International Research Journal of Natural and Applied Sciences
ISSN: (2349-4077)
Impact Factor 5.46 Volume 8, Issue 8, August 2021
Website- www.aarf.asia, Email : editor@aarf.asia , editoraarf@gmail.com

OPTIMIZATION OF SOLUBILITY ENHANCEMENT METHODS FOR THE POORLY WATER-SOLUBLE DRUG ITRACONAZOLE

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Abstract

Itraconazole was characterized prior to its formulation by means of analyses such as its saturation solubility, ultraviolet (UV) spectroscopy, melting point, partition coefficient, effect of pH, Fourier transform infrared (FTIR), and solubility profile in a number of buffer solutions. To determine the absorption maxima, a solution containing 10 g/ml of Itraconazole in distilled water with 0.75 % SLS, acetate buffer of "pH 1.2, and phosphate buffer of pH 6.8" and 7.4 was scanned independently between the wavelengths 200-400 nm with a UV/Vis double beam spectrophotometer for quantitative estimation calibration curves. The applicability of the method was confirmed by correlation coefficients between 0.99 and 1.

Key words: *Solubility, Itraconazole, water-soluble drug.*

Introduction

Poor solubility is one of the most prevalent issues in the world of pharmaceutics, which is universally recognized. Oral bioavailability is sometimes hampered by low solubility and associated inadequate dissolving rate. The quantity of candidates for poorly soluble drugs has grew dramatically as a consequence of the widespread use of high throughput screening for potential therapeutic properties by the "pharmaceutical industry". Therefore, it is crucial to upsurge the solubility & dissolution rate of poorly soluble substances.

The pharmaceutical business is currently dealing with two major problems: poor medication bioavailability in the body following delivery and poor water solubility. This issue has been the main obstacle to the introduction of new developments in chemical products. Consequently, pharmaceutical companies are concentrating on discovering a technique or technology that will recover the aqueous solubility & absorption ability of a drug. A range of techniques has been

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employed to alter active pharmaceutical ingredients, encompassing physical, chemical, & controlled solid-state approaches. Each of these methods has certain limitations that restrict its use in the modification of active pharmaceutical components to enhance water solubility & bioavailability (1).

In this paper **Itraconazole was characterized prior to its formulation by means of analyses such as its saturation solubility, ultraviolet (UV) spectroscopy, melting point, partition coefficient, effect of pH, Fourier transform infrared (FTIR), and solubility profile in a number of buffer solutions.**

2.0 Material and method

2.1. PRE-FORMULATION STUDIES-

2.2.1. Physicochemical properties of Itraconazole-

2.2.1.1. Saturation solubility study- The saturation solubility investigations were conducted in triplicate (4).

2.2..1.2. Melting point determination- The determination of the melting point serves as a crucial physical characteristic that is employed in the identification of the active therapeutic ingredient.

2.2.1.3. Partition coefficient determination-

2.2.1.4. Effect of pH on solubility of Itraconazole- The solubility of piroxicam was assessed in different buffers, “including hydrochloric acid buffer at pH 1.2, acetate buffer at pH 4.5, phosphate buffer at pH 6.8, and phosphate buffer at pH 7.4 (5)”.

2.2.1.5. UV spectrum of Itraconazole- Ultraviolet spectroscopy, or UV spectroscopy is a chemical form of optical spectra that makes use of obvious ultraviolet radiation, and infrared light. It is based on the Beer-Lambert principle, and that says that a solution's absorbance correlates exactly with its absorbent the species' amount and direction width..

2.2.1.6. Standard curve determination- In order to forecast a specimen's concentrations and understand how the equipment responds to an analyte, calibration curves are used. Usually, the

unfamiliar substance that is of significance is synthesised in a series of common samples at various levels & the instrumented reaction is noted at every concentration. (6).

2.2.1.6.1. Preparation of standard stock solution (100µg/ml)- The 100 mg Itraconazole standard was moved, disintegrating, and diluted with formaldehyde to the appropriate level in a volumetric flask with a capacity of 100 m to create a standard solution of a density of 1000 g/ml.

2.2.1.7. "Fourier transmission infrared (FT-IR) spectroscopy"- The infrared spectrum of the drug sample was obtained by employing a potassium bromide (KBr) pellet as the medium, with a resolution of 4 cm^{-1}, spanning the range of 4000-400 cm^{-1}.

2.2.1.8. Solubility studies of Itraconazole by using standard curves-

Different pH buffers, 1.2 (acetate), 6.8 (phosphate), 7.2 (phosphate) were prepared in accordance with the Indian Pharmacopoeia's instructions (7).

2.2.1.8.1. Preparation of reagents and solutions-

a) **0.1 N Hydrochloric acid**

b) **"Acetate buffer pH 1.2"**

c) **"Phosphate buffer pH 6.8"**

d) **"Phosphate buffer pH 7.2"**

2.2.1.8.2. Standard calibration curve in standard dissolution media

a) Standard calibration curve of Itraconazole in 0.75 % SLS in water

b) "Standard calibration curve of Itraconazole in 0.1 N HCl"

c) Standard calibration curve of Itraconazole in pH 6.8 phosphate buffer-

d) "Standard calibration curve of Itraconazole in phosphate buffer pH 7.2"-

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3.0 Result and discussion

Saturation solubility study-

The saturation solubility of particles plays a crucial role in determining the rate which a medication releases itself into a dissolving medium, its the drug's bio and, in the end, "the efficacy for treatment of the prescription medication."

Table 1: Physicochemical properties of Itraconazole

Parameter	Observed value	Reported value
Saturation solubility (mg/ml)	0.48 ± 0.024	0.49
Melting point (°C)	163 – 167	166.3
Partition coefficient	5.68 ± 0.43	5.66

Effect of pH on solubility of Itraconazole- The effect of pH on Itraconazole solubility was studied in various pH buffers. The solubility of Itraconazole varied between different buffers. The solubility of Itraconazole did not change significantly until pH 5, but increased swiftly thereafter. Weakly acidic (pKa 3.7), Itraconazole exhibits pH-dependent ionization and solubility (8).

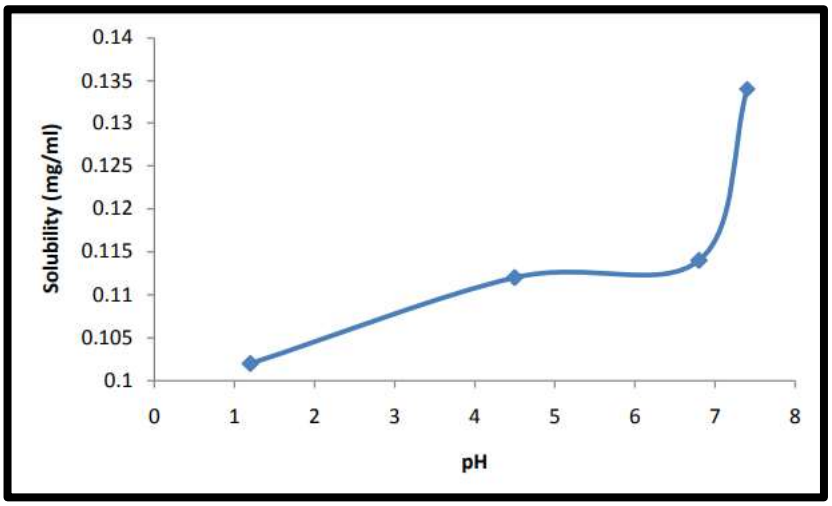

Figure 1: pH solubility profile of Itraconazole

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UV Spectrum of Itraconazole- The linearity of the drug's reaction was confirmed within the concentration range of 10–60 µg/ml. This was a measurement curves generated by graphing the absorbance values against the corresponding concentration data. Subsequently, linear regression analysis was performed on the data, as shown in Table 4.2. The generated calibration curve for lafutidine can be represented by the equation y = 0.0100x + 0.035.

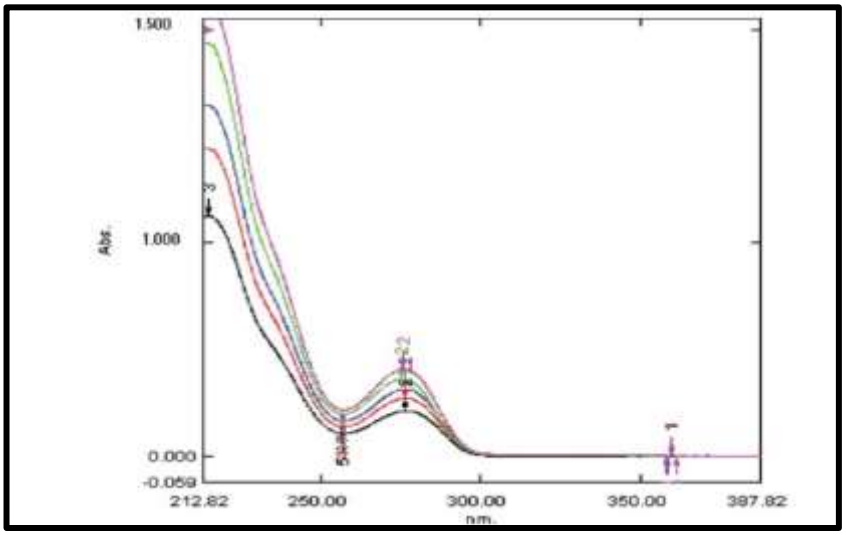

Figure 2: Overlay spectra of Itraconazole by UV Visible spectrophotometer

Table 2. Calibration readings of Itraconazole under UV Visible Spectrophotometer

S.No.	Concentration (µg/ml)	"Absorbance mean ± S.D.(n=5)"	%C.V.
1	10	0.140 ±0.0018	0.85
2	20	0.232 ±0.0022	0.74
3	30	0.338 ±0.0014	0.39
4	40	0.441 ±0.0027	0.57
5	50	0.534 ±0.0042	0.74
6	60	0.635 ±0.0058	0.92

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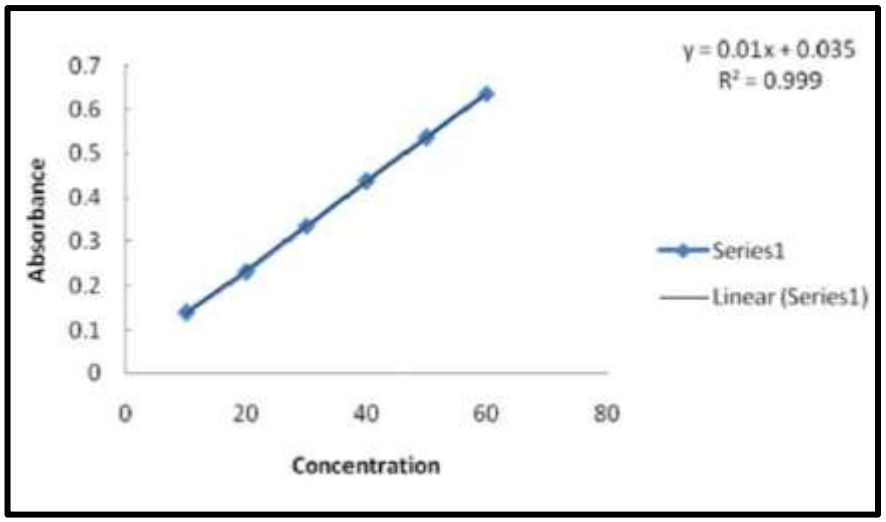

Figure 3: Standard curve of Itraconazole by UV Visible Spectrophotometer

Table 3: Validation parameters of Itraconazole

Parameter	Results
"Absorption maxima (nm)"	280
Linear range (µg/ml)	10-60
"Standard regression equation"	"Y= 0.0100X + 0.035"
Correlation coefficient (R^2)	0.999
Molar absorptivity	"80000 M^{-1} cm^{-1}"
"A (1%, 1 cm)"	1889.14
"Accuracy (% recovery ± S.D.)"	99.998
"Precision (% CV)"	0.6548
"Limit of quantitation (µg/ml)"	9.89
"Limit of detection (µg/ml)"	3.25

Fourier transmission infrared "(FT-IR) spectroscopy"- "The Fourier Transform Infrared spectrum (FTIR)" of pure itraconazole was generated and displayed in Figure 4.4. In the spectrum of the pure drug, distinct peaks were observed at 2828.25- 3126.12 cm^{-1}, whereby disturbances are responsible for the -C-H- bonds. The peak observed at 3052.03 cm^{-1} indicates the stretching of aromatic rings. Additionally, the range between 3132.32- 3392.45 cm^{-1} can be attributed to the N-H stretching of amide groups.

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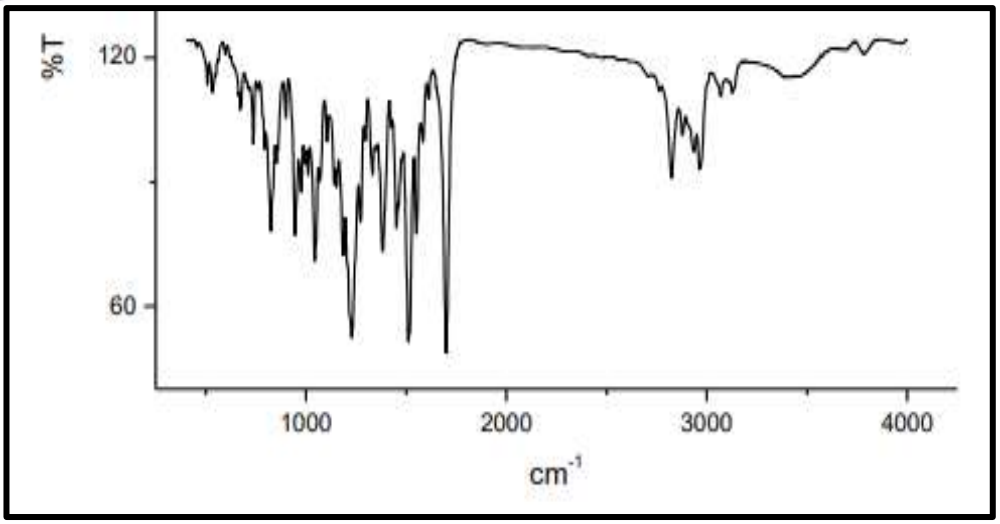

Figure 4: **FTIR Spectra of Itraconazole**

SOLUBILITY PROFILE OF ITRACONAZOLE IN BUFFER SOLUTIONS

Itraconazole is categorized as a "Class-II drug based on the Biopharmaceutical Classification System (BCS)", indicating its strong transparency and insufficient lubricity. The solubility of Itraconazole in water is pH-dependent (9). Solubility, generally described as the quantity of a material that degrades at certain temperatures in a given volume of solution, was determined to be 7.347 ± 0.24 mg/mL in water.

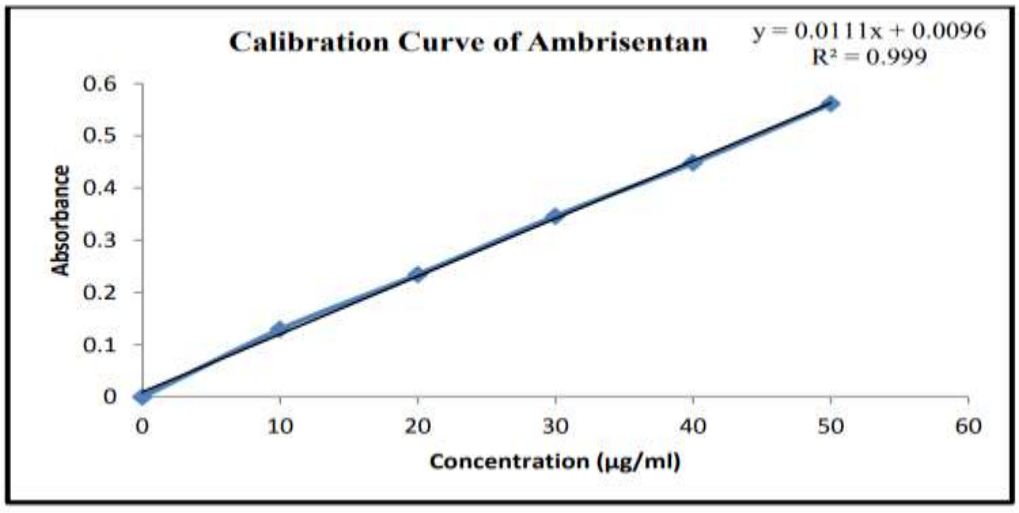

Figure 5: Standard calibration curve of Itraconazole in distilled water with 0.75% SLS

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Table 4: Solubility of Itraconazole in different solvents

S.No.	Media	Solubility (µg/ml)
1.	Water	7.347 ± 1.06
2.	"Acetate buffer pH 1.2"	5.173 ± 1.16
3.	"Phosphate buffer pH 6.8"	28.507 ± 1.52
4.	"Phosphate buffer pH 7.4"	35.391 ± 1.65

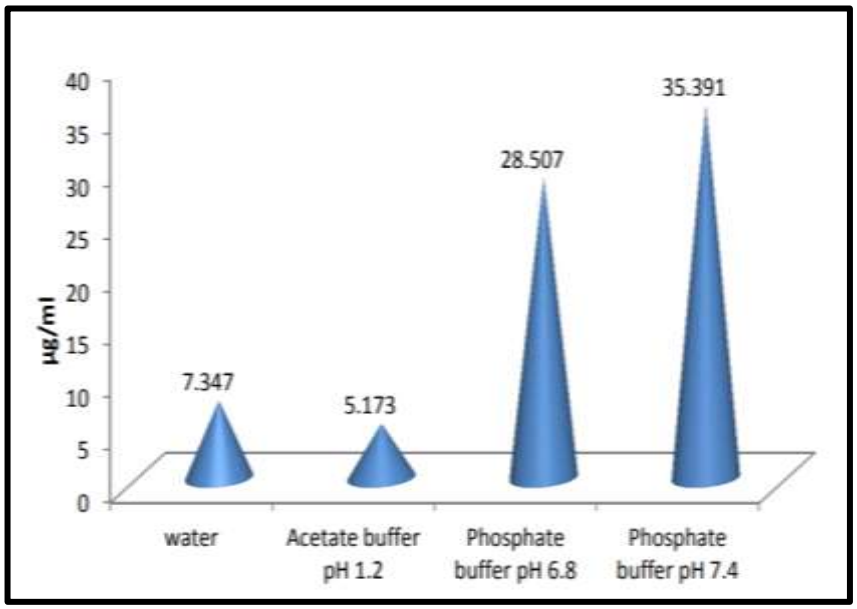

Figure 6: Solubility profile of Itraconazole in different solvents

Conclusion

Preformulating drug characterization, such as saturation solubility study, UV spectroscopy, melting point, partition coefficient, effect of pH, FTIR, solubility profile in several buffer solutions of Itraconazole were studied in order to under the basic characteristics of pure drug powder. The solubility of Itraconazole was 0.48 ± 0.024 mg/ml, melting point 163-167°C, and partition coefficient 5.68 ± 0.43 was observed. To determine the absorption maxima, a solution containing 10 µg/ml of the Itraconazole in distilled water with 0.75% SLS, acetate buffer of pH 1.2, and

phosphate buffer of "pH 6.8 and 7.4" was subjected to independent scanning between the wavelengths of "200-400 nm using a UV/Vis" double beam spectrophotometer for quantitative estimation calibration curves.

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