A Broad Spectrum Formulation Platform for Sustained Release of Silica-Based Ordered Mesoporous SBA-15 Ketoconazole Composite

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ABSTRACT

In this aid we describe the preparation, loading and sustained release of SBA-15-Ketoconazole composite. Silica-based ordered mesoporous material (SMM) called SBA-15 is synthesized and loaded with ketoconazole by incipient wetness method and characterized by UV-visible spectrophotometer and small angle powder X-ray diffraction (PXRD). The successful invading of Ketoconazole in host material SBA-15 was confirmed by UV-visible spectrophotometer with high encapsulation efficiency 72.67% in the composite material. The controlled release effect of the Ketoconazole drug in fluid was studied by examining the drug release profile of composite into simulated gastric fluid. The composite showed sustained released with higuchi model. So, this high loaded silica based composite are used as a womb for sustained delivery of Ketoconazole drug to in order to improve the release of ketoconazole in its preferential absorption region.

Keywords: Silica; Ketoconazole; Composite; Release mechanism; Mesoporous SBA-15

INTRODUCTION

Therapeutic effectiveness of many drugs is frequently diminished because of their poor bioavailability and pharmacokinetics, mainly due to its modest solubility. Ketoconazole is a poor water soluble antifungal drug which is used to treat skin infections. Ketoconazole has low bioavailability and randomized pharmacokinetic profile. High dose levels of ketoconazole result in teratogenesis when administered in high doses where its oral administration may cause severe liver injuries and adrenal gland problems [1]. Therefore, there is a need for the development of drug delivery systems (DDS), which is able to improve its release in its targetable absorptive region by the enhancement of drug bioavailability with fewer side effects.

A drug delivery system (DDS) should be biodegradable, biocompatible, controlled and minimum premature release rate with high loading. Nanotechnology provide a novel drug delivery system with unique advantages which enhance therapeutic activity by increasing bioavailability and hydrophobic drug solubility, reducing side effect by controlled and sustained drug release. A wide range of nanoparticles (polymeric, liposome, dendrimers, carbon, ceramics and silica etc.) has been used, to create a novel drug delivery system [2, 3]. Among all nanoparticles SMMs (Silica-based ordered mesoporous material) have the potential to create NCDDS (novel and control drug delivery system). Silica-based ordered mesoporous material (SBA-15), have as an attribute to act as a strong and contractive womb for drug delivery due to their specific leases such as a simple synthesis technique, tunable pore size, pore surface area and surface chemistry [4-6], and in vivo biocompatibility and biodegradability [7]. For this reason, SBA-15 is the first choice among all nanoparticles because they can adsorb as well as invade the drug
molecules by forming weak hydrogen bonding which can be easily broken in biological fluids allowing a rapid drug release [8].

In this paper, SBA-15 is engaged to create a new sba-15-ketoconazole composite to promote its release with fewer side effect in the targetive region.

**EXPERIMENTAL SECTION**

**Reagents used for the synthesis of SBA-15**

Pluronic P123 [ethylene oxide–propylene oxide–ethylene oxide (EO20PO70EO20), Mw= 5800], tetraethoxy orthosilicate [(C2H5O)4 Si, TEOS], and HCl (35%) were procured from Sigma-Aldrich. Reagents used for the preparation of human simulated gastric fluid (SBF): Phosphate buffer solution (PBS), HCl (hydrochloric acid), NaCl (sodium chloride), KCl (potassium chloride), KH2PO4 (potassium dihydrogen phosphate), NaOH (sodium hydroxide), Na2HPO4 (di sodium hydrogen phosphate) were procured from Merck, India. Ketoconazole is purchased from himedia research lab pvt. Lmt., Mumbai.

**Synthesis of SBA-15 matrix**

The synthesis of mesoporous silica was performed by following our earlier reported work [9]. In a typical process, initially 4 g triblock copolymer, P123 was dissolved in 140 ml distilled water at 40°C under high acidic conditions produced by the addition of 20 ml HCl (2 M). A clear solution was achieved after 3 h of continuous mechanical stirring of the solution. Then, 9.6 ml TEOS was added to the above mentioned solution followed by continuous stirring for another 24 h at 40°C. Thereafter, the solution was transferred to a Teflon lined stain-less steel autoclave and hydrothermally treated at 100°C for 24 h. After cooling down to room temperature, the solid products were filtered, washed and dried at 70°C. Finally, the solid product was calcined at 600°C with a heating rate of 1°C/min for 4 h in air to remove organic templates and to obtain mesoporous powder form SBA-15 (Figure 1).

**Ultraviolet absorption maxima (λmax)**

10 mg of Ketoconazole was dissolved in 100 ml of ethanol in a volumetric flask to yield stock solution with concentration of 100μg/ml. This solution was diluted with ethanol to get a concentration of 10μg/ml of Ketoconazole. The solution was scanned in the wavelength range of 200-800 nm on UV–VIS spectrophotometer for identifying λmax.

**Standard curve of ketoconazole in ethanol**

Standard curve of Ketoconazole was prepared by using stock solution (100μg/ml) in ethanol. In order to obtain standard graph, different aliquots of Ketoconazole solution were diluted with ethanol in order to obtain solutions with concentrations ranging from 10-100 μg/ml. The UV-Vis absorption intensity was measured at 244 nm against ethanol used as a blank. The linear relationship between intensity and Ketoconazole concentration was obtained in the range of 10 to100 μg/ml (Figure 2).
Drug Loading
The loading of Ketoconazole was achieved by incipient wetness method. 200 mg of SBA-15 was impregnated with 850 mL of a 50 mg/mL drug solution in ethanol under stirring for 24 h. This SBA-15-Ketoconazole composite was obtained by centrifugation (15000 rpm at 4° C for 1 h) and preserved under vacuum at room temperature for further characterization. Loading, release and characterization of ketoconazole from SBA-15-Ketoconazole composite
The amount of drug entrapped was determined by centrifuging the solution and supernatant was analyzed for drug content spectrophotometrically by measuring the absorbance at 244 nm in UV Spectrophotometer (Shimadzu UV 2450). In order to determine the percentage release and drug release kinetics, 15 mg of each nanocomposite was suspended into 250 mL of phosphate-buffered saline at pH 1.2. A quantity of medium solution (5 mL) was removed for analysis at given time intervals and replaced with 5 mL of the same buffered solution. The % released of ketoconazole into the solution was measured at different time intervals using an ultraviolet-visible spectrophotometer at 244 nm.
Powder small-angle (PXRD) patterns were obtained on a Bruker D8 advance diffractometer using Cu-Kα as target material. For small-angle analysis; signal was recorded from 1° to 4° with a scanning step of 0.01° and a time per step of 10 s.

RESULTS AND DISCUSSION

Drug loading efficiency
The spectrophotometry was used for calculating the entrapment efficiency of ketoconazole in the SBA-15-Ketoconazole composite using equation no.1.

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\text{% Encapsulation Efficiency} = \frac{\text{Total drug} - \text{free drug}}{\text{Total drug}} \times 100 \quad (1)
\]

The low angle XRD (LAXRD) spectra for SBA-15 and composite are shown in Fig. 2. Three well resolved peaks are (1 0 0), (1 1 0), (2 0 0) obtained in pure SBA-15 and indicate the hexagonal mesoporous structure of SBA-15. The decline of 1 1 0, 2 0 0 and steeply decrease intensity of 100 in SBA-15-Ketoconazole composite should be due to the pore filling of mesoporous SBA-15 with the drug.

In-vitro release of ketoconazole
The in-vitro drug release profile of Ketoconazole up to 120 hours is shown in fig. 3. The composite material shows high drug loading most of which present inside the pore of SBA-15 and very small amount on the surface. All over the 120 h in SGF the amount of drug release is longer and controlled in nature. In 120 h the release ratio of ketoconazole drug already achieved 99.4%. At last release ratio was retained at 100.0%. After 120 h, controlled release basically finished (Figure 3).
Drug release mechanism
The in vitro diffusion of Ketoconazole drug from composite into the simulated gastric fluid is evaluated [10]. SBA-15 is porous in nature and silanol groups are present inside and outside the surface of SBA-15 and drug form the weak hydrogen bonding with these silanol groups [11-12]. In this case of porosity matrix, the release of impregnated drug occurs through penetration of acidic medium into pores of the matrix. The drug slowly dissolves into the permeating acidic medium by leaving the silanol group and drug diffuse out from the mesoporous system [13]. Therefore, these results propose a clear effect of the pore size on diffusion behavior.

CONCLUSION
In summary, successful invading of ketoconazole in womb SBA-15 was estimated. This thermo stable womb also gave sustained delivery of drug which will reduce its cytotoxicity and improve the drug therapeutic effectiveness. This SBA-15-Ketoconazole composite will improve bioavailability and regularized the random pharmacokinetic profile of this hydrophobic drug. So, Ketoconazole will be a safe, targetable and long range fighter against its relative fungal and of skin diseases.

REFERENCES