Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
5(2), 2016, 116-121

ISSN 2321 – 0958

Original Research Article

MESOPOROUS SILICA SOLID DISPERSION CARRIER SYSTEMFOR SCANTY WATER SOLUBLE DRUG TO ESTABLISH CLINICAL DOSAGE FORMS

P Ambedkar* and Dr.E Harikrishna

Department of Pharmaceutics, Bharat Institute of Technology, Mangalpally (V),
Hyderabad Telangana 501510

Abstract: Mesoporous MCM-41 is one of the mesoporous materials, used now-a-days as drug carrier. Itraconazole (ICZ) is a highly hydrophobic, BCS System class II drug.ICZ on oral administration results in poor bioavailability and inters individual variations in plasma drug concentrations due to poor aqueous solubility. Proximate target of the present study is to ameliorate the dissolution and bioavailability of Itraconazole by formulating the solid dispersions using mesoporous material as a carrier (MCM-41).

Itraconazolesolid dispersions were prepared by solvent evaporation method polyethylene glycol-4000, 6000, polaxomer-407, HPMC, Gelucire 50/13, Gelucire 44/14, and mesoporous silica (MCM-41), among all the carriers mesoporous silica has delineated good results and exhibited dissolution enhancement confronts with the Itraconazole plain drug and marketed product. Stability was performed according to the ICH guidelines, accelerated, intermediate, and long term in stability results clearly demonstrated that mesoporous silica solid dispersions were stable.

Key Words: Itraconazole, mesoporous silica, solubility, solid dispersions and gelucire

Introduction: Oral delivery is still the preferred route for drug administration, because of Good patient compliance, Low invasive nature, Easy of administration and Low cost of manufacturing processes.

Many active pharmaceutical ingredients (API'S) show inadequate physicochemical (aqueous solubility, stability) and or biopharmaceutical (dissolution rate, permeability) properties which limits their bioavailability significantly[(1)].

The solubility behavior of drugs remains one of the most challenging aspects in formulation development, with the advent of combinatorial chemistry and a high throughput screening the number of poorly water soluble compounds has

For Correspondence:
ambiarticle@gmail.com
Received on: June 2016
Accepted after revision: June 2016
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increased solubility, a success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends on the bioavailability and ultimately upon the solubility of drug molecules especially in oral formulation poorly water soluble drugs after oral administration often require high dose in order to reach therapeutic concentration[2].

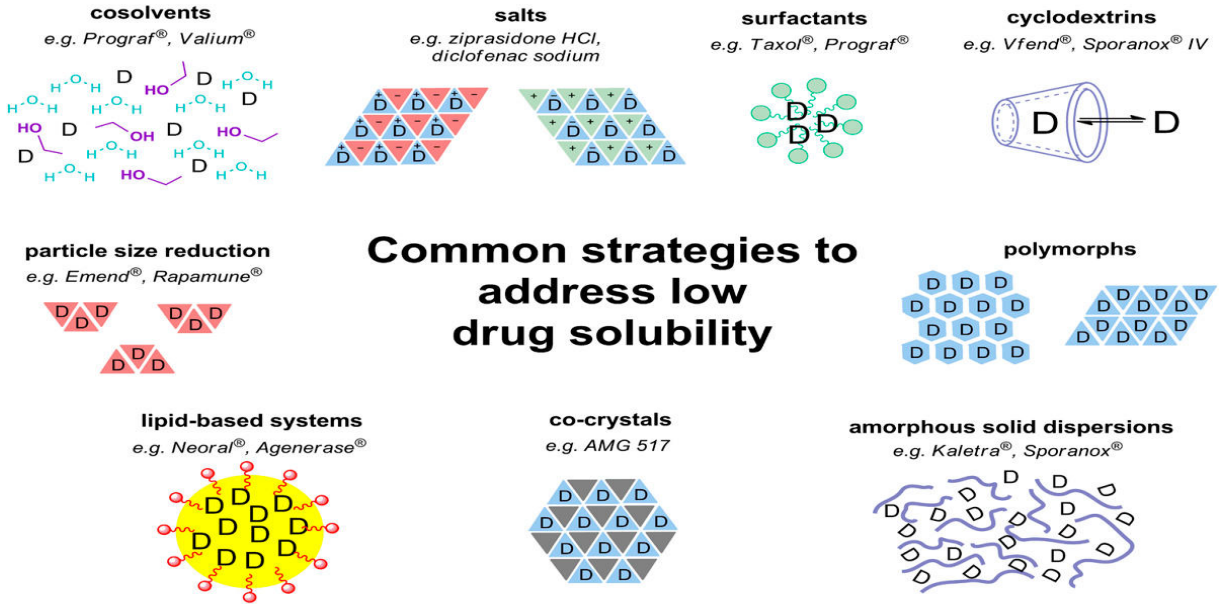

Fig.1. Common strategies to address low drug solubility [3]

Materials: Itraconazole was obtained as a gift sample from M.S Theredose Pharmaceuticals Hyderabad. Mesoporous silica was obtained from Merck chemicals, Mumbai. Polyethylenes glycol, Polaxomer-407, Gelucire 44/14, Gelucire 50/13 and Dichloromethane was obtained from Merck chemicals, Mumbai.

Methods: Experimental design:

Experiment-I: Screening of different solid dispersion carriers for improved dissolution rate

Experiment-II: Characterization, Stability of final formula

Experiment-I: Screening **of different solid dispersion carriers for improved dissolution rate:** The solubility of Itraconazole was determined in the following organic solvents in order to select appropriate solvent for formulation of solid dispersion, 1ml of each organic solvent was taken in the test tubes to this 10mg packets of Itraconazole was added until it gets saturated and kept it equilibrium shaker of 24 hrs, the solution was centrifuged and spectrophotometrically estimated at 255 nm [4]

Solid dispersions were prepared using different polymers like Polyethylene glycol-4000, Polyethylene glycol-6000, Polaxomer-407, Hydroxy Propyl methyl cellulose, Gelucire 50/13, Gelucire 44/14, Polyethylene glycol-4000&6000, and mesoporous silica. Solvent evaporation was selected as a method of preparation of solid dispersion and dichloromethane selected as solvent for dissolving the both drug and polymers. Solid dispersion were prepared in three different ratio's by keeping the weight of the drug constant and changing the weight of the polymers from 100 mg to 300 mg.

S.No	Polymer	Ratio's Drug: polymer	Weight of drug	Weight of polymer
1	PEG-4000	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg
2	PEG-6000	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg
3	Polaxomer-407	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg
4	HPMC	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg
5	Gelucire 50/13	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg
6	Gelucire 44/14	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg
7	PEG-4000& PEG-6000	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg
8	Mesoporous silica	1:1 1:2 1:3	100 mg 100 mg 100 mg	100 mg 200 mg 300 mg

Table: 1: List of polymer with the ratios

Method of preparation: Solvent evaporation: Procedure for formulation of solid dispersion (Solvent Evaporation): Accurately weighed 100mg of Itraconazole and dissolved in 10 ml beaker containing 5 ml of dichloromethane, simultaneously 100 mg, 200 mg, 300 mg each carrier was weighed accurately and dissolved in 10 ml beaker containing 5 ml of dichloromethane, the drug solution was added to polymer solution, the above solution poured into the petriplate and evaporated on water bath at 60^{o}C temperature then it was kept in desiccators for 24 hr until the residual solvent was evaporated.

Invitro Characterization: Experiment-II: characterization, Stability of final formula

Drug Content: Solid dispersions equivalent to 10mg were weighed accurately and transferred to the 25ml beaker which previously consists of 10ml of simulated gastric fluid without pepsin pH 1.2 and they were ruptured with a glass rod and kept for 2hrs a side, from the above solution dilutions were made and measured using UV.Visible spectrophotometer at 255nm.

FT IR spectroscopy: About 1 mg of sample added to 99mg of potassium bromide and grounded well. These quantities are suitable for a disc in 13 mm diameter. The grounded powder was compressed to pellet using hydraulic KBr press under vacuum at a pressure of about 800 Mpa. The resultant pellet was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and IR spectra of samples were recorded from 600-4400 cm^{-1} in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes[(5)].

PXRD analysis: pXRD patterns of Itraconazole, mesoporous silica, physical mixture, and optimized formulation were obtained on a powder XRD D-5000 semen's X-ray diffractometer, using Ni-filtered Cu K_a radiation (Wave length=1.5406 A^{o}). The data were recorded over a scanning 2θ range of 2^{o} to 50^{o} at step time of 0.030 steps/0.5 sec (6). The relative intensity I/I^{o} inter planner distance (d) corresponding to the 2θ values was reported.

In-vitro Dissolution Study: The dissolution rate of Itraconazole solid dispersion were performed by USP apparatus II (paddle veegam model xxxx dissolution system using simulated gastric fluid (SGF) without pepsin at P^{H} 1.2).solid dispersion equivalent to 20mg were taken and were added to each dissolution vessel containing 900 ml dissolution medium (Simulated gastric fluid without pepsin pH 1.2), bath temperature and paddle rotation speed were maintained at 37°C and stirred at 100 rpm. Samples were collected periodically at required time interval and replaced with the fresh dissolution medium. After collection of all the samples were analyzed spectrophotometrically at 255 nm using UV.Visible spectrophotometer (Perkin Elmer). The data treatment was done for each and every sample to determine the

percentage of drug release and determination of release kinetics[7].

Stability: Stability was performed in stability chambers according to the ICH guidelines such as long term, accelerated, intermediate and % of drug remaining was analyzed using U.V Visible spectroscopy[8].

Results and Discussion: FTIR Spectroscopy:

The IR spectra's of plain Itraconazole showed characteristic peaks at 400-1800cm-1. They might have arisen from the stretching and vibrations of functional groups such as –C=C- of aromatic groups. A peak observed at 1600-1800 cm-1 can be attributed to –C=O stretching and vibration, whereas peaks for alkane and amine groups were noticed at 2800-3200 cm-1. Peak of mesoporous silica has shown characteristic peaks at between 790 & 3400cm-1 representing the characteristic peaks of mesoporous silica. The same peaks were seen in the spectra of formulation also. Also the major peaks observed for Itraconazole before and after the preparation of solid dispersion formulation at 400-1800cm-1 were almost super imposable. This suggested the absence of any significant interactions between Itraconazole and excipients used to make the solid dispersion formulation.

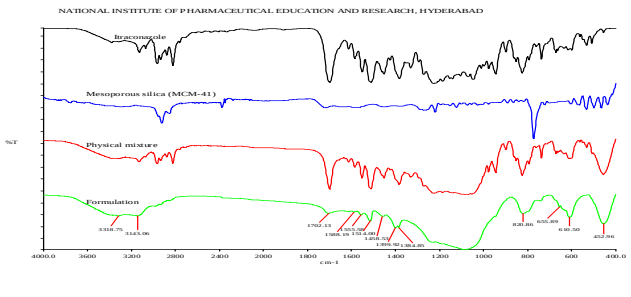

Fig 2: FTIR Spectroscopy of Itraconazole, mesoporous silica, physical mixture, formulation

PXRD analysis: PXRD of Itraconazole shows numerous sharp peaks, indicative of its crystalline nature. It shows intense peak at d = 5.086 and some other characteristic peaks observed. Mesoporous silica shows characteristic peak at d = 23.98. Physical mixture shows characteristic peaks of Itraconazole at d = 5.085, 4.195 and shows characteristic peaks of mesoporous at d = 22.26. Formulation shows characteristic peak of mesoporous silica at d = 22.924 but intensity was decreased which may be due to reduction of size during formulation. There exists a possibility of conversion of drug to amorphous form during formulation.

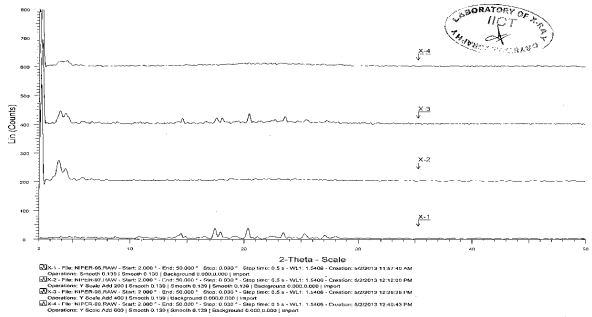

Fig: 3 PXRD Patterns of Itraconazole, mesoporous silica, physical mixture, formulation

Invitro Dissolution Studies

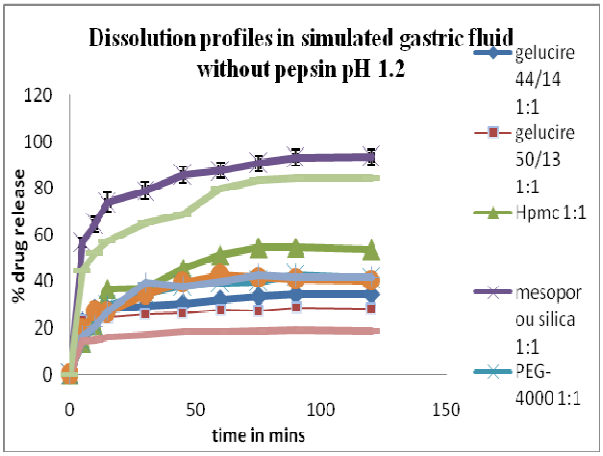

Fig 4: Dissolution profile of the different solid dispersion carriers (1:1) along with the plain drug and marketed product

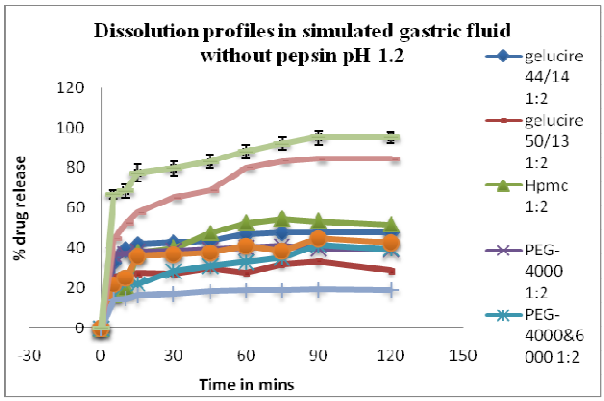

Fig 5 Dissolution profile of the different solid dispersion carriers (1:2) along with the plain drug and marketed product

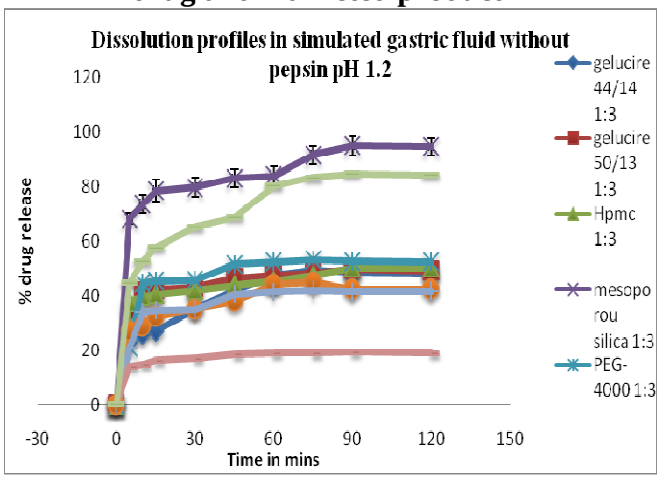

Fig 6 Dissolution profile of the different solid dispersion (1:3) carriers along with the plain drug and marketed product

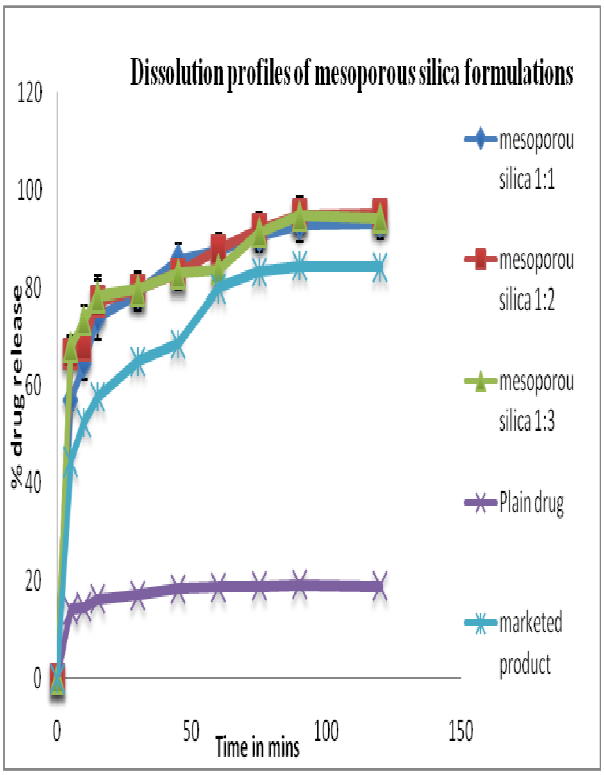

Fig 7 Dissolution profile of the different solid dispersion carriers along with the plain drug and marketed product

Discussion: In-vitro dissolution was performed in USP dissolution apparatus II in simulated gastric fluid without pepsin pH 1.2, results showed that solid dispersions prepared with mesoporous silica having better dissolution rate than plain drug and marketed product and 60% of drug was released in 5-10 mins.

Stability Data Table

Table: 2 Stability data

Stability conditions		**% of remaining**	
Temperature	**Relative humidity**	**Initial**	**After 1 month**
25°C	60%	100	98.0
30°C	65%	100	97.72
40°C	75%	100	97.08

Discussion: stability was performed according to the ICH guidelines and the stability conditions were accelerated, intermediate, and long term and stability results showed that formulation were stable

Conclusion: Utilization of mesoporous silica in the enhancement of oral bioavailability of poorly soluble drugs has become prominent. Solid dispersion of mesoporous silica in three different ratios results authenticated enhanced dissolution rate when compared to solid dispersion of polyethylene glycol, poloxamer, hpmc, Gelucire 50/13, Gelucire 44/14, and alsoauthenticatedaugmented dissolution rate correlate with plain drug and marketed product.

The results of the current study suggest that solid dispersions of Itraconazole prepared by the solvent evaporation method with various polymers, polyethylene glycol, poloxamer, hpmc, Gelucire 50/13, Gelucire 44/14 can be used to enhance the solubility and subsequent dissolution rate of this poorly soluble drug.

Stability studies clearly manifested that mesoporous solid dispersions were stable. Mesoporous silica (MCM-41) is the best platform for the improving the solubility of poorly water soluble drugs.

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