

Research Article



Formulation and Evaluation of Apremilast Co-crystals Loaded in Gel

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Received: 08-11-2021; Revised: 16-01-2022; Accepted: 25-01-2022; Published on: 15-02-2022.

ABSTRACT

Apremilast has low solubility and irritant effect in GIT can cause ulcerative colitis with bleeding. In this study, pharmaceutical cocrystals were designed to efficiently deliver Apremilast (APR) 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 APR 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 APR by using the solvent evaporation method. The cocrystals of APR were prepared in 1:1 molar ratio with urea. APR cocrystals showed the improvement in solubility and dissolution as compared to pure APR. 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 APR cocrystals was formulated using Carbapol-940 and hydroxypropyl methylcellulose (HPMC) as a gelling agent. The cocrystals with altered physicochemical properties of APR were prepared with Urea and formulated as a topical gel to overcome the problems related to oral administration. F2 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: Apremilast, Urea, Solvent evaporation, Solubility, Co-crystals, Gel.

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DOI:
10.47583/ijpsrr.2022.v72i02.009



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2022.v72i02.009>

INTRODUCTION

Psoriasis is an immune-mediated, genetic disorder manifesting within the skin or joints or both. The high physical burden of disease isn't so well understood by scientists but could be associated with symptoms like itching or burning sensations.¹ Symptoms repeatedly reported by patients include pain, itch, and bleeding.² Individuals with psoriasis are at an increased risk of developing other chronic and high health diseases. These comorbid diseases include atrophic arthritis, metabolic syndrome or components of the syndrome, cardiovascular disorders, and variety of other diseases like anxiety and depression, non-alcoholic disease, Crohn's disease, and lymphoma.^{3,4} Topical therapies like glucocorticosteroids, vitamin D derivatives, or combinations of both are usually sufficient to manage the mild disease. Results from a recent meta-analysis⁴ showed that a mixture of corticosteroids and vitamin D3 was the foremost effective treatment for the scalp. Practicability (time needed to use treatment), convenience, and adverse

effects like skin irritation limit the utilization of topical drugs. Established systemic drugs for the treatment of psoriasis include methotrexate, cyclosporin, acitretin, and in some countries acid esters. Additionally, the oral phosphodiesterase-4 inhibitor apremilast has been approved within the USA and Europe.

Apremilast (Otezla, Celgene Corporation, Summit, NJ) was approved by the US Food and Drug Administration (FDA) in 2014 and by the European Commission in 2015 for treatment of psoriasis and psoriatic arthritis.^{5,6} It specifically inhibits phosphodiesterase⁴.

Cocrystals

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.^{7, 8, 9}

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. 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.

Topical drug delivery offers several advantages compared to oral administration. Without entering the bloodstream, the active ingredient can reach the site of inflammation, increase in the concentration of the drug on the skin, which helps in increasing the amount of the drug in the formulation without fearing from toxicity or GIT problems. It is also possible to avoid systemic adverse effects in this way. Besides, by targeting the drug directly to the affected area, the first-pass effect can be reduced.¹⁰

The current study is conducted to formulate, and evaluate the APR cocrystal loaded with topical gel. Since the APR has two major problems when administered orally; first, it has low solubility and irritant effect in GIT can cause ulcerative colitis with bleeding.

MATERIALS AND METHODS

Materials

APR was obtained as gift sample from Mylan Laboratories Limited (Unit-7), Telangana, India. Urea, methanol and all other chemicals were obtained from Hyderabad. Double distilled water and analytical grade quality solvents were used throughout the research work.

Method

Formulation of cocrystal

APR cocrystals were prepared using the solvent evaporation method. Accurately weighed APR and conformer urea in 1:1 molar ratio was dissolved in an appropriate quantity of methanol as a solvent. The prepared mixture was heated on a hot plate till clear solutions were obtained and allow standing for evaporation of solvent at room temperature. The fine crystals were obtained after a few days which were collected, dried, and stored in an airtight container until further use.¹¹

Preparation of APR Cocrystal loaded 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 APR 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 APR 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 1.

Table 1: Formulation of Apremilast cocrystal loaded gel

INGREDIENTS	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
Apremilast	5	5	5	5	5	5
Urea	5	5	5	5	5	5
Carbopol 940	0.5	1.25	0.2	0.5	0.7	0.7
HPMC K4M	0.5	1.25	0.5	0.2	0.7	0.5
10 % NaoH	2	3	2	3	5	4
Glycerin	30	30	30	30	30	30
Methyl Paraben	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Methanol	40	40	40	40	40	40

Characterization of cocrystal

Physical appearance

Prepared APR cocrystals were visually characterized to study its color, odor, and texture.

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.¹²

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 APR and APR 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.¹³

Drug content

Weighed quantity (10 mg) of prepared APR cocrystals was taken and dissolved in 100 ml methanol. 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.¹⁴

Saturated solubility study

Accurately weighed dried APR cocrystal equivalent to APR 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 APR and physical mixture of APR:Urea (1:1).¹⁵

In vitro dissolution study of cocrystal

The dissolution studies (%) were carried out in pH 6.8 phosphate buffer solution (900ml) for 60 min at 37 ± 0.5 and 50 rpm using United States Pharmacopeia (USP) type II dissolution test apparatus. The pure drug APR and APR cocrystal equivalent to 20 mg of drug were used for the study. Five milliliters of samples were withdrawn after a specified time interval and immediately replaced with an equal volume of fresh dissolution medium. The sample was filtered using Whatman filter paper. Later suitable dilutions of the sample were done and analyzed using a UV-visible spectrophotometer at 230 nm.¹⁶

Characterization of gel loaded with APR

Physical appearance

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

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.⁵⁹

pH determination

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

Spread ability

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.

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.⁶³

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 $37 \pm 1^\circ\text{C}$. 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.

Stability studies

Prepared APR 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.

RESULTS AND DISCUSSION

Preformulation study

Appearance of drug substance

Prepared APR cocrystals were found to be white in color.

Determination of drug content

The drug content of the APR cocrystals was found to be 86.3%. The obtained drug content was quite sufficient to the formulation of cocrystals in a suitable dosage form.

DSC

DSC analysis was used to evaluate the phase transformation during the formation of cocrystals. DSC thermogram of APR in (Fig.1) showed an endothermic peak at 156.45° corresponding to its reported melting point and the reported melting point of urea was 228.8° . There was a shift in the thermogram observed in the case of APR cocrystal (Fig.2) 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 non-covalent 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.



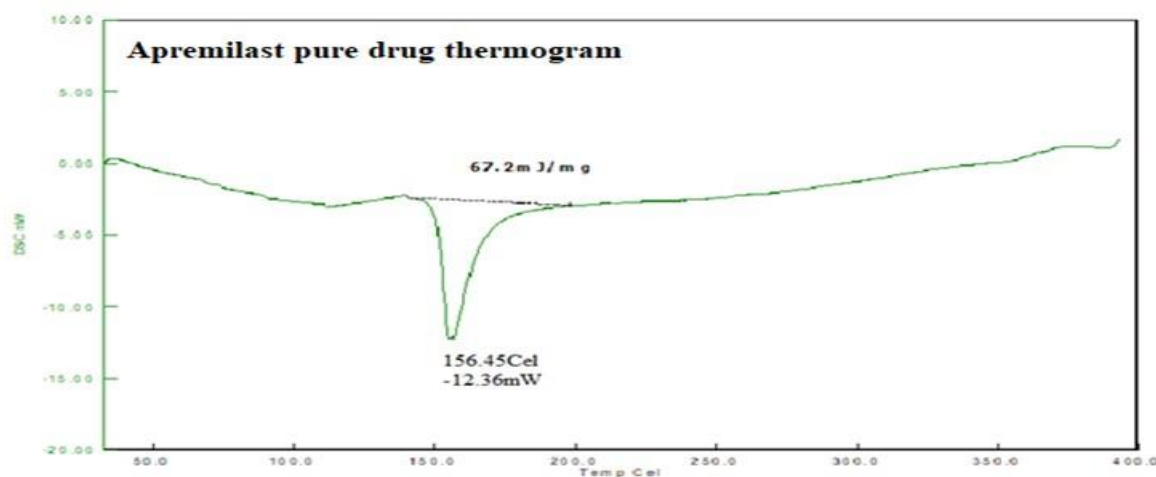


Figure 1: Differential Scanning Calorimetry of Pure Apremilast

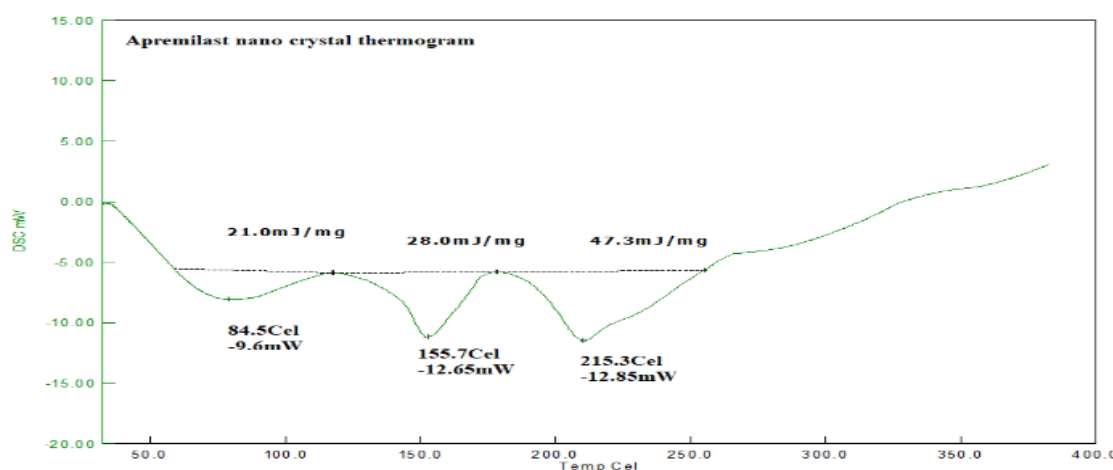


Figure 2: Differential Scanning Calorimetry of Apremilast Cocrystals

FTIR spectroscopy study

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 APR and APR cocrystals was recorded and shown in Figs.3 and 4. The principle bands were identified and significant changes were recorded. The pure APR spectra of IR showed the characteristics peak which was recorded at 2944 cm^{-1} -NH stretching, 1763 cm^{-1} aromatic -C=O ketone stretching, 1617 cm^{-1} -C=O amide stretching, and 2944 cm^{-1} C-H stretching. The IR spectra of the APR 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 APR cocrystal with a new crystalline phase.

Saturated solubility study

Saturated solubility ($\mu\text{g}/\text{ml}$) of pure APR and APR cocrystals was performed successfully. The solubility of pure APR was found to be 6.89 $\mu\text{g}/\text{ml}$ and the cocrystals was found to be 11.02. It clearly stated that the solubility of APR 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.

In vitro dissolution study

In vitro dissolution (%) study of pure APR and APR cocrystals were carried out successfully. The dissolution curve of pure APR and an APR cocrystal in 6.8 pH phosphate buffer is shown in Figure 5; it was an evident that the cocrystals of APR with urea clearly showed the improvement in dissolution rate as compared to pure drug.

Evaluation of APR cocrystals loaded gel

Physical appearance

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

Viscosity and pH

The viscosity and pH of all formulations were determined successfully. The obtained data were given in Table 2.

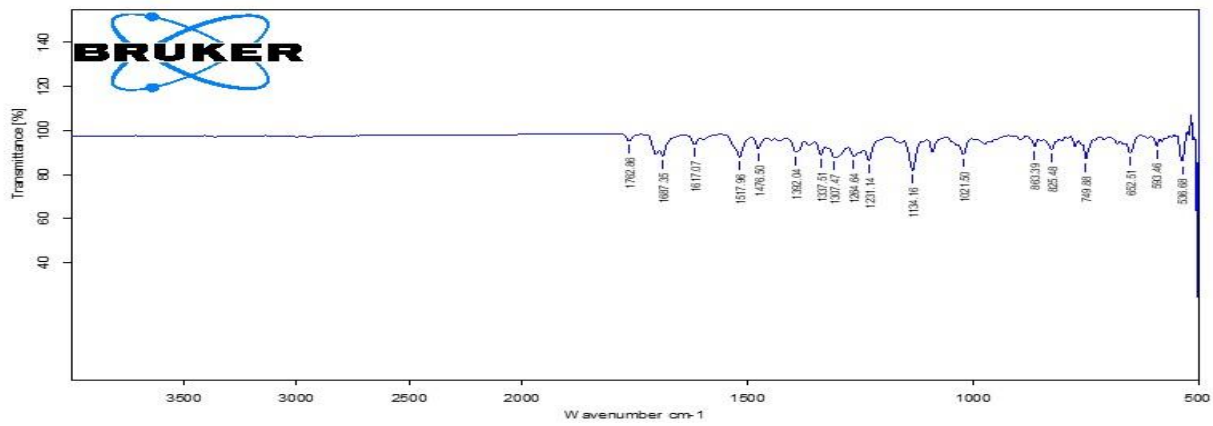


Figure 3: FTIR Spectra of Apremilast Pure Drug

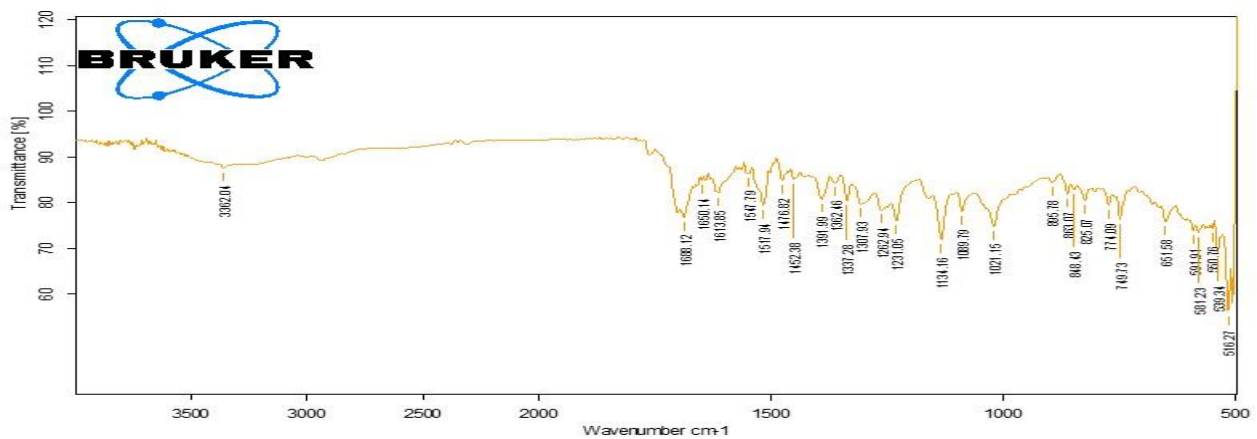


Figure 4: FTIR Spectra of Apremilast Cocrystals

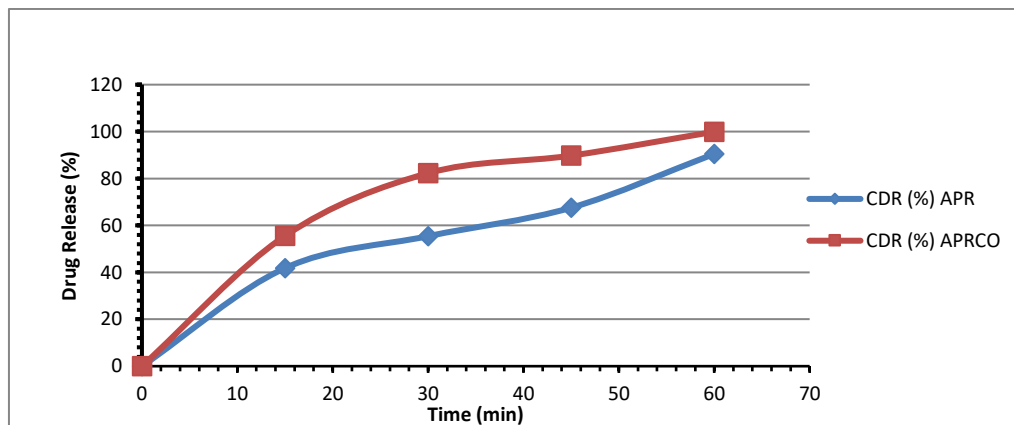


Figure 5: In-vitro dissolution of APR and APR Cocrystals

Spreadability (cm)

The spreadability of all the gels was ranging from 4.3cm to 6.4cm. It was observed that formulations F1, F2, and F5 showed higher spreadability, which may be due to an increased concentration of carbopol 940. The spreadability test results are interpreted in Table 2.

In vitro drug release (%)

From the drug release study, it was observed that formulations F1, F2, F5, and F6 showed the drug release from 65.4 to 98.9 up to 1 hour. This might be due to the

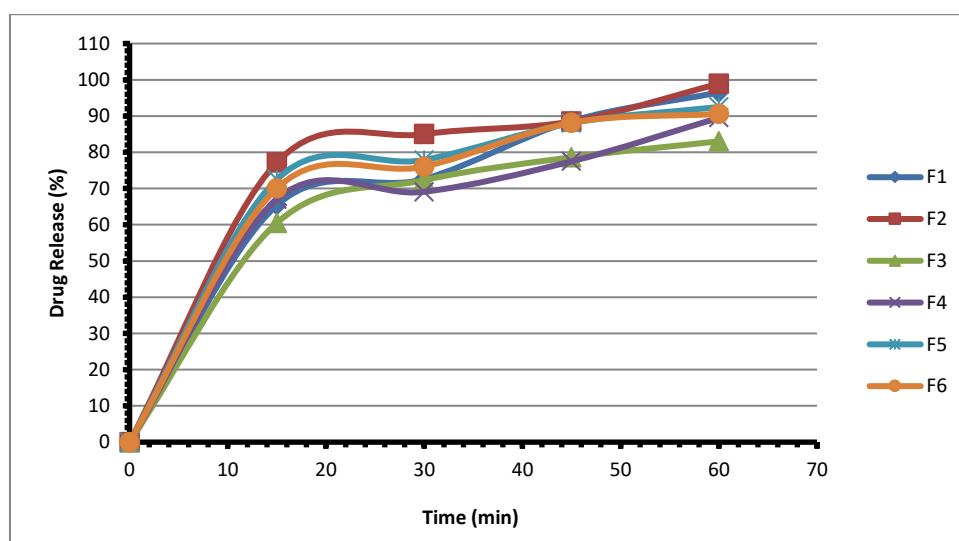
increase in the concentration of carbopol 940 from 0.5 to 1.25% along with increase in the amount of HPMC added. The gel F3 and F4 showed drug release of 83.02 and 89.5 up to 1 hour which may be due to the fact that increased concentration of carbopol 940 was led to increasing the viscosity of these formulations which in turn makes the diffusion of drug through the dialysis membrane slower. Among all the six gels formulated, formulation F2 containing 1.25% of carbopol 940 and 1.25% of HPMC showed highest drug release of 98.9% and was optimized as the best. The drug release profile of apremilast gels is depicted in Table 3 and Figure 6.

Table 2: Result of Viscosity, pH and Spreadability of different formulations

Formulation Code	Viscosity (cps)	pH	Spread ability (cm)
F1	569.7	6.7	5.5
F2	592.2	7.0	6.4
F3	390.2	6.4	4.3
F4	436.4	6.5	5.3
F5	552.6	6.7	5.4
F6	511.6	6.5	5.1

Table 3: Percentage Drug release of Apremilast gels

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	65.4	77.2	60.5	67.05	72.5	70.06
30	72.6	85	72.3	69.08	77.89	76.05
45	88.6	88.5	78.6	77.5	88.06	88.15
60	96.5	98.9	83.02	89.5	92.5	90.6

**Figure 6:** Drug Release of Apremilast Gel

Stability study

During the storage of APR 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 APR loaded gel was stable at both conditions. The obtained data were given in Table 4.

Table 4: Result of Stability Study

Month	0	1
Room temp (25°C, 60% RH)	100%	100%
Accelerated temp (40°C, RH 75%)	100%	99.21%

CONCLUSION

The Cocrystals of APR and Urea were prepared using the solvent evaporation technique. The prepared APR-cocrystals exhibit good physicochemical properties such as solubility and dissolution. The prepared APR-cocrystals were formulated into a topical gel. Carbapol-940 and HPMC were used as a gelling agent as independent variables. F2 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 APR with Urea showed increased solubility and dissolution rate and it was given in topical formulation to overcome problems related to oral administration of drug.

Acknowledgments: The authors are sincere thankful to principal and management of Anwarul Uloom College Pharmacy, New Mallepally, Hyderabad.

REFERENCES

- Dubertret L, Mrowietz U, Ranki A, and the EUROPSO Patient Survey Group. European patient perspectives on the impact of psoriasis: the EUROPSO patient membership survey. *Br J Dermatol* 2006; 155: 729–36.
- Griffiths CEM, Barker JNWN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; 370: 263–71
- Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; 361: 496–509.
- Mason AR, Mason JM, Cork MJ, Hancock H, Dooley G. Topical treatments for chronic plaque psoriasis of the scalp: a systematic review. *Br J Dermatol* 2013; 169: 519–27
- Hägg D, Eriksson M, Sundström A, Schmitt-Egenolf M. The higher proportion of men with psoriasis treated with biologics may be explained by more severe disease in men. *PLoS One* 2013; 8: e63619.
- Shmidt E, Wetter DA, Ferguson SB, Pittelkow MR. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor- α inhibitors: the Mayo Clinic experience, 1998 to 2010. *J Am Acad Dermatol* 2012; 67: e179–85.
- Fong SYK, Ibisogly A, Bauer-Brandl A. Solubility enhancement of BCS class-II drug by solid phospholipid dispersions: Spray drying versus freeze-drying. *Int J Pharm* 2015; 496: 382-91.
- Jones W, Motherwell WDS, Trask AV. Pharmaceutical co-crystals: An Emerging approach to physical property enhancement. *MRS Bull* 2006; 31: 875-879.
- Zaworotko M. Crystal engineering of co-crystals and their relevance to pharmaceuticals and solid-state chemistry. *Acta Cryst* 2008; 64: 11-12.
- Otezla [package insert]. Summit, NJ: Celgene Corporation; 2014.
- Sevukarajan M., Thanuja B, Sodanapalli R, Nair R. Synthesis and characterization of pharmaceutical co-crystal: Aceclofenac: Nicotinamide. *J Pharm Sci Res* 2011; 3: 1288-93.
- Payghan SA. Preparation and characterization of molecular complexes of finofibrate co-crystal. *Asian J Pharm* 2017; 11: 745-58.
- Panzade P, Shendarkar G. Design and preparation of zaltoprofen-nicotinamide pharmaceutical co-crystal via liquid assisted grinding method. *Indian J Pharm Educ* 2019; 53: S563-70.
- Sai Priyanka NV, Neeraja P, Mangilal T, Kumar MR. Formulation and evaluation of gel loaded with microspheres of aprimilast for transdermal delivery system. *Asian J Pharm Clin Res* 2019; 12: 411-7.
- Sopyan I, Fudholi A, Muchtaridi M, Sari IP. Simvastatin-nicotinamide co-crystal: Design, preparation and preliminary characterization. *Trop J Pharm Res* 2017; 16: 297-303.
- Sopyan I, Fudholi A, Muchtaridi M, Sari IP. Co-crystalization: A tool to enhance the solubility and dissolution rate of simvastatin. *J Young Pharm* 2017; 9: 183-6.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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