International Journal of Research in Social Sciences
Vol. 10 Issue 06, June 2020,
ISSN: 2249-2496 Impact Factor: 7.081
Journal Homepage: http://www.ijmra.us, Email: editorijmie@gmail.com
Double-Blind Peer Reviewed Refereed Open Access International Journal - Included in the International Serial Directories Indexed & Listed at: Ulrich's Periodicals Directory ©, U.S.A., Open J-Gate as well as in Cabell's Directories of Publishing Opportunities, U.S.A

SOLID DISPERSIONS AND THE MICROMETRIC PROPERTIES EVALUATION OF THE ITRACONAZOLE DRUG

Neetu Verma[1], Dr. K Saravanan (Professor)[2]
Department of Pharmacy
[1,2]OPJS University, Churu, Rajasthan

Abstract

The current research study formulate and assess solid dispersions of Itraconazole in two ways, first by forming an inclusion complex and then Itraconazole complexes were blended with Captisol through the kneading method, co-evaporation and physical mixture technique, and secondly, mixed hydrotropic solid dispersion was employed by using sodium benzoate, niacinamide and PEG 4000 as a hydrotropic agent for enhancing the solubility of the drug Itraconazole in an aqueous medium. The micrometric properties of Itraconazole Hausner ratio (1.843), Carr index (46.46, angle of repose (51.056^0), and bulk density (0.176 g/mL) showed that the drug has very poor flow characteristics in its pure state.

Keywords*: Itraconazole, solubility, micrometric properties.*

1.0. Introduction

The development of drugs is hampered by the poor water solubility of drug compounds (1). When given orally, it may also result in delayed breakdown in biological fluids, limited and unpredictable systemic exposure, and subpar patient effectiveness. For absorption to take place, it is necessary for the medicine to be present in the aqueous solution at the site of absorption. To transport a drug to the systemic circulation after oral administration, solid dosage forms must dissolve in gastro intestinal fluids. The solubility of the pharmacological material in the surrounding media affects how easily it dissolves. Contrary to non-polar solutes, polar drugs are more soluble in water than in organic phases. The solubility of ionized species in water is higher than that of their unionized counterparts. Therefore, "pH affects the total solubility of acids or bases in aqueous media. The drugs with low water solubility often have a slower oral absorption rate than those with high aqueous solubility for drugs that are absorbed through passive diffusion" (2).

The discovery of several recently manufactured drugs falling under "Biopharmaceutical Classification System (BCS) classes II, III, and IV" has prompted research in the field. "The US Food and Drug Administration (FDA)" established the biopharmaceutics categorization system, categorizing drugs based on permeability and solubility (3). The rate at which a drug penetrates the intestinal epithelium, determined by its physico-chemical characteristics, can be a limiting factor for systemic circulation. Drugs in BCS classes II and IV face challenges due to poor solubility, leading to low oral bioavailability. This study aims to enhance the bioavailability and solubility of Itraconazole, a BCS class II compound with low water solubility, using solid dispersion and hydrotrophic solubilization methods (4).

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2.0 Material and method

MICROMETRIC STUDIES-

Itraconazole micromeritic properties have been studied to learn more about the drug's powder properties, flow property, and compressibility. In the following sections, we will describe how to measure various parameters (5).

A. Bulk density-

The determination was made utilizing an EI-Instruments tap densitometer apparatus. A weighing scale with graduations, having a capacity of 25ml, was employed to accurately measure and add a quantity of 3g of the pure drug. In order to remove the particles adhered to the inner wall of the cylinder, a gentle tapping motion was applied to the cylinder on two occasions.

B. Tap density- A graded cylinder was tapped 100 times with a tap densitometer to ensure that the volume remained constant. The tapped volume is the volume measured after draining directly from the measuring cylinder. Using the following formula, the tapped density was calculated from the tapped volume.

C. Hausner's ratio- The densities of the powdered substance were measured in both bulk and tapped states in order to determine their values.

Table 1: Standard value for Hausner's ratio

"Hausner's ratio = Tapped density/ bulk density"

Flow Character	Hausner's Ratio
Excellent	1.00 - 1.11
Good	1.12 - 1.18
Fair	1.19 - 1.25
Passable	1.26 - 1.34
Poor	1.35 - 1.45
Very poor	1.46 - 1.59

D. Percentage Compressibility index (Carr's Index)- There is a theory that the compressibility index can be used as a proxy for the bulk density of a material, given that all of these factors influence the reported compressibility of the index. Utilizing the powder's bulk and extracted volumes, this value is determined.

3. Result and discussion

The micromeritic properties were examined to determine the particle features, flow property, and compressibility. Formulation development is influenced by several interconnected parameters, namely density, porosity, compressibility, and flow characteristics. The presence of a non-free-flowing powder can be attributed to a range of forces, such as cohesive/Van der Waals forces and mechanical forces arising from uneven surface topography and frictional interactions. In addition to variations in particle size, density, charge, shape, and adsorbed moisture, the occurrence of inadequate flow can also be attributed to these factors. If the Carr compressibility index exceeds 40 or the Hausner ratio is above 1.67, it can be inferred that the powder exhibits very inadequate flow characteristics(6).

Table 2:Micromeritic characteristics of Itraconazole

Micromeritic characteristics of Itraconazole	Results
"Bulk density (g/ml)"	0.176 ± 0.02
"Tapped density (g/ml)"	0.398 ± 0.06
"Angle of repose (^{0})"	51.056 ± 1.532
"Hausner's Ratio (%)"	1.843 ± 0.05
Carr's Compressibility Index (%)	46.467 ± 1.673

All values represent mean ± SD, n=3

Development Of Solid Dispersion-

Solubility studies-

To conduct solubility studies, Itraconazole salts were first prepared. This process involved "synthesizing Itraconazole hydrochloride (ITRH), Itraconazole mesylate (ITRM)", and "Itraconazole besylate (ITRB) salts from the base compound itraconazole (ITR)". This synthesis was achieved through Benzene carboxylic acid, methyl phosphonic acid, and hydrochloric acid are combined in an acid addition process. The salts were created with a customised acid additive process method that has been documented in previous research. (7).

Table 3: Solubility studies of Itraconazole and its respective complexes

Reagent	Itraconazole (ITR) (µg/mL)	Itraconazole hydrochloride (ITRH) (µg/mL)	Itraconazole besylate (ITRB) (µg/mL)	Itraconazole mesylate (ITRM) (µg/mL)
Purified water	1.576	311.45	201.43	177.62
0.1N HCl	6.98	101.45	621.47	398.46

Table 4: Phase solubility studies of Itraconazole and its respective salt complexes

S. No	**Concentration of Captisol (mM)**	**Concentration of ITR (mM)**	**Concentration of ITRH (mM)**	**Concentration of ITRM (mM)**	**Concentration of ITRB (mM)**
1	0	0.000068	0.00027	0.234	0.248
2	5	0.00407	0.389	0.402	0.735
3	10	0.00535	0.627	0.688	1.208
4	20	0.00872	1.732	0.773	2.479
5	40	0.0282	2.658	1.576	4.134
6	80	0.0625	5.108	3.688	8.010
Stability Constant		48.612 M^{-1}	304.34 M^{-1}	255.52 M^{-1}	408.95 M^{-1}

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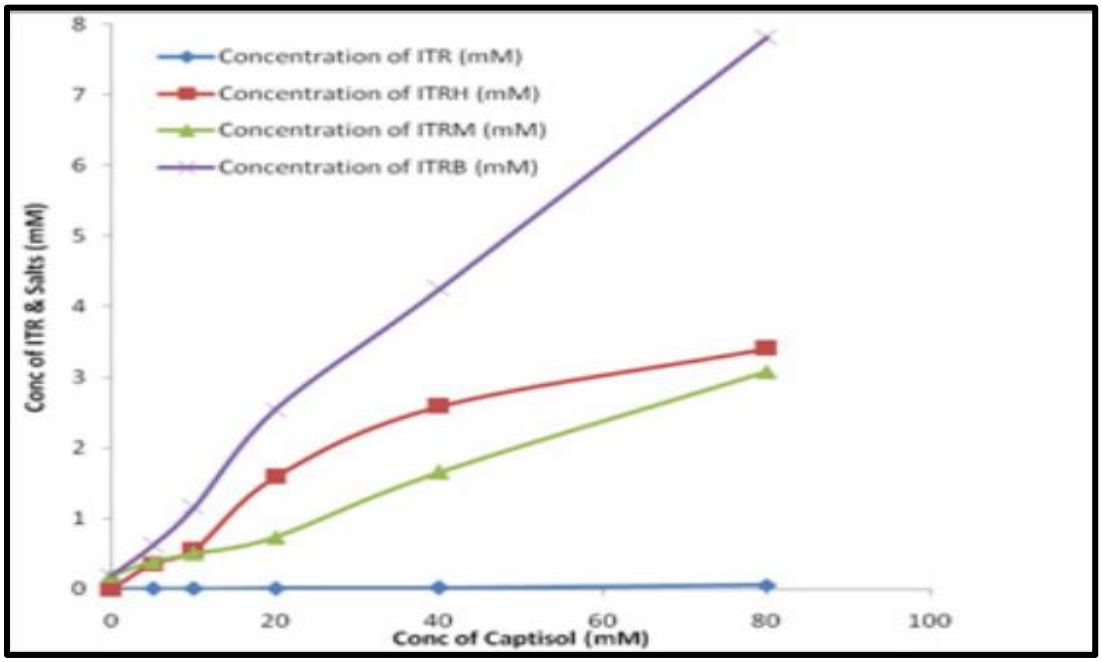

Figure 1:"Phase Solubility Graph of ITR and ITR salts with Captisol"

Table 5:"Different itraconazole complexes and their drug content"

Complexes	Method	Terminology	Drug content (% w/w)	
			1:2	1:3
ITR + C	KN	ITR-C-KN	96.02 ± 1.02	88.36 ± 1.07
	EV	ITR-C-EV	94.36 ± 1.23	84.17 ± 1.31
	PM	ITR-C-PM	84.92 ± 1.20	71.66 ± 1.04
ITRH + C	KN	ITRH-C-KN	97.51 ± 1.08	94.67 ± 1.26
	EV	ITRH-C-EV	93.48 ± 1.21	92.23 ± 1.42
	PM	ITRH-C-PM	90.13 ± 1.43	89.45 ± 1.31
ITRM + C	KN	ITRM-C-KN	99.42 ± 1.25	96.18 ± 1.22
	EV	ITRM-C-EV	95.11 ± 1.35	95.08 ± 1.06
	PM	ITRM-C-PM	90.05 ± 1.09	78.74 ± 1.03
ITRB + C	KN	ITRB-C-KN	99.89 ± 1.43	94.16 ± 1.25
	EV	ITRB-C-EV	93.19 ± 1.22	92.87 ± 1.06
	PM	ITRB-C-PM	88.74 ± 1.09	81.13 ± 1.21

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Powder X-ray Diffraction (PXRD)

Differential scanning is a thermal analysis technique that is commonly used in materials science and chemistry to investigate the thermal behavior of a substance. Calorimetry, often known as differential scanning calorimetry (DSC), is a thermo-analytical method that involves quantifying the thermal energy necessary to raise the temperature of a sample, while considering the temperature as an independent variable. The temperature protocol utilized in a differential scanning calorimetry (DSC) investigation is formulated in such a manner that the temperature of the sample holder exhibits a linear increase with respect to time (8).

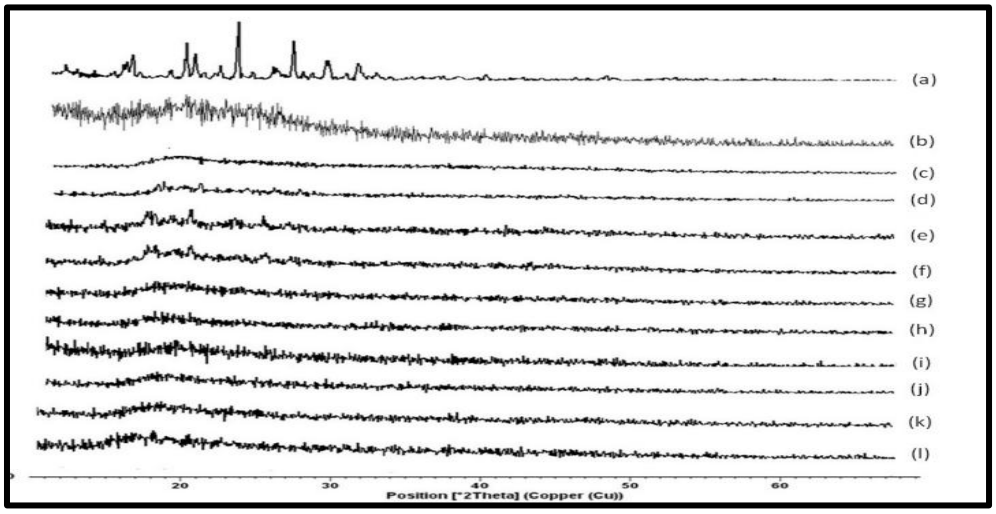

Figure 3:"XRD Pattern of (a) ITR, (b) ITRM, (c) ITRB, (d) ITRH, (e) ITRH-C-PM, (f) ITRH-C-EV, (g) ITRH-C-KN, (h) ITRM-C-PM, (i) ITRM-C-EV, (j) ITRM-C-KN, (k) ITRB-C-EV, and (l) ITRB-C-KN"

4.0 Conclusion

The micromeritic properties were examined to determine the particle features, flow property, and compressibility. The results of solid dispersion technique to enhance the solubility of Itraconazole showed that the solubility of ITR was enhanced by the addition of Captisol through the creation of an inclusion complex, wherein the guest and host molecules exist in a state of dynamic equilibrium with the complex. The study's conclusions show that the results are correct solubility rate of itraconazole can be improved by forming a complex with Captisol by the kneading approach. The bulk density of Itraconazole at 0.176 g/mL, angle of repose at 51.0560 degrees, and Hausner ratio of 1.843 all indicate that the drug has relatively poor flow characteristics in its purified form.

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