Formulation and Evaluation of Orodispersible Tablets of Apremilast by Inclusion Complexation using β-Cyclodextrin

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ABSTRACT

Introduction: The present study was carried out to formulate and evaluate orodispersible tablets of Apremilast with a purpose of providing better patient compliance to geriatric, pediatric, impaired, travelling and non-cooperative patients suffering from psoriasis. Such patients are in need of fast and easy swallowing drug delivery system. **Materials and Methods:** The Apremilast-β-cyclodextrin inclusion complex was prepared by physical blending method with a principle of increasing the solubility and permeability of drug. The inclusion efficiency of Apremilast: β-cyclodextrin ratios (1:1,1:2,1:3) were calculated and it was investigated that 1:2 ratio complex is highest. The orodispersible tablets of apremilast (F1 to F9) were prepared by simple and cost effective direct compression technique using different concentrations of super disintegrate croscarmellose sodium. **Results:** The results of pre-compression characteristics of powder blends and post-compression parameters of tablets were studied and showed satisfactory. Among all formulations studied, Formulation F6 showed less disintegration time and percent cumulative drug release 98.7% so it was declared as an optimized formulation. **Conclusion:** Therefore, It can be concluded that drug dissolution, absorption, therapeutic effect and bioavailability can be significantly greater than those as compared with conventional treatment of psoriasis in a cost-effective manner with better patient compliance.

Key words: Psoriasis, Orodispersible Tablet, Inclusion Complexation, Apremilast-β cyclodextrin, Croscarmellose sodium.

INTRODUCTION

Tablet is the most convenient among all drug delivery systems because of its convenience of self-administration, compactness and easy manufacturing. However dysphasia or difficulty in swallowing in case of geriatric patients, pediatric, travelling patients who may not have ready access to water, uncooperative patients are common phenomenon's which leads to poor patient compliance.[1] To overcome these disadvantages, Orodispersible tablets has emerged as alternative oral dosage forms.

Orodispersible tablets are also called as orally disintegrating tablets (ODTs), mouth-dissolving tablets (MDTs), rapid-dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets (FDTs), porous tablets and rapimelts. European Pharmacopoeia seventh edition and United States Pharmacopoeia (USP) has used the term orodispersible tablets and defined as uncoated tablets intended to be placed in the mouth where they disperse or disintegrate readily within 3 min before swallowing. Orodispersible tablets are solid unit drug delivery system composed of super disintegrates, which disintegrate or disperse the tablets within 3 min in the presence of saliva in mouth without any difficulty of swallowing.[2] It has numerous advantages with respect to its administration

without water, accurate dosing, easy manufacturing, small packaging size, stability and handling. Its ease of administration in the population especially for pediatric, geriatric, or any mentally retarded persons makes orodispersible tablets a very popular drug delivery system. Due to the presence of super disintegrates, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action. Since the absorption is taking place directly from the mouth, so, bioavailability of the drug increases. Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its several advantages.[3]

The present invention relates to the development of orodispersible tablets of Apremilast by inclusion complexation Using β-Cyclodextrin. Apremilast is a PDE-4 (Phosphodiesterase 4) inhibitors, an orally administered small molecule, which has shown great promise in treating patients with psoriasis, few other dermatologic disorders and certain type of arthritis (psoriatic arthritis). Apremilast decreases pain and swelling in patients those are suffering from psoriatic arthritis and help to improve flexibility in the affected joints. It help to reduce the redness, thickening and scaling of the skin in the treatment of plaque psoriasis. In this way apremilast plays a noteworthy anti-inflammatory and anti-psoriatic role.[4]

Being BCS class-4 Drug, Apremilast has low solubility and low permeability. Many attempts or means have been used to increase the solubility and permeability of Apremilast. It can be increased by forming a complex with β-Cyclodextrin. β-Cyclodextrin enhances the aqueous solubility of drugs and hence permeability through inclusion complexation (Table 1) which will be used to formulate orodispersible tablets. This will not only enhance the bioavailability of the drug but also reduce the onset of action due to fast absorption of drug from GIT as drug will be available as ready to absorption i.e. in solution form from the mouth cavity itself.[5]

MATERIALS AND METHODS

Materials

Apremilast was provided for the study by Glenmark Pharmaceuticals Ltd., (Pune, India). β-cyclodextrin, mannitol, Croscarmellose sodium and magnesium stearate were obtained from Research Lab Fine Chem Industries (Mumbai, India). Apremilast tablets (Aprezo, Glenmark, the reference tablet) were purchased. All other chemicals and reagents used were of analytical grade.

Methods

Preparation of Apremilast-β-cyclodextrin complex by Physical blending method

Complex can be prepared using β-cyclodextrin. In the present study one carrier was used. The complex was made by Physical blending method (Table 2). The required molar (1:1,1:2,1:3) quantities of the Drug: β-cyclodextrin were weighed accurately and blended together thoroughly in a mortar at laboratory scale, with vigorous trituration, for about 30 min. These mixtures then passed through sieve no 44 and finally stored in airtight containers till further use. The physical mixtures were also prepared at large scale by blending Apremilast with β-CD in a rapid mass granulator for 30 mins. These powdered physical mixtures were then stored in the room at controlled temperature ($25° ± 2.0°$) and humidity conditions (Relative humidity 40-50%) for comparison with the corresponding solid complex powders.[6]

Evaluation of complex

Production Yield

The production yield of complex's of various combinations was calculated using the weight of final product after drying with respect to the initial total weight of the drug and carrier used for the preparation of complex. Percent production yields were calculated as per the formula mentioned below,

$$P_Y = \frac{W_O}{W_T} \times 100$$

Where,
P_Y = Product yield,
W_O = Practical mass (complexs)
W_T = Theoretical mass (carrier + drug)

Drug Content (Inclusion efficiency)

About 10 mg drug equivalent of complexes (theoretical) were weighed accurately and transferred to 100 ml volumetric flask. From this stock solution (100 μg/ml), 1 ml was withdrawn and further diluted up to 10 ml with methanol. This solution was used for the assay for drug content by UV spectrophotometer at 230 nm. Concentration of drug in stock solution was calculated by using calibration curve and from which percent drug content in complex was calculated.

$$\% \text{ Drug Content} = \frac{W_A}{W_T} \times 100$$

Where,
W_A = Actual drug content,
W_T = Theoretical drug content.

Table 1: Enhancement of Absorption of BCS Class 4 Drug.

BCS Class	Solubility	Permeability	Rate Determining Step to drug absorption	Effect of Cyclodextrin Complication
1	High	High	Good Bioavailability	Can decrease absorption
2	Low	High	Aqueous diffusion	Can enhance absorption
3	High	Low	Membrane Permeation	Can decrease absorption
4	Low	Low	Aqueous diffusion and Membrane Permeation	Can enhance absorption

BCS stands for Biopharmaceutical Classification System.

Table 2: Different ratios used for preparation of complex.

Sr. No.	Carrier	Drug(Apremilast): Carrier (β-Cyclodextrin) Ratio (w/w)		
1.	β-Cyclodextrin	1 : 1	1 : 2	1 : 3

Saturation Solubility Study

Saturation solubility studies was carried out for complex prepared. This study was the basic criteria to identify and judge a complex of choice, which would enhance the solubility and so, would show good results in *in-vitro* dissolution studies. The following procedure remains same for the drug and their complex. Solubility studies were carried out in glass vials. In each of these vials, 10 ml distilled water was added. Excess quantities of complexes were added into each of vials. These vials were shaken continuously for 24 hr on a lab shaker and the resulting solutions were filtered, appropriate dilutions were made and UV absorbance's were recorded at 230 nm.

Dissolution Studies of Complex

The *in vitro* dissolution studies for complex were carried in USP Apparatus 2. Samples equivalent to 10 mg of Apremilast were added to 900 mL of phosphate buffer pH 6.8 at 37 ± 0.5°C and stirred at 50 rpm. 10 ml aliquots were withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 45, 60 min. and filtered through Whatman No. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analysed spectrophotometrically at 230 nm. Cumulative percentage of labelled amount of drug released was calculated.[7]

Method of Preparation of Powder Blend

Complex of Apremilast: β-cyclodextrin (containing appropriate amount of complex which is equivalent to 10 mg of apremilast) and other inactive ingredients along with varying % of Croscarmellose sodium at three concentration levels. Formulations coded as F1 to F9 respectively. In the first step, active and inactive ingredients weighed accurately and were screened through a 60-mesh sieve. The complex (Apremilast: β-cyclodextrin) and superdisintegrant Croscarmellose sodium were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 20 min. Finally the blend is passed through mesh #40 and used for evaluation of flow characteristic.[8] Formula for Orodispersible tablet of apremilast is shown in Table 3.

Evaluations of powder blend for flow properties

Bulk Density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. Bulk density of powder blends was determined using the following formula.

$$\text{Bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}}$$

Tapped density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped densities (TD) of powder blends were determined using the following formula.[9]

$$\text{Tapped bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}}$$

Angle of Repose

Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles. The angle of repose (θ) for powder was determined by placing the powder in a funnel. The tip of the orifice of the funnel was fixed from the ground horizontal surface at a height of 1cm and the powder were allowed to flow only under the force of gravity. The angle of repose, θ was calculated from the following relationship.

Sr. No.	Ingredients (mg)	Formulations								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1.	Apremilast	10	10	10	10	110	10	10	10	10
2.	β-cyclodextrin	15	15	15	20	20	20	25	25	25
3.	Croscarmellose Sodium	1	3	5	1	3	5	1	3	5
4.	Mannitol	72	70	68	67	65	63	62	60	58
5.	Magnesium stearate	2	2	2	2	2	2	2	2	2
6.	Orange Flavour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total (mg)	100	100	100	100	100	100	100	100	100

Table 3: Formula for orodispersible tablet of apremilast.

$$\tan \theta = h/r$$

Where, *h* is height of the pile of powder (*h*=1) and *r* is the radius of the base of cone.

Hausner Ratio

Hausner's ratio was determined by following equation, Hausner's Ratio=Tapped bulk density/Loose bulk density. A hausner ratio less than 1.12 indicates good flow while greater than 1.35 indicate poor flow.

Compressibility Index

It is a simple index that can be determined on small quantities of powder. In theory, the less compressible a material the more flow able it is.[10] The compressibility indices of the powder blends was determined using following formula,

$$\text{Carr's Compressibility Index}(\%) = \frac{[(\text{Tapped Bulk Density} - \text{Loose Bulk Density})}{\text{Tapped Bulk Density}]} \times 100$$

Preparation of Apremilast Orodispersible tablets using the direct compression technique

After evaluation of powder blend the Orodispersible tablets were prepared by direct compression method using tablets using 10-station rotary tablet compression machine (karnavati) equipped with flat-faced 6 mm punches before compression, the surfaces of the die and punch were lubricated with magnesium stearate. Nine types of formulations containing variable amount of superdisintegrant were prepared. All the preparations were stored in airtight containers at room temperature for further study.[11]

Evaluation of Orodispersible Tablet of Apremilast

Thickness

The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier Calliper. Three tablets from each batch were used.

Hardness

For each formulation, the hardness of three tablets was checked using the Monsanto hardness tester.

Drug Content Uniformity Study

Five tablets were weighed individually and powdered. The powder equivalent to 10 mg of Apremilast was weighed and dissolved in methanol. The volume was made to 100 ml with methanol. From this stock solution, 10 μg/ml dilution was prepared. The drug contents of the resulting solution were calculated from UV absorbance at 230 nm.[12]

Friability

Friability is the measure of tablet strength. In this test number of tablets subjected to combined effect of shock abrasion by utilising a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche Friability tester (Kumar Mfg. Ltd.) This was then operated for 100 revolutions. The tablets then dedusted and reweighed. Permitted friability limit is 1.0%. Tablets were then weighed and friability values were determined.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where,

W_1 = weight of the tablets before test,

W2 = weight of the tablets after test

Weight Variation Test

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits

(±7.5%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Wetting Time

A piece of tissue paper folded double was placed in a petri dish containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C. Wetting time corresponding to the time taken for the tablet to disintegrate when kept motionless on the tongue was calculated.[13]

Water Absorption Ratio

The water absorption ratio is used to determine the amount of water absorbed by the tablet. A piece of tissue paper folded twice was placed in small Petri dish (7.5cm) containing 7ml water. A tablet was put on the tissue paper and allows wetting completely. The wetted tablet was then weighed. The water absorption ratio R was determined using following equation.

$$R = \frac{W_a - W_b}{W_a} \times 100$$

Where;

W_a = weight of a tablet after absorption
W_b = weight of a tablet before absorption

Disintegration Time

The *in-vitro* disintegration studies were carried out using Tablet Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing distilled water maintained at 37±2°C. The basket was then moved up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded. The test was performed for tablets of all type of formulation (F1-F9).

In- vitro Drug Release Study

An *in-vitro* drug release studies of the prepared nine formulations of Orodispersible Tablets were conducted for a period of 15 min using an eight station USP type 2 apparatus (paddle type). The agitation speed was 50 rpm. Apremilast tablets were added to 900 ml of phosphate buffer pH 6.8 at 37 ± 0.5°C.5 ml aliquots were withdrawn at time intervals of 1, 3, 5, 7, 9, 11, 13, 15 min. and filtered through Whatman No. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analysed spectrophotometrically at 230 nm. Cumulative percentage of labelled amount of drug released was calculated.[14]

Stability Studies

The optimized formulation was wrapped in aluminum foil and subjected to 40 ±2°C temperature and 75±5% RH in oven for the period of Three months. The formulation was analyzed for organoleptic characteristics, Thickness, hardness, drug content, wetting time, Disintegration time, weight variation and dissolution. In any rational design and evaluation of dosage forms for drugs, the stability of the active component is the major criteria in determining their acceptance or rejection. Stability studies were carried out as per ICH Q_1A guidelines. During the stability studies, the product is exposed to normal conditions of temperature and humidity. The optimized Apremilast formulations were subjected for stability studies.

Packaging material: The tablets were wrapped in aluminum foils.

Sampling points: The optimized formulations were subjected to stability for a period of Three months. The samples were withdrawn at the end of three months.[15]

RESULTS AND DISCUSSION

Preparation of Apremilast-β-cyclodextrin complex

Complexes were prepared using β-Cyclodextrins with the principle of increasing the solubility and permeability of drug. Drug: Carrier ratios were decided arbitrarily (1:1, 1:2, 1:3) based on the literature review and success achieved with a range of ratios for any carrier. Complex was made by Physical blending method.[16]

Evaluation of Complex

Production Yield

The production yield of all Drug: Carrier ratios by physical blending method was found to be in the range of 98 to 99%. Any loss in yield can be attributed to the product remaining adhered to the walls of the evaporating dish or the mortar which could not be retrieved.

Drug content (Inclusion efficiency)

The drug content of different ratios was calculated and found to be in range of 95 to 98%.The% drug content

Sr. no	Apremilast: carrier combination	Saturated Solubility (µg/ml)	Drug content (%)
	Table 4: Saturation solubility data for apremilast and carrier combinations.		
1.	Apremilast: β-CD (PM 1:1)	5.8446	95.68 ± 0.76
2.	Apremilast: β-CD (PM 1:2)	12.7840	98.80 ± 0.44
3.	Apremilast: β-CD (PM 1:3)	9.6401	96.53 ± 0.56

CD is Cyclodextrin and PM stands for Physical blending Method.

of 1:2 ratio complex is highest (Table 4) and hence found satisfactorily.

Saturation solubility study

The effect on solubility of Apremilast after preparation of their complex using physical blending methods, saturation solubility studies were performed in distilled water. The results for saturation solubility of apremilast was shown in Table 4. It was studied that an increase in solubility of about 2.4-fold with β-Cyclodextrins (1:2 PM) was achieved when compared to the solubility of APM:CD (1:1). Correlating the solubility data with the concentration of carrier with respect to drug, it was observed that the solubility increased with increasing concentration of the carrier Upto 1:2. Based on the literature review, the most common ratio of drug/β-cyclodextrin complexes is the 1:2 where the 1:2 complex is formed when one additional β-cyclodextrin molecule forms a complex with an existing 1:1 complex. Hence, saturation solubility of different ratios was calculated, that shows 1:2 complex is highest.[17]

Dissolution studies of complex

The *in-vitro* profiles of the drug and complexes are shown in Table 5. Standard deviation up to 5% is allowed. The drug exhibited a slow dissolution, suggesting that its absorption *in vivo* would be dissolution rate limited, whereas complexes showed a marked enhancement in dissolution rate. Thus, dissolution up to 101.48% for 1:2 complex was recorded in 10 min contrast to 47.53 % drug release within 10 min observed from marketed preparation of drug (Aprezo, the reference tablet, Glenmark). Further, the dissolution profile of complexes with different mixing ratios also demonstrated variability and it was found to be dependent on the drug-carrier ratio. Hence, from all the ratios used, maximum dissolution was investigated for Apremilast:β-cyclodextrin 1:2.[18]

Evaluation of powder blend

Evaluation of powder blend Containing Apremilast-β-Cyclodextrin Complexare Table 6.

Time (Min.)	(%) Drug Release			
	Drug	**1:1**	**1:2**	**1:3**
	Table 5: Results of dissolution studies of complexes of apremilast.			
1	21.39± 0.74	22.45±0.45	66.45±0.65	32.46±0.23
5	26.39±0.67	22.88±0.89	97.73±0.56	32.88±0.44
10	47.53±0.65	31.25±0.65	101.48±0.46	42.18±0.67
15	56.85±0.66	46.85±0.32	93.94±0.23	50.55±0.34
30	62.35±0.23	51.34±0.46	83.64±0.66	56.35±0.23
45	65.34±0.45	64.18±0.42	67.79±0.59	70.68±0.43
60	69.10±0.64	65.05±0.98	52.90±0.96	73.71±0.87

Data expressed are average of triplicate (n=3±SD)

Bulk Density

The powder blends of formulations have the bulk density ranged between 0.4564 to 0.5674 gm/ml.

Tapped density

The powder blends of formulations have the tapped bulk density ranged between 0.5123 to 0.6578 gm/ml.

Angle of repose

The flow properties of blend were analyzed by determining angle of repose which was found to be between 25-30 indicating good flow property.

Hausner's Ratio

The hausner ratio for the formulations was found to be <1.00-1.11, indicating excellent flow properties and 1.12-1.18 indicating good flow property.

Carr's Compressibility Index

The Carr's index for the formulations was found to be below <10% indicating that the powders have a excellent compressibility and 11-15 indicating good compressibility.[19]

Formulation of Orodispersible tablet by direct compression technique

The present investigation was undertaken to formulate and evaluate orodispersible tablets of apremilast-β-CD complex by direct compression method. Nine different formulations (F1 to F9) were prepared by using various concentrations of super disintegrant Croscarmellose sodium to assist fast disintegration.[20]

Evaluation of Tablets

All batches of prepared tablets were evaluated for the different parameters and are shown in Table 7 and Table 8.

Table 6: Evaluation of powder blend.					
Formulation Batches	**Physical properties**				
	Bulk density (gm/ml)	**Tapped density (gm/ml)**	**Angle of repose (°C)**	**Compressibility Index (%)**	**Hausner Ratio**
F1	0.4761±0.05	0.5263±0.06	27.09±0.98	12.3±0.68	1.12±0.07
F2	0.4657±0.03	0.6578±0.09	28.05±0.86	11.45±0.76	1.06±0.06
F3	0.4856±0.08	0.5345±0.07	29.76±0.52	13.45±0.94	1.12±0.07
F4	0.5634±0.06	0.5643±0.06	27.57±0.86	21.45±0.46	1.25±0.05
F5	0.5674±0.07	0.5123±0.03	28.35±0.55	15.5±0.98	1.17±0.02
F6	0.4658±0.04	0.5263±0.09	26.09±0.97	9.52±0.67	1.10±0.09
F7	0.5378±0.07	0.5134±0.08	28.79±0.45	9.35±0.65	1.19±0.07
F8	0.4978±0.03	0.5867±0.05	29.34 ±0.73	13.5±0.89	1.16±0.05
F9	0.4564±0.09	0.5467±0.07	27.89±0.84	14.57±0.68	1.03±0.04

Data expressed are average of triplicate (n=3±SD)

Table 7: Evaluation of Apremilast Orodispersible Tablets.				
Formulation Batches	**Parameters**			
	Weight variation(mg) (± SD)	**Wetting time(sec.) (± SD)**	**Water absorption ratio (%) (± SD)**	**Disintegration Time (sec.) (± SD)**
F1	100.87 ± 0.55	93.67 ± 2.59	78.49 ± 1.68	70.66 ± 3.78
F2	99.29 ± 0.75	83.34 ± 1.52	53.39 ±0.76	69 ± 2
F3	98.75 ± 1.0	82.34 ± 1.52	77.7 ± 1.68	67.67 ± 4.04
F4	102.57 ± 0.86	76.66 ±1.52	68.48 ± 1.31	73 ± 5.2
F5	101.49 ± 1.57	68 ± 0.57	69.33 ± 2.51	68.34 ± 3.05
F6	98.44 ± 0.77	62.67 ± 0.57	82.52 ±1.76	61.67 ± 2.51
F7	101.30 ± 0.94	74.66 ± 1.52	67.44 ±1.53	73.67 ± 2.08
F8	98.82 ± 0.99	72.66 ± 2.08	68.18 ±0.70	71 ± 3
F9	97.56 ± 0.56	67.67 ± 1.52	58.15 ±1.66	68.35 ± 2.43

Data expressed are average of triplicate (n=3±SD)

Thickness

Thickness of Tablet formulations was found to be ranging from 3.5 mm to 3.73 mm. Variation of thickness in Tablet formulations (F1 to F9) was found within the acceptable limits.

Hardness

Hardness of Tablet formulations was found to be ranging from 2.4 Kg/cm² to 3.4 Kg/cm². Results obtained are within acceptable limit and indicated good mechanical strength.

Drug content uniformity study

Percent drug content of Apremilast was found in between 98.31%-102.53% and found to be satisfactorily.

Friability

Friability of Tablet formulations was found to be ranging from 0.67% to 0.91% which is within the acceptable limits. Friability values below 1% indicate a good tablet mechanical strength.

Weight variation

Weight variation of tablet formulation was found to be in 97.56 mg to 102.57mg which is within acceptable limit and up to 7.5% standard deviation is allowed, according to the I.P.

Wetting time

Wetting time of all formulation (F1-F9) was found satisfactorily and in between 62 to 93 sec. From F1 to F9 formulations, F6 formulation required less wetting time.

Formulation Batches	Thicknes (mm) (±SD)	Hardness (Kg/cm²) (± SD)	Drug content (%) (± SD)	Friability (%) (± SD)
Table 8: Further Evaluation of Apremilast Orodispersible Tablets.				
	Parameters			
F1	3.5±0.30	3.1 ± 0.57	99.40 ± 1.78	0.76 ±0.02
F2	3.7±0.05	2.4 ± 0.28	98.77± 2.61	0.68 ± 0.11
F3	3.7±0.23	2.7 ± 0.28	101.09 ± 1.43	0.67± 0.12
F4	3.6±0.05	3 ± 0.5	102.53 ± 1.79	0.73 ± 0.12
F5	3.5±0.1	2.5 ± 0.5	98.87 ±2.58	0.91± 0.05
F6	3.7±0.15	2.4 ± 0.28	101.27 ± 2.41	0.77 ± 0.01
F7	3.6±0.05	3.4±0.28	99.72 ± 3.37	0.74±0.03
F8	3.73 ± 0.15	3.1 ± 0.28	98.31 ± 3.27	0.67 ± 0.01
F9	3.5 ±0.4	2.83 ± 0.57	98.67 ± 0.73	0.75 ± 0.02

Data expressed are average of triplicate (n=3±SD)

Formulation Code	1	3	5	7	9	11	13	15
Table 9: Dissolution data of orodispersible tablet of apremilast.								
	Time (Min)							
F1 %CDR	24.06 ±1.89	38 ±0.98	56.07±0.56	74.19±0.65	80.45±1.64	83.76±0.51	85.78±1.89	87±2.76
F2 % CDR	28.23±0.60	39.37±1.93	51.45±0.68	63.54±1.23	74.26±2.67	82.21±1.34	86.93±0.54	89.39±1.89
F3 %CDR	31.01±0.04	43.07±0.56	54.23±2.67	60.31±1.52	73.34±1.87	84.53±0.23	88.32±0.50	92.59±0.35
F4 %CDR	29.62±±0.65	42.15±1.32	59.78±0.43	72.81±0.58	83.54±1.54	85.48±1.78	88.32±2.87	90.77±1.69
F5 %CDR	33.32±0.34	46.48±0.45	54 ± 1.63	77.11±1.87	90.77±2.45	92.59±0.43	94.87±0.35	96.85±0.41
F6 %CDR	30.54±0.67	43.54±0.34	62.5±1.34	74.2±0.23	85.39±0.78	87.34±1.73	92.56±1.61	98.7±0.48
F7 %CDR	26.38±1.23	42.61±2.67	53.3±1.34	61.23±0.41	70.55±0.42	79.89±0.60	85.53±0.79	88.4±1.20
F8 %CDR	29.92±1.45	42.68±2.67	57.93±0.44	74.66±2.89	81.64±1.98	85.67±0.32	89.56±1.47	94.67±1.65
F9 %CDR	30.54±0.40	44.46±0.57	56.08±1.56	63.09±1.66	72.42±0.78	82.66±0.98	88.67±0.54	95.88±0.65

% CDR is Percent Cumulative Drug Release.

Water absorption ratio

Water absorption ratio was found in ranging from 53.39 % to 82.52 % and the results indicated that formulation F6 had higher water absorption ratio when compared to other formulations.

Disintegration time

According to European Pharmacopoeia, Orodispersible Tablets should disintegrate within three minute. The disintegration time for formulation F1-F9 was found to be in the range of 61 to 73 sec and from all formulations, F6 formulation required less disintegration time.[21]

In-vitro drug Release Study of Apremilast Tablet

Percent drug release data expressed in Table 9 and Figure 1 Indicate *in-vitro* release study was shown 98.7% release of apremilast through F6 formulation in 15 min and up to 5% standard deviation is allowed. Formulation F6 showed less disintegration time and percent cumulative drug release 98.7% so it was declared as an
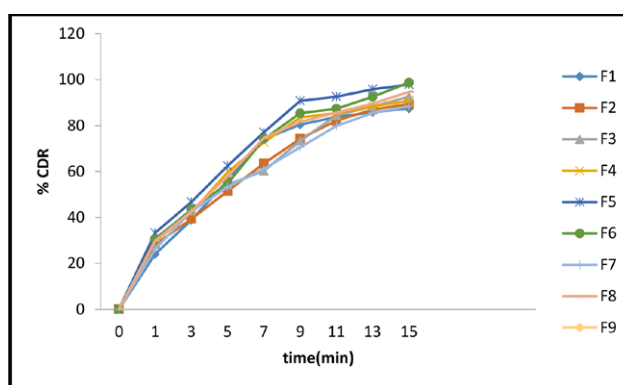

Figure 1: Dissolution profile of Orodispersible tablets of Apremilast. % CDR is Percent Cumulative Drug Release of F1 to F9 formulations within 15 min.

optimized formulation and was subjected for further evaluation (Table 10) and stability studies.[22]

Stability Study

The accelerated stability study was carried out on optimized formulation F6. The tablets were wrapped

Table 10: Evaluation parameters of f6 optimized batch.

Sr. No.	Parameters	Results
1	Weight variation (mg)	98.30 ±1.90
2	Thickness (mm)	3.8 ± 0.05
3	Hardness (kg/cm²)	2.17 ± 0.28
4	Friability (%)	0.72 ± 0.05
5	Wetting time (sec)	67.66 ± 3.51
6	Disintegration time (sec)	61.66 ± 2.51
7	Uniformity of content (%)	98.46 ± 1
8	Water absorption ratio (%)	58.28 ± 6.26

Data expressed are average of triplicate (n=3±SD)

Table 11: Parameters studied of [f6] formulation before and after stability study.

Parameters	Before stability study	After stability study
Colour	White	White
Thickness (mm)	3.87 ± 0.05	3.67 ±0.20
Hardness (kg/cm²)	2.17 ± 0.28	2.34 ± 0.28
Content uniformity (%)	98.46 ± 1	97.66 ± 1.15
Weight variation(mg)	99.73 ± 1.90	99.73 ± 1.90
Friability (%)	0.72 ± 0.05	0.74±0.5
Disintegration time (sec.)	61.66 ± 2.51	62.33 ± 2.08
Wetting time (sec.)	67.66 ± 2	66.67 ± 1.52
Water absorption ratio (%)	58.27 ± 6.26	57.54 ± 6.21
Dissolution study (%)	98.7 ± 0.48	98.2 ± 0.64

Data expressed are average of triplicate (n=3±SD)

in aluminium foil and stored at 40 ± 2°C and 75 ± 5 % RH for a three months. After three months samples were withdrawn and tested for physical parameters, thickness, hardness, percent friability, content uniformity, disintegration time, wetting time, Water absorption ratio (%) and *in-vitro* drug release studies.[23] Table 11 showed that there was no considerable change in thickness, hardness, percent friability, content uniformity, disintegration time, wetting time, Water absorption ratio (%) and dissolution data of formulation F6 before and after accelerated stability study. Also formulation F6 showed white color after stability studies. Hence, Orodispersible tablet (F6) prepared was found to be stable.[24,25]

CONCLUSION

The major problem of BCS-Class 4 Apremilast drug is low solubility and low permeability. Results revealed that it is possible to enhance the dissolution rate and bioavailability by preparing inclusion complex of apremilast with β-cyclodextrin and direct compression technique using super disintegrant Croscarmellose sodium. The overall results indicate that among all formulations (F1 to F9) studied, Formulation F6 which contains 5% Croscarmellose sodium with 1:2 ratio of apremilast:β-cyclodextrin which shows less disintegration time and percent cumulative drug release 98.7%,was better and hence F6 formulation satisfies all the criteria as a orodispersible tablet and achieve better patient compliance in Cost-effective manner as compared with conventional treatment of psoriasis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.
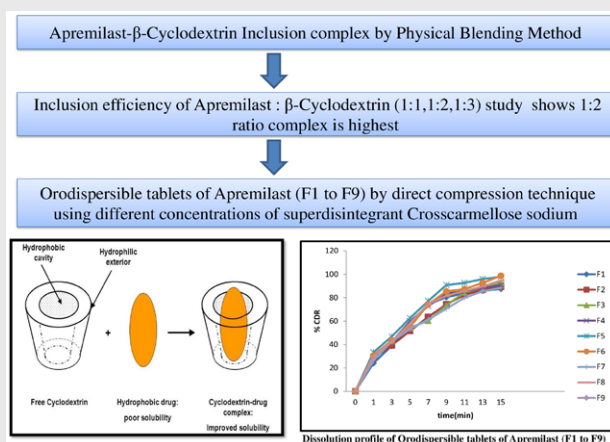
ABBREVIATIONS

APM: Apremilast; **CD:** Cyclodextrin; **PM:** Physical Mixture; **Min:** Minutes; **Hrs:** Hours; **Sec:** Seconds; **mg:** Milligram; **ml:** Milliliter; **µg:** Micro gram; **gm:** Grams; **m:** Meter; **cm:** Centimeters; **RH:** Relative Humidity; **rpm:** Revolutions per minute; **UV:** Ultra-violet; **w/w:** weight by weight; **nm:** Nanometer; **SD:** Standard Deviation.

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PICTORIAL ABSTRACT

Dissolution profile of Orodispersible tablets of Apremilast (F1 to F9)

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SUMMARY

Apremilast was successfully formulated in orodispersible tablet by inclusion complexation with β–cyclodextrin. F6 formulation was selected as optimized formulation based on disintegration time and percent cumulative drug release. Acceptable stability profile was observed after subjecting the optimized F6 formulation to various conditions of temperature and humidity. Hence, it can be concluded that Apremilast orodispersible tablets prepared with β-cyclodextrin and cross Croscarmellose can be a choice for oral antipsoriasis treatment in a cost-effective manner with better patient compliance.