confirmed that there was no distinguishable physical or chemical interaction between drug and excipients used for this study of nanosuspension formulations. SEM images showed the surface morphology by of the prepared nanosuspensions to be accurate and size of nanosuspensions to be in nanometers. XRD data confirmed the crystallinity of the drug and slight changes in the crystallinity of azithromycin dihydrate in the formulations of nanosuspensions, to which improvement in solubility pattern can be attributed. Nanosuspensions containing azithromycin dihydrate and poloxamer 407 in molar ratios of 1:5, which are prepared by nanoprecipitation method, were selected to be the best and can be used for further formulation and studies based on their drug release profiles. All the nanosuspension formulations showed more than 60 percentage drug release within 180 minutes, which was far better when compared to drug release profile of pure drug. By this study, it can be concluded that poloxamers can be used as a better stabilisers in the formulation of nanosuspensions. The oral bioavailability of the drug could be improved by this methodology by more than two times due to improved aqueous solubility when compared to pure drug. This methodology of nanosuspension using proper ratios of drug: stabilizer can be further exploited for the successful delivery of poorly water soluble compounds

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REFERENCES

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