World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

SOLUBILITY ENHANCEMENT OF ORNIDAZOLE BY COMPLEXATION WITH BETA CYCLODEXTRIN.

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Received: 01-07-2025 / Revised Accepted: 05-07-2025 / Published: 10-07-2025

ABSTRACT:
This research explores the formulation of fast dissolving tablets enriched with beta cyclodextrin (β-CD) to augment dissolution characteristics. Beta cyclodextrin β-CD, a cyclic oligosaccharide, offers a unique molecular cavity that accommodates drug molecules, thereby enhancing their solubility and bioavailability. Various formulations were prepared and assessed for parameters including disintegration time, dissolution rate, and drug content uniformity. Results demonstrate that the inclusion of β-CD significantly improves dissolution rates, leading to enhanced drug release compared to conventional tablets. Optimized formulations exhibit rapid disintegration, facilitating swift drug delivery.

Keywords: Ornidazole, Beta cyclodextrin (β-CD), Dissolution rate, solubility enhancement.

INTRODUCTION

A substance's solubility in a specific solvent is one of its properties. It is the amount of dissolved solute in a saturated solution at a given temperature, expressed quantitatively. It refers to a transparent, uniform molecular dispersion formed by the continuous interaction of two or more compounds. Gastrointestinal permeability, dissolution, and solubility are fundamental factors that regulate the speed, volume, and bioavailability of medication absorption. The drug's water solubility is a significant factor in how well the medication is absorbed when taken orally. A major obstacle in the creation of novel pharmacological products is the insufficient solubility of active medicinal components. Insufficient solubility in water leads to low bioavailability. For this reason, solubility is crucial to achieving the intended concentration of the drug in the systemic circulation, optimizing its usefulness in newly designed medications, and boosting therapeutic efficacy1,2 .

A solid solute dissolves into a solution through a process known as dissolution. The amount of drug material that dissolves under uniform compositional conditions in a given amount of time is known as dissolution. One of the most significant quality control tests for pharmaceutical dosage forms is dissolution, which is also evolving into a tool for bioavailability prediction and, in certain situations, a replacement for clinical investigations in the determination of bioequivalence. The pharmacological activity of a medication is significantly influenced by its dissolution behaviour. To ensure ongoing product quality and manufacturing process performance, as well as to direct the development of novel formulation processes towards product optimization, bioavailability and bioequivalence data generated from dissolution testing can be utilized

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How to Cite this Article: M.Yamini, SOLUBILITY ENHANCEMENT OF ORNIDAZOLE BY COMPLEXATION WITH BETA CYCLODEXTRIN, World J Pharm Sci 2025; 13(03): 1-7; https://doi.org/10.54037/WJPS.2022.100905

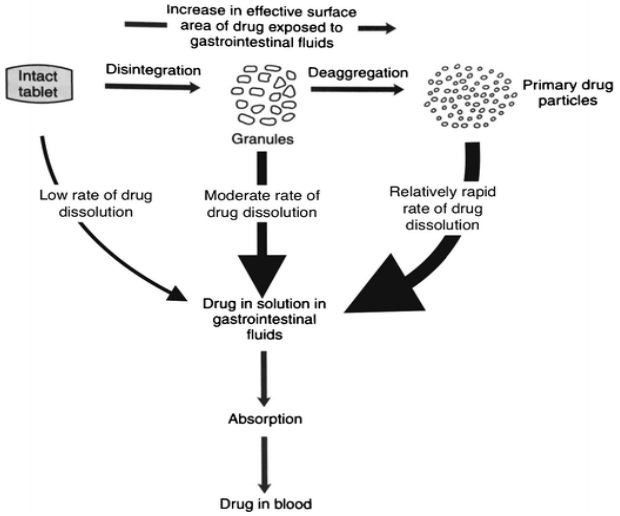

Figure.1 Drug release process

Many descriptive words that are dependent on the quantity of drug dissolved in the solvent are used to characterize a drug's solubility.

Table. 1 Parts of solvent required for one part of solute. Definition of solubility [3]

Very soluble	<1
Freely soluble	1-10
soluble	10-30
Sparingly soluble Slightly soluble	30-100 100-1000
Very slightly soluble	1000-10,000
insoluble	> 10,000

It divides the medication into four groups based on its solubility and permeability. Low solubility causes a soluble barrier in Class II and Class IV of the system, where dissolution is the rate-limiting stage for medication absorption[4].

Table.2 BCS classification

class	permeability	Solubility	example
I	High	High	Metoprolol, propranolol
II	low	High	Nifedipine, naproxen, Ornidazole
III	High	low	Cimitidine, metformin
IV	low	low	Taxol, clorthiazole

Many approaches can be modified to improve the solubilization of medications that are not very soluble in water and to increase the drugs' bioavailability. The frequent processes include micronization, chemical modification, pH shift, solid dispersion, co-solvency, complexation, and hydrotropy.

Solubility enhancement techniques

The process through which a solid dissolves in a liquid phase to create a homogenous mixture is known as solubility. To demonstrate a pharmacological impact, the drug must dissolve well enough in the bloodstream. This is a critical component of solubility. The novel medication molecule's limited water solubility is the main formulation issue. Poorly soluble medicines need large doses to achieve the maximum therapeutic plasma concentration after oral delivery5. The biopharmaceutical classification system (BCS) divides compounds into groups according to how soluble and permeable they are. Regulatory bodies and health organizations have

employed this classification scheme to enable the use of dissolution as a means of demonstrating bioequivalence for chemicals that are both highly soluble and highly permeable. When taken orally, medications with low water solubility typically exhibit sluggish dissolving rates and low bioavailability. The goal of this review article is to increase bioavailability and promote efficient absorption6.

Methods of solubility enhancement:

1. Physical Modification

I. Particle Size Reduction

- Micronization
- Nanosuspension

II. Modification of Crystal Habit

- Polymorphs
- Pseudo polymorphs

III. Drug Dispersion in Carrier

- Solid solutions
- Solid dispersions

IV. Solubilization by Surfactants

- Microemulsion
- Self-micro emulsifying drug delivery system

V. Complexation[7.]

2. Chemical modification
    I. Hydro trophy
    II. Co-solvency
    III. Nanotechnology
    IV. Salt formation
3. pH adjustment
4. Supercritical fluid process
5. Liquisolid methods[8.]

Ornidazole:

Amoebiasis, giardiasis, trichomoniasis, and bacterial vaginosis are among the bacterial parasite infections that can be treated with the antibiotic and antiprotozoal drug ornidazole. Because ornidazole is a medicine classified as BCS class II and has a low solubility, it is a good choice for a solubility enhancement study. Oflod-oz, senof-oz, oftrail-oz, oristel, orridaz 500 mg, or well 500mg9.It functions by interfering with the synthesis of microorganisms' DNA, which prevents them fromgrowingandprocreating10. Infections caused by bacteria and parasites are treated with ornidazole. It is used to treat infections in the skin, vagina, gastrointestinal tract, brain, and reproductive system, among other parts of the body11-31.

MATERIALS AND METHODS

Materials

Ornidazole, β-hydroxy cyclodextrin, methanol, distilled water.

Methods

Preparation of ornidazole cyclodextrin Complex by kneading method

The required quantities of the drug and hydroxyl propyl β-Cyclodextrin were weighed accurately in a molar ratio of 1:1, 1:2 and 1:332-35. A homogenous paste of cyclodextrin was prepared in a mortar by adding water: methanol mixture (1:1) in small quantities, then the drug36 was added with continuous kneading it was triturated for 1 hour, an appropriate quantity of water: methanol (1:1)37-39 . Mixture was added further to maintain the consistency of the paste 40.Then the paste was dried on hot air oven at 55℃ for 24 hours. Then the dried complexes were then pulverized and passed through sieve no 120 and then stored.

Preparation of ornidazole cyclodextrin complex by solvent evaporation method

The required quantities of the drug and hydroxyl propyl β-Cyclodextrin were weighed accurately in a molar ratio of 1:1, 1:2 and 1:3. Cyclodextrin is dissolved in 1:1 ratio of methanolic water. Then the drug is added and dissolved with continuous stirring. After some time the beaker is kept in a hot air oven at 500c for an over night, such that the solvent gets evaporated and the complex is produce.

Table.3 Preparation of drug: cyclodextrin complexes

S.no	composition	Ratio
1	Ornidazole: βcyclodextrin (kneading method)	1:1, 1:2, 1:3
2	Ornidazole: βcyclodextrin (solvent evaporation method)	1:1, 1:2, 1:3

RESULTS AND DISSCUSSION

STANDARD CURVE

Preparation of stock and working standard solution

Accurately weighed quantity of 100 mg of ornidazole was taken into 100 ml volumetric flask. It was dissolved in 100 ml of 0.1M hydrochloric acid to get a strength of 1000 µg/mL. working standard solution (100 µg/mL) was prepared by diluting 10 mL of stock solution to 100 mL with 50:50 ratios of methanol and water solution.

Construction of calibration curve

Ornidazole(50mg) was weighed accurately and dissolved in 50ml of Hcl to get a concentration of 1mg/ml in the volumetric flask.

$$\%assay = \frac{sample\ absorbance}{standard\ absorbance} \times \frac{standard\ concentration}{test\ concentration} \times 100$$

Preparation of 0.1M hydrochloric acid

Accurately measure 8.33ml of Hcl in an volumetric flask and transfer it into a 1000ml volumetric flask and then measure 1000ml of distilled water in volumetric flask and transfer it to the volumetric flask and mix them.

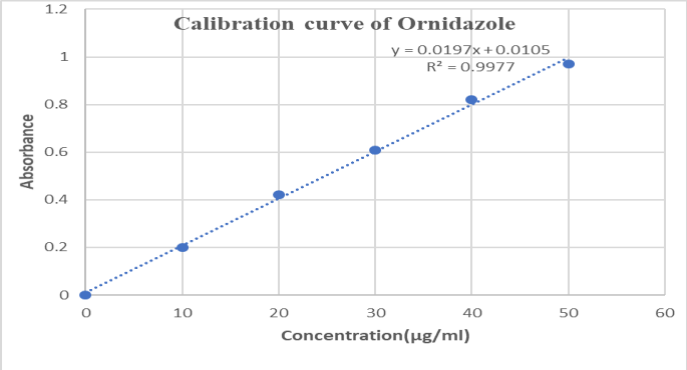

Figure.2 Calibration curve of Ornidazole

Table. 4 Data for Standard Plot

Concentration(µg/ml)	Absorbance
0	0
10	0.2
20	0.42
30	0.61
40	0.82
50	0.97

Preparation of working standard solutions

From the stock solution, 1, 2, 3, 4, 5 and 6 mL of the solutions were taken from 100 mL volumetric flasks and were made up to the volume using water, to get solutions of 10, 20, 30, 40, 50 and 60µg/mL concentrations respectively. The above absorbance of the above dilutions was determined at 325 nm, using UV spectrophotometer 0.1M hydrochloric acid solution as the blank. The results are tabulated in table 4 calibration curve (Figure 2) was constructed by plotting the absorbance against the concentration of Ornidazole. A regression equation was derived from the plot, which was used for the estimation of Ornidazole.

The method obeyed Beer's law in the concentration range of 10-60µg/mL and the regression value was found to be 0.998 indicating a positive correlation between the concentration of Ornidazole and the corresponding absorbance values. The regression line describing the relation between concentration and absorbance was as follows.

Dissolution studies

Dissolution studies were performed for all the samples given below by using dissolution apparatus

Apparatus number **:** Type 2 (paddle)
Medium **:** 900ml of 0.1M HCl
Speed **:** 75rpm
Time **:** 1hr

The sample is added into the baskets and suitable volumes of samples are taken at specific time intervals. The absorbance of the samples are measured by using uv-visible spectrophotometer at the maximum absorbance at 277nm. Calculate the percentage of drug release by using the formula

x=y-c/m

Where
X=unknown value
Y=absorbance
C=0.0105
m=0.0197

Table. 5 Dissolution table of Ornidazole and β-cyclodextrin by solvent evaporation method

Time interval	1:1	1:2	1:3
0 min	0	0	0
5min	29.89	30.84	33.93
10 min	32.183	35.136	53.31
20min	36.183	40.896	60.58
30min	45.288	48.996	66.63
40min	52.704	57.096	79.85
50min	60.48	63.54	90.18
60min	64.548	67.572	92.84

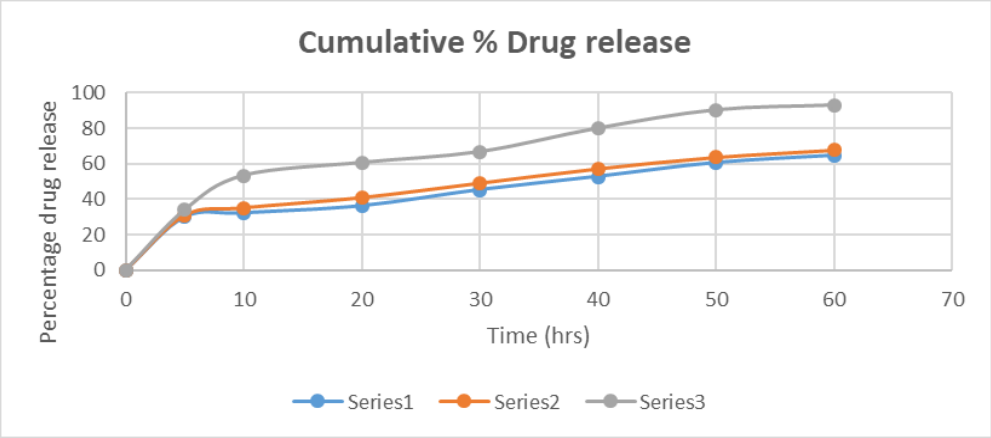

Figure. 4 Cumulative % Drug release graph Dissolution graph of Ornidazole and β-cyclodextrin by kneading method (1:1, 1:2, 1:3)

In-vitro dissolution study:
Based on the dissolving profiles of each formulation, it was discovered that as the concentration of β-cyclodextrin varied in ratio, the cumulative percentage drug release increased. 1:3 Kneading technique ratio 1:3 The optimal drug release profile was demonstrated using the solvent evaporation technique ratio.

CONCLUSION:
The purpose of this work is to use the solubility enhancement technique (complexation) to increase the solubility and dissolution rate of ornidazole. One BCS Class-II medication that is utilized as an antifungal is ornidazole. Ornidazole dissolves easily in methanol and only marginally in aqueous solutions. Ornidazole was chosen as a potential medication option to increase its solubility and rate of dissolution based on its biopharmaceutical characteristics. By using the kneading and solvent evaporation methods, complexes were created. They were assessed in light of a dissolution investigation. Ornidazole and β-cyclodextrin (1:3) drug release by kneading method demonstrates 95% at 60-minute intervals, while solvent evaporation method demonstrates 92% at 60-minute intervals. Therefore, by complexing with hydroxy propyl β cyclodextrin, ornidazole's solubility is increased, enabling in vitro drug release investigations. The optimal drug: βcyclodextrin complexes with high solubility and high dissolution were identified using solvent evaporation and kneading methods.

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