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Design, Development and Formulation of Fluconazole Nitrate Co-Crystal Loaded Gel: A Comprehensive Approach for Topical Antifungal

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ABSTRACT:

In this study, pharmaceutical cocrystals were designed to efficiently deliver FL by topical administration to overcome this issue. Cocrystallization of drug with conformer is an immense approach used to explore the physicochemical properties of drug. Formulation and evaluation of FL co-crystals by solvent evaporation method for solubility enhancement were the objective of the current research. All the prepared formulations were evaluated by powder Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), dissolution, and solubility studies. Dissolution and solubility studies of the formulations confirmed that solubility enhanced as compared to the solubility of the available market drugs. From all these studies, it can be concluded that the co-crystallization technique enhanced the solubility of FL by using the solvent evaporation method. The cocrystals of FL were prepared in 1:1 molar ratio with succinic acid. FL cocrystals showed the improvement in solubility and dissolution as compared to pure FL. The formation of cocrystals was confirmed from change in endothermic peak of DSC and from shifting of FTIR spectra of cocrystals. The topical gel of FL cocrystals was formulated using Carbapol-940 and hydroxypropyl methylcellulose (HPMC) as a gelling agent. The cocrystals with altered physicochemical properties of FL were prepared with Succinic acid and formulated as a topical gel to overcome the problems related to oral administration. FCG4 formulation was found to be optimized batch and selected variables show a significant effect on the responses that are drug release and spread ability.

Keywords: Co-Crystal, Antifungal, Topical, Fluconazole Nitrate

1. INTRODUCTION

Fluconazole, [FLZ, 2-(2,4-difluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)propan-2-ol, a bis-triazole multifunctional antifungal drug used in the prevention and treatment for superficial and systemic fungal infections, was firstly reported by Richardson in 1983 [1]. To our knowledge, solid forms display variability and exist in polymorphic forms, which refer to crystalline and amorphous forms as well as solvates and hydrates. FLZ has been found to exhibit at least seven anhydrous polymorphs, including three main earlier reported polymorphs, namely I, II, and III by Lo et al. [2], Gu and Jiang [3], Dash and Elmquist [4], It was reported to exhibit a poor aqueous solubility ranging from 2 to 8 mg mL−1 [5]. In this respect, it is of paramount importance to modulate the physicochemical properties of this widely prescribed drug in terms of stability and aqueous solubility.

However, marketed formulations such as topical cream, ointment, powder affiliated with subordinate skin permeability and short retention time on skin of drug [6, 7]. FLZ shows its antifungal action by prohibiting the ergosterol synthesis, which is an important constituent of fungi cell membrane. It shows antifungal activity against fungi species such as Candida albicans, tinea-corporis, tinea-pedis [8]. Topical fungal infection and for skin care topical treatment of skin diseases a large range of commercially formulations are available but it requires more time for showing its result. So, the goal of current research study is to improve solubility of drugs in aqueous medium and incorporate them into the topical dosage form [9].

Cocrystals are multicomponent molecular crystals where all components are at a stoichiometric ratio and comprise of two or more chemically different molecules includes modification of drugs to alter physical properties of a drug, especially a drug's solubility without altering its pharmacology effect. [10, 11, 12] Co-crystals can be prepared by solvent and solid based methods. The solvent-based methods involve slurry conversion solvent evaporation, cooling crystallization and precipitation. The solid based methods involve net grinding; solvent-assisted grinding and sonication (applied to either to wet or dry solid mixtures) 80 to 85° C. Solvent evaporation is the most convenient method in the case of crystallization. [13] In this technique, the material is mixed with the

common solvent and evaporated completely. In the evaporation stage, the solution of molecules is expected to undergo various hydrogen bonding reactions. The current study is conducted to formulate, and evaluate the FLZ cocrystal loaded with topical gel.

2. MATERIALS AND METHODS

2.1 Materials: Fluconazole drug was purchased from TCI Chemicals, Japan. 2-chloro-4-nitrobenzoic acid, 2,3-dihydroxybenzoic acid, 2,6-dihydroxybenzoic acid, and 2,4-dinitrobenzoic acid were purchased from Sigma-Aldrich. All the chemicals were used as such without any further purification. Analytical grade/HPLC grade solvents were used for the crystallization experiment. Deionized purified water was used in the experiments.

2.2 Synthesis By Cooling Crystallization Method: The most common method are based on solution method and grinding method. In this work the co-crystals were prepared by cooling crystallization method. [14, 15]

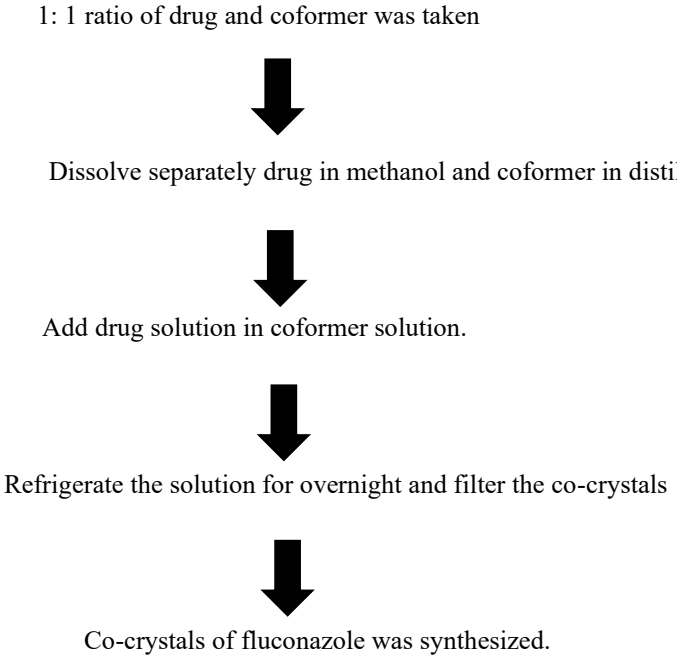

Table 1: Formulation Of Cocrystals

Formulation batches of cocrystals (Drug: Coformer)							
Ingredients	FC1 (1:1)	FC2 (1:2)	FC3 (1:3)	FC4 (1:4)	FC5 (1:5)	FC6 (2:1)	FC7 (3:1)
Fluconazole	100 mg	100 mg	100 mg	100 mg	100 mg	200 mg	300 mg
Succinic acid	100 mg	200 mg	300 mg	400 mg	500 mg	100 mg	100 mg
Methanol	10 ml	10 ml	10 ml	15 ml	15 ml	20 ml	20 ml
Water	10 ml	10 ml	10 ml	15 ml	15 ml	20 ml	20 ml

FC1-FC7- Formulation batches which are prepared by (drug: conformer) ratio

2.3 Evaluation Of Synthesized Co-Crystal [16-19]

2.3.1 Physical appearance: Synthesized cocrystals were visually characterized to study its colour, Odor, and texture. Microscopic characterization also done to see the shape of crystals. These are the identification tests for cocrystals.

2.3.2 Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetry, or DSC, is a thermal analysis technique that looks at how a material's heat capacity (Cp) is changed by temperature. A sample of known mass is heated or cooled and the changes in its heat capacity are tracked as changes in the heat flow. This allows the detection of transitions such as melts, glass transitions, phase changes, and curing. Because of this flexibility, since most materials exhibit some sort of transitions, DSC is used in many industries, including pharmaceuticals, polymers, food, paper, printing, manufacturing, agriculture, semiconductors, and electronics.

2.3.3 Fourier-transform infrared (FTIR) spectroscopy study: Fourier transform infrared (FTIR) spectroscopy probes the vibrational properties of amino acids and cofactors, which are sensitive to minute structural changes. The FL and FL cocrystals FTIR spectra were obtained using FTIR spectrophotometer. The samples were mixed with potassium bromide in 1:1 molar ratio and compressed into a disc before scanning between 4000 and 400 cm−1 with a resolution of 4 cm−1 the IR spectroscopy was used to determine the interaction between drug and conformer.

2.3.4 Drug content: Weighed quantity (10 mg) of prepared FL cocrystals was taken and dissolved in 100 ml ethanol. Then, the solution was ultrasonicated for 15 min to get a uniform solution. After that, the absorbance of the obtained solution was measured using an ultraviolet (UV)-visible spectrophotometer at 230 nm.

2.3.5 Saturated solubility study: Accurately weighed dried FL cocrystal equivalent to FL 100 mg of reconstituted with 50 ml of distilled water in a conical flask plugged with cotton. It was shaken for 48 h using orbital shaker. The samples were collected after the specified time interval, and it is filtered and analyzed. The diluted samples were analyzed using UV spectrophotometer. The same procedure was repeated for pure FL and physical mixture.

2.4 Preparation Of Co-Crystal Gel: Accurately weighed quantity of Carbopol 940 and HPMC was dissolved in 10 ml of distilled water (70°C) in beaker A. In another beaker B, 100 mg of FL cocrystal was dissolved in 8 ml of glycerin. Then, 2 ml of 10% NaOH and sufficient quantity of methyl paraben was added to a mixture containing FL cocrystal. Finally, beaker B containing solution was added into the beaker A. Properly mixed the above mixture and stirred well using mechanical stirrer to get a homogeneous mixture. Six different formulations were designed by varying the concentration of Carbopol 940 and HPMC given in Table 2. [20, 21]

Table 2: Formulation of FL cocrystal loaded gel

Ingredients	FCG1	FCG2	FCG3	FCG4	FCG5	FCG6
Drug	5	5	5	5	5	5
Succinic acid	10	10	10	10	10	10
HPMC K4M	0.5	1.25	0.5	0.2	0.7	0.2
Carbopol 940	0.5	1.25	0.2	0.5	0.7	0.7
10% NaOH	2	3	2	3	5	4
Glycerine	30	30	30	30	30	30
Methanol	40	40	40	40	40	40
Methyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01
Water	QS	QS	QS	QS	QS	QS

2.5 Characterization Of Gel Loaded With FLZ [22-25]

2.5.1 Physical appearance: The formulated gels were inspected visually for its color, consistency, and appearance.

2.5.2 Homogeneity: The formulated gels were checked for its homogeneity by visual inspection after filled into a suitable container. The gels were observed for their appearance and presence of any particulate matter.

2.5.3 pH determination: pH of the formulated gels was determined using digital Ph meter and observed readings were noted.

2.5.4 Spreadability: The spread ability (cm) of the gel formulations was determined by placing accurately weighed 1 g of gel between two horizontal glass plates and 500g of weight applied over the plate for 1 min. Later, the spread ability was determined by measuring the diameter of gel spread over the plate in 1 minute.

2.5.5 Viscosity: The viscosity (cps) of the prepared gels was determined using Brookfield Viscometer. The spindle was rotated at 10 r/min and the sample was allowed to settle for 30 min at temperature 25°C before the readings were taken.

2.5.6 In vitro drug release study: In vitro drug release study (%) was carried out using fabricated vertical Franz diffusion cell apparatus. The cellophane membrane was used for this study. An accurate amount of gel (0.5 g) was applied on cellophane membrane. Entire surface of the membrane was in contact with a receptor compartment filled with 20 ml phosphate buffer of pH 6.8 as a diffusion media. The whole assembly was placed on a magnetic stirrer and the solution was stirred continuously at 200 rpm with the temperature maintained at 37±1°C. The sample (1 ml) was withdrawn at a specific time interval and replaced with the same

volume of fresh phosphate buffer to maintain sink condition. Further suitable dilution of the sample was made and analyzed using a UV-visible spectrophotometer at 230 nm.

2.5.7 Stability studies: Prepared FL cocrystal loaded formulations were filled in a suitable container and subjected to stability study as per ICH guidelines. Formulations were kept at 40°C/75% RH, 25°C/60% RH, and room temperature for 1 month. Samples were evaluated for pH, physical appearance, viscosity, spreadability, and drug release.

3. RESULTS AND DISCUSSION

3.1 FTIR Spectra: The FTIR analysis performed of fluconazole and stearic acid for better compatibility analysis of leading moiety before and after formulation. FTIR spectra of fluconazole is shown in Figure 1. These detected principal peaks confirmed purity and authenticity of fluconazole as similar to referenced report.

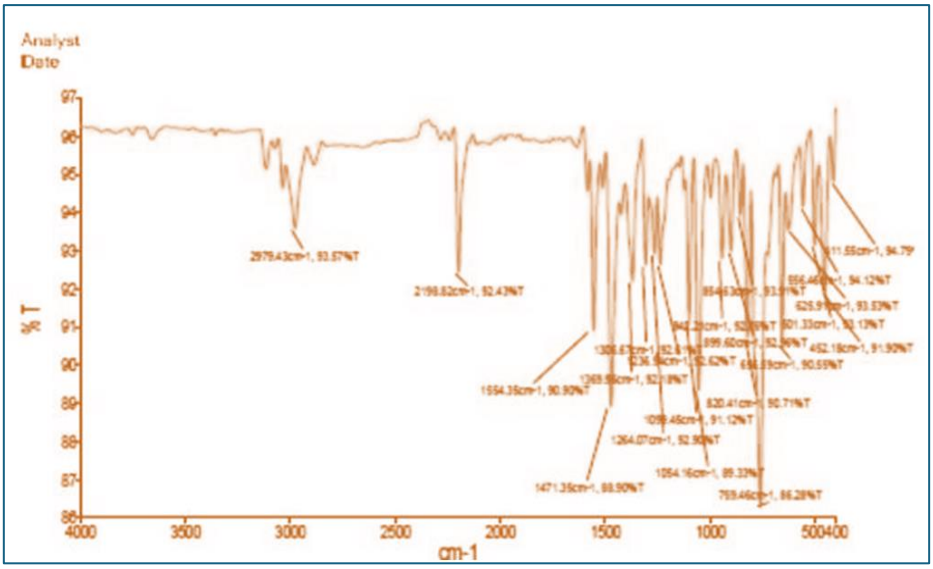

Figure 1: FTIR spectrum of fluconazole

3.2 EVALUATION AND CHARACTERIZATION

3.2.1 Microscopic characterization of cocrystals: Microscopic characteristics of prepared cocrystals were observed cocrystals by light microscope. Microscopic images are shown in following Figure 2.

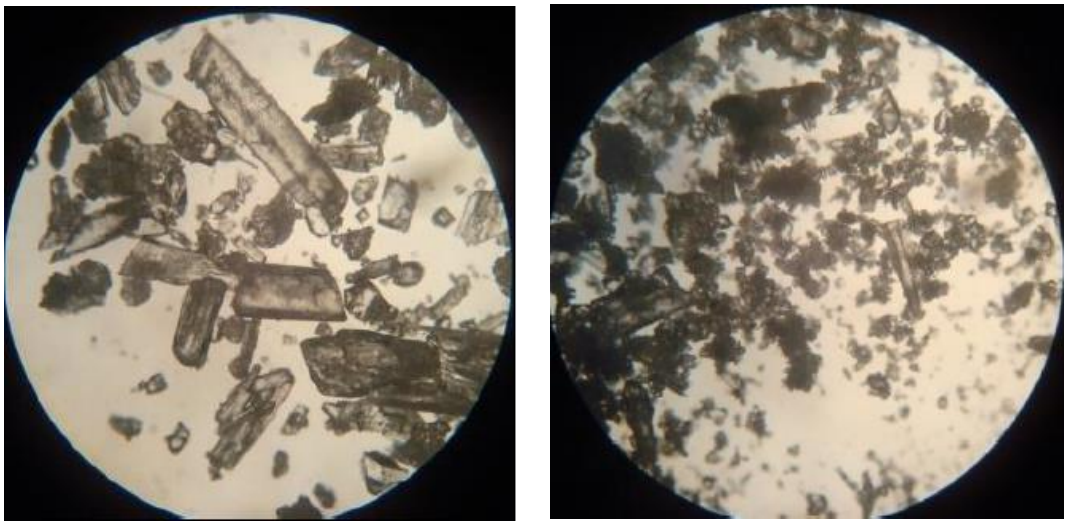

Figure 2: Microscopic Images Of Cocrystals.

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3.2.2 DSC Analysis: DSC analysis was used to evaluate the phase transformation during the formation of cocrystals. There was a shift in the thermogram observed in the case of FL cocrystal (Fig.3) and the peak was showed at 136°. The non-covalent interaction between the drug and conformer is an indication of the formation of cocrystals. This noncovalent interaction between drug and conformer is occurred due to the formation of a hydrogen bond between the polar functional group. This interaction resulted into the change in the molecular structure of the cocrystals formed which gives a new crystalline form of drug with altered physical properties such as solubility and melting point.

3.2.3 FTIR Spectrum: FTIR is an important medium used for the conformation of cocrystals formation and it showed the formation of hydrogen bond between pure drug and conformer. FTIR peak for pure FL and FL cocrystals was recorded and shown in Figure 3.5. The principle bands were identified and significant changes were recorded. The IR spectra of the FL cocrystals were showed the peak at 2578 cm−1, 1704 cm−1, 1519 cm−1, and 3363 cm−1 for C-H, –NH, C=O ketone, and C=O amide, respectively. The change in peak shape, peak intensities, and peak broadening was observed which indicates the formation and confirmation of the FL cocrystal with a new crystalline phase.

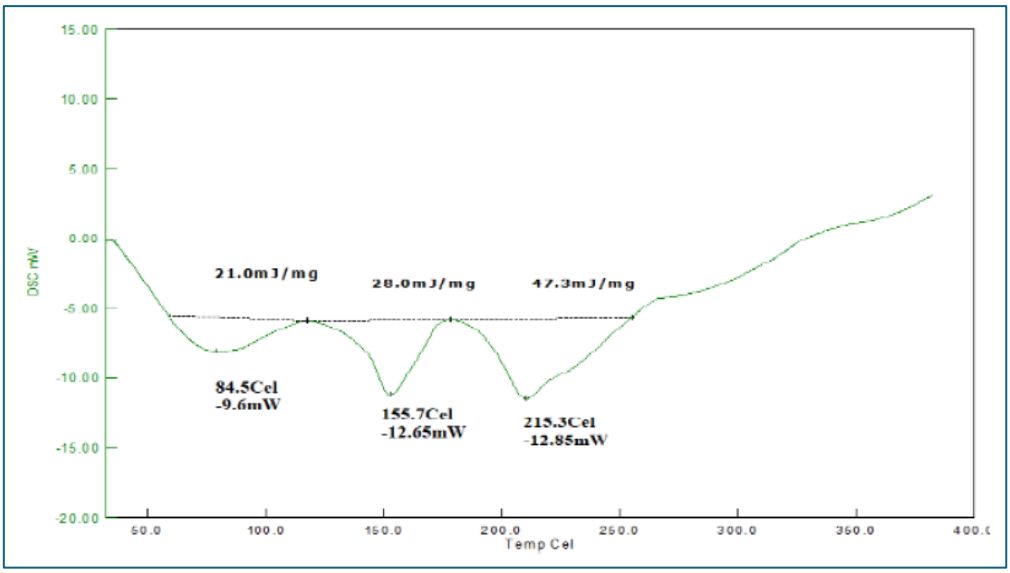

Figure 3: DSC Spectrum of Co-crystal

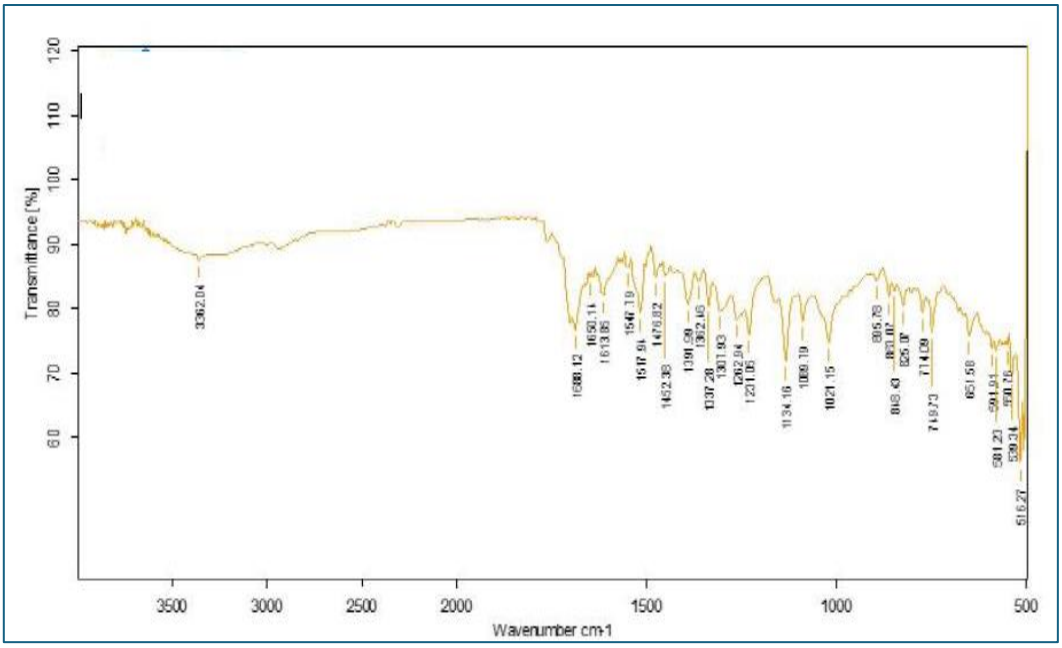

Figure 4: FTIR of FL Co-crystals

3.2.4 Saturated solubility study: Saturated solubility (µg/ml) of FL cocrystals was performed successfully. The corystals was found to be 11.02. It clearly stated that the solubility of FL was increased in the cocrystal form of drug. The solubility of cocrystals was increased due to molecular interaction of non-covalent bonds and hydrogen bond formation between drug APR and conformer urea.

3.2.5 % Drug Content: After successful synthesis of different batches of co-crystals, percentage DC of fluconazole determined. Percentage of DC evaluated spectrophotometrically at 230 nm. Thereafter results reveal that FC2 and FC5 have highest and lowest % DC of fluconazole co-crystals by 94.76% and 63.75% respectively.

3.3 EVALUATION OF GEL

3.3.1 Physical appearance: The formulated FLZ cocrystals loaded gels were inspected visually. The gel was found to be white in color and smooth appearance.

3.3.2 Viscosity and Ph: The viscosity and pH of all formulations were determined successfully. The obtained data were given in Table 3.

3.3.3 Spreadability (cm): The spreadability of all the gels was ranging from 4.3cm to 6.4cm. It was observed that formulations FCG4 showed higher spreadability, which may be due to an increased concentration of carbopol 940. The spreadability test results are interpreted in Table 3.

3.3.4 In vitro drug release and kinetics study: Statistical models are commonly used to forecast release mechanism and compare release profile. In-vitro release profile of drug performed in prepared buffer system using dialysis bag technique for 24 hrs. desolvation percentages of fluconazole from co-crystals are increased in proportion of time. Pieces of evidence of release profiles show that developed is proficient to release drug in regulated manner. Slow release of leading moiety from most Co-crystal form is based on homogeneous drug entrapment throughout systems.

Table 3: pH and Viscosity

Formulation	pH	Viscosity (cps)	Spreadability cm.g/sec
FCG1	7.16	6797.54	5.1
FCG2	6.24	3278.65	4.3
FCG3	7.15	2986.55	5.3
FCG4	6.89	5986.64	6.4
FCG5	7.07	7592.23	4.9
FCG6	6.84	6396.12	6.2

Table 4: Percentage Drug Release

1. Sr. no.	**2. Time inhours**	**3. Percentage drugrelease of FCG4**	**4. Percentage drug releaseof control gel**
5.1	6.0	7.0	8.0
9.2	10. 0.25	11. 7.375±0.153	12. 1.923± 0.011
13. 3	14. 0.5	15. 14.002±0.185	16. 2.052± 0.155
17. 4	18. 1	19. 22.064±0.102	20. 14.042± 0.158
21. 5	22. 2	23. 33.289±0.173	24. 19.182± 0.162
25. 6	26. 3	27. 40.622±0.165	28. 22.094± 0.122
29. 7	30. 4	31. 48.048±0.151	32. 26.815± 0.205
33. 8	34. 6	35. 54.582±0.163	36. 28.706± 0.215
37. 9	38. 8	39. 62.309±0.134	40. 36.387± 0.118
41. 10	42. 10	43. 72.939±0.115	44. 38.035± 0.205
45. 11	46. 12	47. 80.578±0.213	48. 39.773± 0.158

Furthermore, “an in-vitro drug release profile for optimized formulation applied to various kinetic models (zero-order, first-order, Higuchi, and Krosmayer Peppas model)”. To state kinetics profiling of drug release, obtained data were analyzed statistically in respect of rate constant and highest correlation. Best-fitted line found in all models except little suitability in zero-order equation. Resulting data describe dissemination of drug in controlled or regular manner from homogenous matrix systems and it states why

drug disseminates at slower rate. Observations concluded that FCG4 is far efficient as potential topical formulation for sustained drug delivery.

3.5 Stability study: During the storage of FL cocrystals loaded gel, there may be chances of changes in the physicochemical parameters. Hence, the prepared formulations were subjected for the stability study at room temperature and accelerated condition for a period of 1 month to define the stability. It was found that the FL loaded gel was stable at both conditions. The obtained data were given in Table 3.5.

Table 5: Result of Stability Study

Month	0	1
ROOM Temperature (25 C, 60% RH)	100	98.76
Accelerated Temperature (40 C, RH 75%)	100	98.21

4. CONCLUSION

The Cocrystals of FL and succinic acid were prepared using the solvent evaporation technique. The prepared FL cocrystals exhibit good physicochemical properties such as solubility and dissolution. The prepared FL-cocrystals were formulated into a topical gel. Carbapol-940 and HPMC were used as a gelling agent as independent variables. FC4 formulation was found to be optimized batch and selected variables show a significant effect on the responses that are drug release and spreadability.

From the overall conducted study, we can conclude that the newly developed crystalline form of FL with succinic acid showed increased solubility and dissolution rate and it was given in topical formulation to overcome problems related to oral administration of drug.

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