Evaluation And *In-Vitro* Dissolution Study Of Clotrimazole By Solid Dispersion

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ABSTRACT
Clotrimazole, a medication with low water solubility, was formulated into solid dispersions utilizing polyethyleneglycol and various molecular weight polyvinyl pyrrolidones as carriers in varying weight ratios. Furthermore, binary and ternary b-cyclodextrin complexes were synthesized using various molar ratios. Solid dispersions and β-cyclodextrin complexes were both produced using the solvent evaporation approach. The impact of the carriers on clotrimazole's solubility in water was assessed using a phase solubility technique. All the preparations' dissolution was assessed using the USP paddle method. The solid dispersions and inclusion complexes were analyzed using differential scanning calorimetry and X-ray powder diffractometry to determine the impact of the carriers on reducing clotrimazole's crystallinity and forming complexes. After evaluating the physical characteristics and medication release behavior, polyvinylpyrrolidone solid dispersions and ternary cyclodextrin complexes were chosen as the best formulations for suppositories. Suppocire AM/50 mg carbopol 940 was selected as the suppository foundation, and the suppositories were made using the molding technique. The suppositories were analyzed for weight consistency, softening duration, and medication concentration. All these features were deemed optimal. The drug release pattern in an artificial environment was analyzed in citrate buffer with a pH of 4.5 and 1% sodium lauryl sulfate. Clotrimazole release from solid dispersions and inclusion complexes in suppositories was significantly enhanced compared to suppositories containing the intact medication. Suppositories containing solid dispersions of polyvinyl pyrrolidone exhibited outstanding antifungal properties.

Keywords: - Clotrimazole, In-vitro study, Polymers

1. INTRODUCTION

The most straightforward and convenient method to deliver medications is through the oral route. Oral dosage forms offer several advantages over other types of dosage forms, including improved stability, precise dosing, decreased volume, and straightforward manufacture.[1,2]

Currently, one of the most common and significant issues for formulation scientists in pharmaceutical manufacture is developing strategies to improve the oral release of poorly soluble chemicals. Approximately 40% of the potential new medications discovered by the pharmaceutical sector have low solubility in water. Water-insoluble chemicals have decreased release rate and low bioavailability. Hence, a high dosage is required to get the desired effect, which may result in drug toxicity. The best strategy to enhance the release rate is to improve solubility using formulation methods. [3,4]

Fungal infections are primarily linked to the use of broad-spectrum antibiotics, corticosteroids, anticancer medications, dental prosthesis, catheters, permanent implants, and the onset of AIDS. The disruption of host defense mechanisms by the mentioned substances allows saprophytic fungus to easily infiltrate live tissues.[5,6]

1.1 A suspension of solid particles

The term "solid dispersion" is shortened and refers to a medication dispersed in a solid matrix. Enhancing the oral bioavailability of novel chemical entities with low water solubility is a highly successful and promising strategy to increase solubility. This method is really promising.[7] [8] Sekiguchi et al.'s proposition in 1961 was identified as an original representation of the previously discovered concept. They created clotrimazole SD using urea as a carrier, which significantly enhanced its solubility without delving into the detailed mechanics. Nevertheless, they failed to provide an explanation for how this happened.[9] [10]

The concept of solid dispersion (SD) has been revised to state: "a combination of drugs that are not easily soluble in water-based substances, with a drug release pattern influenced by the characteristics of the polymer."[11, 12] An alternative term for the dispersion of active substances in an inert vehicle or matrix, where the active ingredient can be in a finely crystalline, amorphous, or solubilized condition, also known as SD. [13] [14] Due to its extensive incorporation of cutting-edge technologies that facilitate potential selection despite its poor solubility in water, the technology saw a significant resurgence in the early 1990s, despite being researched for the previous fifty years. Despite being familiar to the scientific community in the pharmaceutical sector, this technology is not new. [15] [16]

2. METHODS

2.1 Using fusion approach to prepare the solid dispersion (SD) matrix

Guar gum and high-performance microcapsules were used to create six different formulations of Clotrimazole solid dispersion tablets. The fusion method was used to melt urea in a water bath by gradually increasing the temperature until the urea was completely liquefied. The drug was added to the melted urea while continually stirring the mixture, and then allowed to cool at room temperature. The drug and urea were taken in equal proportions, with a 1:1 ratio. After being dehydrated, crushed, and ground, the mixture was sieved through a #60 sieve before being stored in desiccators.

2.2 Tablet preparation process

A single punch tablet compression machine was used to apply the direct compression method for manufacturing Clotrimazole tablets in the form of SD. The comprehensive combination of clotrimazole, HPMC or guar gum, and MCC was guaranteed. After drying, talc and magnesium stearate were dispersed inside the granules. Granules were placed into a tablet compression machine to ensure uniform size and shape of the tablets during manufacture.

2.3 Formulation of tablets

Formulation Ingredients	F1	F2	F3	F4	F5	F6
Clotrimazole	200	200	200	200	200	200
HPMC	200	250	300	0	0	0
Guar gum	0	0	0	200	250	300
MCC	100	50	0	100	50	0
Magnesium stearate	10	10	10	10	10	10
Talc	5	5	5	5	5	5

2.4 Standard curve of clotrimazole levels

10 milligrams of pure Clotrimazole were accurately weighed and dissolved in 50 milliliters of phosphate buffer with a pH of 6.8 using a volumetric flask. The volume was subsequently raised to 100 milliliters using the identical buffer solution. The stock solution was prepared by diluting it with the same buffer to achieve concentrations of 2, 4, 6, 8, and 10 micrograms per milliliter. A UV Spectrophotometer (Elico SA165) was used to measure the absorbances of standard concentrations at a wavelength of 270 nm, compared to a blank containing fresh buffer solution.

2.5 Characteristics of granules

2.5.1 Density of bulk

Carefully, a known amount (m) of granules was added to the measuring cylinder. When needed, the granules were leveled without being compacted, and the unsettled apparent volume (V) was read to the closest graded unit.

$$Bulk\ density = \frac{Weight\ of\ granules}{Final\ volume\ after\ bulk}$$

2.5.2 Tapped densit

A measured amount of granules was placed in a measuring cylinder and tapped for five minutes using a mechanical tapping device. Both the first and last volumes were mentioned.

$$\text{Tapped } density = \frac{Weight\ of\ granules}{Final\ volume\ after\ tapping}$$

2.5.3 Angle of repose

By measuring the angle of repose, one can determine the frictional forces present in loose powder or grains. This is the greatest angle that can exist between the horizontal plane and the surface of a pile of grains or powder.

2.6 Evaluation of tablets

2.6.1 Weight Fluctuation

Each formulation batch was weighed individually using an electronic scale, with ten tablets per batch. The average weight was determined and each tablet's weight was compared to this average, and the variation was noted.

2.6.2 Friability test

The tablets' friability was assessed using a Roche friabilator. Each formulation involved placing pre-weighed tablet samples (10 tablets) on the friabilator and operating it for 100 revolutions. Subsequently, the tablets were powdered and weighed again.

2.6.3 Hardness assessment

The tablets' hardness was assessed using a Monsanto hardness tester. The force needed to fracture a tablet during a diametrical compression test.

2.6.4 Dimension
The tablets' thickness was measured using Vernier callipers.

2.6.5 Substance in Medication
Five tablets were pulverized in a mortar to create a powder. An exact weight of 515mg of powder was measured and placed into a beaker. The medication was extracted using three volumes of 10 ml of water. The combined extracts were diluted accordingly and the drug concentration was determined by measuring the absorbance of standard and samples at a wavelength of 270 nm using a UV spectrophotometer [Elico SA165] equipped with a photodiode array detector.

2.6.6 Conducting dissolution tests or in-vitro release studies
The Clotrimazole tablet's release rate was measured using the USP dissolution test instrument with a paddle type. A dissolution test was conducted with 900 cc of phosphate buffer at pH 7.8 for 2 hours at a rotation speed of 50 rpm. The temperature of the dissolving medium was kept constant at 37±0.5°C. New dissolving media was used to replace the removed samples. The filtered samples were analysed at a wavelength of 270 nm using a UV Spectrophotometer.

3. RESULTS
3.1 UV spectrum of Clotrimazole

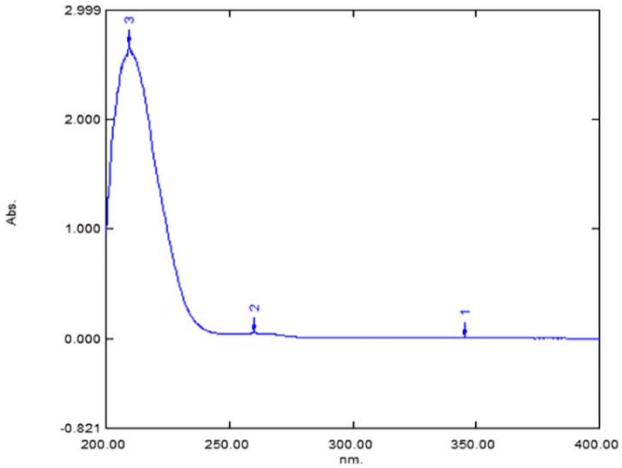

Figure 1. UV spectrum of Clotrimazole

3.2 Standard curve of Clotrimazole

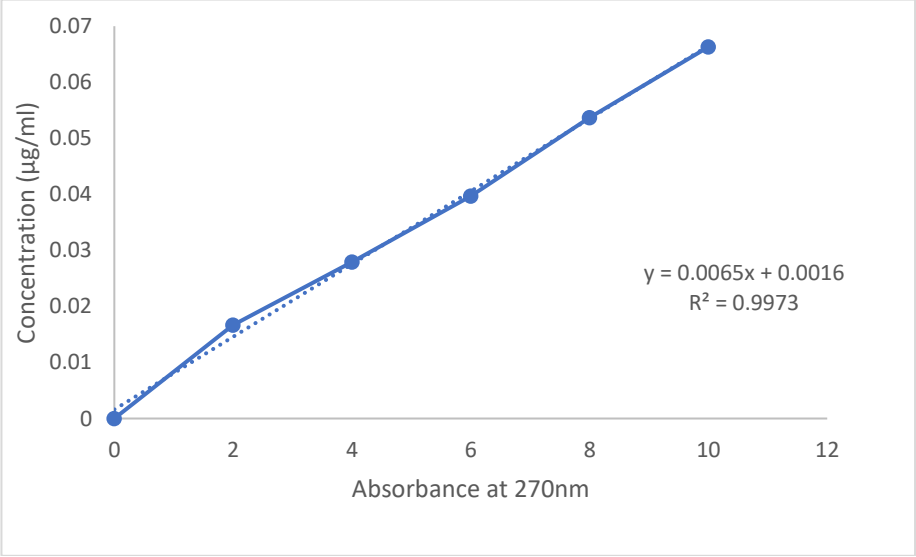

Figure 2. Calibartion curve of Clotrimazole

3.3 Evaluation of granules flow characteristics

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausener's Ratio	Angle of Repose (°)
F-1	0.518±0.018	0.632 ±0.017	18.03±0.014	1.22 ±0.018	29.39±1.47
F-2	0.534±0.022	0.658±0.023	18.84±0.019	1.23±0.016	26.74±1.39
F-3	0.546±0.026	0.664±0.027	17.77 ±0.09	1.21±0.014	25.84±1.47

F-4	0.515±0.017	0.628±0.015	17.99±0.010	1.21±0.017	26.56±1.42
F-5	0.508±0.012	0.615±0.011	17.39±0.007	1.21±0.015	26.58±1.36
F-6	0.528±0.020	0.646±0.019	18.26±0.015	1.22±0.019	29.86±1.56

Figure 3. Granules flow characteristics of batch no. F-1 to F-6

3.4 Determination of physical parameters

Formulation	Hardness (kg/cm2)	Thickness (mm)	% Friability	Weight Variation (mg)
F-1	5.4 ± 0.34	3.92 ± 0.16	0.58 ± 0.27	515.8 ± 1.28
F-2	5.2 ± 0.27	3.95 ± 0.18	0.54 ± 0.24	515.2 ± 1.83
F-3	5.7 ± 0.45	3.79 ± 0.13	0.57 ± 0.26	516.4 ± 1.37
F-4	5.3 ± 0.31	4.05 ± 0.21	0.71 ± 0.31	517.7±2.54
F-5	5.6 ± 0.39	3.98 ± 0.17	0.67 ± 0.29	513.5 ± 1.97
F-6	5.8 ± 0.49	4.03 ± 0.20	0.79 ± 0.27	514.8 ± 1.63

Table 1. Tablet characteristics of batch no. F-1 to F-6

3.5 *In vitro* Dissolution Study of Clotrimazole SD tablets

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	35.682	28.435	19.084	34.194	22.044	17.618
30	39.962	32.130	24.987	37.115	27.949	22.414
45	48.615	39.146	32.470	45.098	33.829	28.014
60	53.262	45.862	36.942	51.592	39.795	34.973
75	65.491	56.538	47.862	61.849	51.408	43.845
90	69.622	61.632	53.504	66.390	55.974	48.987
105	79.481	68.388	57.988	73.200	62.146	51.836
120	84.283	72.769	62.446	78.825	68.128	53.635

Table 2. Cumulative % drug release of batch no. F-1 to F-6 in phosphate buffer pH 6.8

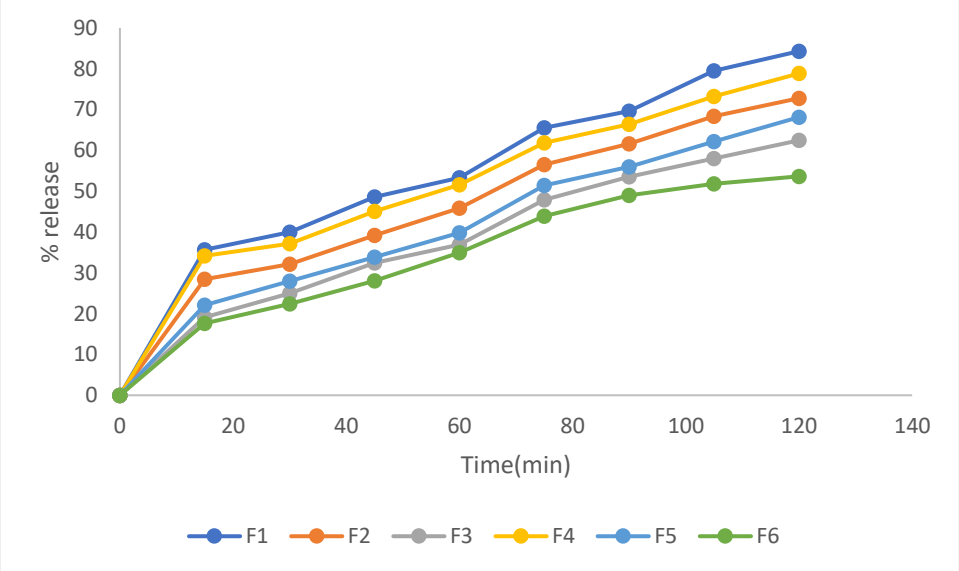

Table 3. Percentage drug release of batch no. F-1 to F-6 in phosphate buffer pH 6.8

Clotrimazole tablets were formulated and their release profiles were evaluated based on different amounts of HPMC and guar gum included. Formulation experiments on clotrimazole SD tablets (F1, F4, and F2) utilizing HPMC and guar gum showed dissolution rates of 84.283%, 78.825%, and 72.769%, respectively, after 2 hours. The tablet's release pattern with guar gum is acceptable. Guar gum, a natural polymer, has a release pattern with superior retarding qualities compared to tablets composed with HPMC.

4. CONCLUSION

The disintegration rate of pure clotrimazole was very slow. When clotrimazole was created in SD form, its disintegration rate was quite fast. After preparing clotrimazole tablets, a release study was done using varying concentrations of HPMC and guar gum. Clotrimazole SD tablets prepared with guar gum showed significantly improved release compared to tablets made with HPMC. Enhancements in the dissolution rate of clotrimazole SD tablets resulted in higher bioavailability of the medicine.

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