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FORMULATION, DEVELOPMENT AND EVALTUATION OF APREMILAST IMMEDIATE RELEASE TABLET FOR MANAGMENT OF PSORIATIC

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ABSTRACT:

The aim of this research paper was to develop and evaluate an Apremilast immediate release tablet for the management of Psoriatic Arthritis by utilizing excipients and checking their compatibility with the API through preformulation studies. The tablets were formed using the direct compression method, and different trial batches were performed to check their activity.The preformulation studies showed that the selected excipients were compatible with the API, and the optimized formulation was found to have good flow and compressibility properties. The tablets were evaluated for their physical characteristics, including size, weight, and hardness. The in vitro dissolution studies were also conducted to assess the drug release profile of the developed tablets.The results of the study showed that the developed Apremilast immediate release tablets had excellent physical characteristics, with uniform size and weight. The in vitro dissolution studies indicated that the tablets had a quick release rate and met the required pharmacopoeial standards. The pharmacokinetic study revealed that the tablets exhibited rapid absorption, with a maximum plasma concentration achieved within 1 hour of administration.In conclusion, the developed Apremilast immediate release tablet utilizing excipients and preformulation studies has the potential to be an effective therapeutic option for the management of Psoriatic Arthritis. Further studies are required to investigate. Sometimes immediate onset of action is considered obligatory immediate release tablets are the final option. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer and lead to better patient compliance. In the present work, we engage in discussion about formulation, development, and evaluation of immediate release tablets. An immediate release dosage form allows a manufacturer to extend market exclusivity. They are also a tool for expanding markets, extending product life cycles and generating opportunities. Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release tablet.

Objective:

The objective of this study was to formulate and evaluate an Apremilast immediate release tablets using direct compression technique, and to investigate their physical and chemical properties.

Methodology:

Pre-formulation studies were performed to assess the physicochemical properties of an Apremilast immediate release tablet. Formulations were prepared using direct compression technique. The prepared tablets were subjected to various physicochemical evaluations such as weight variation, thickness, hardness, friability, drug content, disintegration time, and in-vitro release studies.

Findings:

The formulated an Apremilast immediate release tablet were found to be acceptable with regard to their physical and chemical properties. The tablets showed uniformity in weight, thickness, and drug content. The friability values of the tablets were within the acceptable limits. The disintegration time of the tablets was found to be within the specified limits. In vitro release studies showed that the formulation exhibited sustained release of the drug substance.

Significance:

The study reveals that an Apremilast immediate release tablet can be successfully formulated using the direct compression technique, which is a cost-effective method. The developed formulation can be a potential alternative for commercially available tablets. The study also supports the development of sustained-release formulations of an Apremilast immediate release tablet.

Keywords:

Immediate release, wet granulation, compression, sustained-release.

1.Introduction

Pharmaceuticals have made a major contribution to improving the health status of patients over a past few decades. At the same time, its expenditure has increased rapidly, with spending on medicines outpacing economic growth in many countries. Many economists have speculated that, if spending on healthcare continues to increase at the current rate, the economies of most countries will be severely affected. Most governments have, therefore, begun to implement cost-containment measures to slow the rate of healthcare spending and have concentrated to a larger degree on pharmaceutical spending. Since generics are usually marketed at substantially lower prices than the original brand-name products and, with the rising cost of healthcare; this has made them an attractive option to healthcare providers and governments.

Immediate release oral dosage forms i.e., tablets and capsule are most widely used drug delivery systems available. These products are designed to disintegrate in the stomach followed

by their dissolution in the fluids of the gastrointestinal tract.The release of drug from the conventional tablet dosage form and its absorption from the GIT depends upon two main processes. Firstly, the disintegration of tablet and dissolution of the particles followed by permeation through the GIT into the blood. Disintegration is the rate limiting step in case of highly soluble drugs where as dissolution is the rate limiting step in case of drugs with low solubility.

In most coating methods, the coating solutions are sprayed onto the tablets as tablets are being agitated in a pan, fluid bed, etc. As the solution is being sprayed, a thin film is formed that adheres directly to each tablet. The coating may be formed by a single application or may be built up in layers through the use of multiple spraying cycles. Rotating coating pans are often used in the pharmaceutical industry. Uncoated tablets are placed in the pan, which is typically tilted tan angle from the horizontal, and the liquid coating solution is introduced into the pan while the tablets are tumbling. The liquid portion of the coating solution is then evaporated by passing air over the surface of the tumbling tablets.

Aqueous film coating is applied as a thin polymeric film to the surface of a tablet. Film coating can Protect the tablet from light, temperature and moisture; mask undesirable taste or odor; improve the appearance; provide tablet

identity; facilitate swallowing and control or modify the release of the drug. Aqueous coating of oral solid dosage forms has rapidly replaced solvent- based coating for Safety, environmental and economic reasons.

2.MATERIALS AND METHODS:

2.1.MATERIALS: Apremilast, lactose monohydrate, Microcrystalline cellulose 101, Cross carmellose cellulose, Sodium starch glycolate, sodium lauryl sulfate, Magnesium stearate, Hypromellose 603,Opadry white

2.2.INSTRUMENT: Analytical balance, Moisture analyzer,Octagonal blender, Compression machine, tablet hardness tester, disintegration test apparatus,friability test apparatus,density measurement apparatus, tablet coating machine,dissolution test apparatus,HPLC

2.3.METHODS :

- Preformulation study
- Product development

3.Experiment Work:

3.1.Pre formulation study:

Pre formulation testing is the first step in the rational development of dosage forms of the drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre formulation testing is to generate information useful to formulator in developing stable and bio available dosage forms.

3.2 Organoleptic properties:

An organoleptic property such as color, odor, taste and appearance of API was observed.

Identification of pure drug: -

Identification of API was carried out by melting point determination, UV spectroscopy.

Melting point determination: -

Melting point was determined by taking small amount of API in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was calculated.

6.1.4Particle size determination: -

Particle size of API is determined by using Malvern particle size analyzer.

6.1.5 Loss on drying: -

Loss on drying was carried out by using halogen moisture analyzer at 105˚C.

BCS solubility study: -

The solubility of drug in various solvent was determined by using shake flask method. Excess amount of API can added into 250ml conical flask containing different types of media such as 0.1N HCl, pH 4.5 acetate buffers, pH 6.8 phosphate buffer, pH 7.5 phosphate buffer the shaking process was carried for 24 hours by keeping the conical flask on rotator shaker at 200 rpm. A portion drug dissolved was filtered through (0.45µm) and concentration of drug in the filtrate was determined by HPLC method.

4.Micromeritics properties of drug and blend: -

4.1 Bulk Density: -

It refers to packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in g/ml.

The bulk density of the ingredients was evaluated using a graduated cylinder. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring theweighed quantity of powder into a graduated measuring cylinder and the volume was noted. It is expressed in g/ml and is calculated by using following formula

Bulk density (ρi) = Mass of the powder (M)/ Volume of the bulk powder (Vb)..... (1)

4.2 Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder 10, 500, 1250taps in tap density apparatus (Electro Lab USP II) according to USP. The blend was subjected for 500 taps; % Volume variation was calculated and subjected for additional 1250 taps, % variation is calculated.

Tapped volume (*ρt*) = Mass of the powder (M) / Tapped volume of the powder (VT) .. (2)

4.3 Compressibility index (Carr's index):-

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, less compressible material the more flowable it is. A material having values of less than 20% is defined as the free flowing material. The relationship between % compressibility index with flowability can be given in the table

Compressibility index = Tapped density – Bulk density / Tapped density ×100..... (3)

Table 6.3: Scale of flow ability

% Compressibility	Flow ability	Hauser Ratio
5-15	Excellent	1.00–1.11
12-16	Good	1.12–1.18
18-21	Fairley acceptable	1.19–1.25
23-35	Poor	1.26–1.34
33-38	Very poor	1.35–1.45
< 40	Very very poor	1.46–1.59

4.4 Hausner's ratio:-

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's ratio = Tapped density / Bulk density.....(4)

4.5 Drug Excipients Compatibility Study:-

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation. In this method different excipients were selected and mixed separately with drug in proportion generally used for tablet formulation. The HPLC method was used to investigate any possible interactions between the drug and excipients utilized.

Procedure: -Drug: Excipients ratio Drug and excipients were taken in the ratios as mentioned in table

Pack details: Ambered color glass vial and aluminum seal.

API and excipients were thoroughly mixed in predetermined ratio given in table and passed through the sieve 30# sieve. The blend was to be filled in amber color glass vials and was close with perforated aluminum seal and charged in at above condition. Similarly API should be kept at all condition as for the sample. Samples were withdrawn for analysis and physical observation should be done and HPLC studies were carried out to determine the compatibility of excipients with the drug.

Table 6.4: API/ Excipients name with ratio

Sr.No.	API/ Excipients Name with Grade	Drug: Excipients Ratio
01	API	1
02	API + Microcrystalline Cellulose	1:1
03	API + Lactose Monohydrate	1:1

04	API + Croscarmellose sodium	1:1
05	API + Sodium stach glycolate	1:1
06	API + Sodium lauryl sulfate	1:1
07	API + Magnesium stearate (Hyqual)	1:0.5
08	API + Hypromellose 603	1.05
09	API + Opadry white	1:0.5
10	API + All excipient	1:1

5. Product Development:

Objective of the project was to develop a stable generic product, which should be bio- equivalent to the reference drug product. Development of a generic product starts with the evaluation of innovator product followed by compatibility studies, selection of process and equipment, optimization trials and bio-equivalent studies. In order to develop bio-equivalent generic formulation of selected drug candidate, initial requirement was to choose a suitable manufacturing process.

6.3.1 Manufacturing Process:

Direct compression approach was development of Apremilast immediate release tablet 30 mg. Based on target product profile, evaluation of physiochemical properties of the drug substances and other ingredients, literature search & scientific process below manufacturing process was carried out the development lab scale trial were performed to determine the manufacturing process parameters such as blending compression and coating. Ultimate goal of the experimentation was to obtained a product which will gives satisfactory in vitro dissolution profile.

6.3.2. Selection of Excipients:

The types of Excipients selected for a formulation depend on the basic process used to manufacture the tablets. The selection of Excipients was done considering the process selected i.e. for direct compression and literature review. The grade and physical characteristics and properties of the inactive Excipients were selected accordingly. All the Excipients used in the development trials are suitable for direct compression. The results of the stability studies for the API, in conjunction with the API compatibility with the proposed inactive Excipients, justified the selection of the formulation composition

6.4.3 Manufacturing Steps:

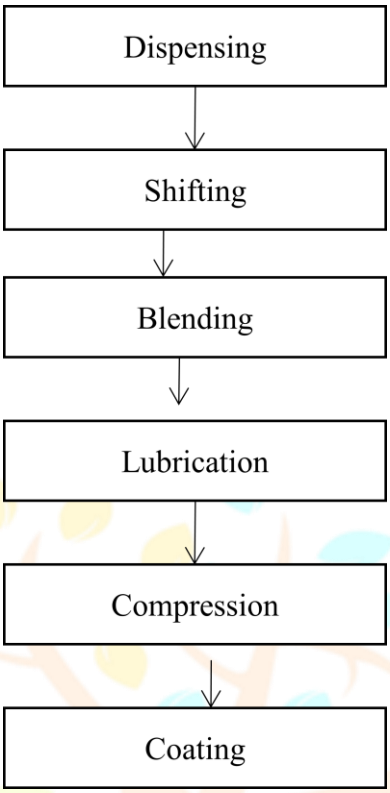
Dispensing
Shifting
Blending
Lubrication
Compression
Coating

Table 6.5: Manufacturing process

Step No	Process
1.0	**Dispensing**
1.1	API, Microcrystalline cellulose (Avicel PH102), Lactose monohydrate (SuperTab SD11), Croscarmellose sodium (Ac-Di-Sol SD 711), Sodium lauryl sulfate, hypromellose & Magnesium stearate (Hyqual) was dispensed
2.0	**Sifting**
2.1	API, Microcrystalline cellulose (Avicel PH102), Lactose monohydrate (SuperTab SD11) and Croscarmellose sodium (Ac-Di-Sol SD 711), Sodium lauryl sulfate was sifted through sieve #30 and placed separately in polybag
2.2	Magnesium stearate (Hyqual) and Hypromellose sifted individual through # 50 and placed separately in polybag
3.0	**Blending & Lubrication**
3.1	Sifted material obtained from above step 2.1 were blended for 30 min. in octagonal blender at 15 rpm
3.2	Sifted magnesium stearate (Hyqual) and hypromellose from step 2.2 added to step no 3.1 and lubricated for 5 minutes in octagonal blender at 15 rpm
4.0	**Direct Compression**
4.1	Lubricated blend from step 3.2 was compressed in to tablets by using suitable punch tooling using compression machine
5.0	**Coating**
5.1	Opadry white was added in Purified water with stirring, stir the solution for 30 minutes and filter through #100 mesh
5.2	Core tablet from step 5.0 were coated by using coating solution of in coating machine until 4.00 %w/w weight gain achieved

Table 6.6: Punch details

Sr. No	Punch Details	Tablet strength(40mg)
1	**Upper punch**	Round concave & Embossed with "APM"
2	**Lower punch**	Round concave & Embosed with "E30"
3	**Diameter**	8 mm
4	**Tooling**	"D"

Table 6.7: Different formulation trial batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Quantity of mg per Tablet								
Apremilast	30	30	30	30	30	30	30	30	30
MCC PH102	28	28	34	34	34	36	36	36	36
Lactose monohydrate	90	90	90	90	90	86	86	86	86
Cross carmelose sodium	--	--	--	10	5	5	9	9	9
Sodium lauryl sulfate	--	--	--	--	--	2	2	4	4
Sodium Starch Glycolate	20	20	20	20	--	--	--	--	--
Hypromellose	--	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4
Total wt.	172	176	182	192	167	167	171	173	173
Opadry white	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
Total wt.	180	184	190	200	175	175	179	181	181

6.4.5 Coating Parameter:

Preparation of coating solution:

Opadry white: 8mg/tab Purified water: q.s
The dispersion was prepared using a mechanical stirrer and kept under the stirrer in 45 min. It was then filtered through a nylon cloth.

Table 6.8: Coating process parameter

Inlet temp.	50-55ºC
Bed temp.	40ºC
Exhaust temp.	40-45ºC
Pan rpm	3-7 rpm
Atomization	1.3 bar
Spray rate	5gm/min

6.

5 Evaluation of tablet:

6.5.1Evaluation of pre compression parameter (blend analysis):

The lubricated blend was analyzed for bulk density, tapped density, Hausner ratio and compressibility index.

6.5.2Evaluation of post compression parameter:

Tablets are evaluated as per Pharmacopoeia specification

1. Weight of tablet:-

Twenty tablets randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch was passes the test for weight variation if not more than two of the individual tablet weight deviates from the average weight by more than the percentage show in officials and none deviate by more than twice the percentage shown in tablet

Table 6.9: Weight variation tolerance or uncoated tablet

Average weight of tablet (mg)		% Deviation
As per USP	As per IP	
130 or less	80 or less	10
130 – 324	80 – 250	7.5
324 or more than 324	250 or more than 250	5

2 Tablet Dimensions:-

Thickness and diameter of the tablets were measured using a Vernier calliper. It was determined by checking ten tablets from each formulation. It is expressed in mm.

3 Hardness:-

Hardness indicates the ability of a tablet to withstand mechanical shock while handling. For each formulation, the hardness of tablet was determined by using. It is expressed in N. Ten tablets were

selected and hardness of the was measured.

4 Friability:-

For tablets with an average weight of 180 mg or less take a sample of whole tablets corresponding to about 1.8mg and for tablet with an average weight of more than 180 mg take a sample of 10 whole tablets. Deduct the tablets carefully and weigh accurately the required number of tablets. Place the tablet in the Roche friabilator. The friability was operated at 25 rpm at 100 revaluation then removes any loose dust from them and weighs them accurately. A maximum loss of weight not greater than 1.0 %is acceptable for tablet. The percent friability was calculated by using following equation.

$$\% F = [1-(W/W_0)] \times 100 \quad (5)$$

Where, % F = friability in percentage

W = weight of table after revolution

W_0 = Initial weight of tablet

5 Disintegration Time:-

In vitro disintegration time of tablets from each formulation was determined by using disintegration apparatus USP (Electrolab). In vitro disintegration test was carried out at 37± 2˚C in 900 ml by using disintegration media. 6 tablets of each formulation were taken and placed in tubes of disintegration apparatus. The time taken for complete disintegration was noted.

6 Assay:-

Mobile phase preparation:

Measure and transferred Water, methanol and Triethylamine in the ratio 30:70:2 *v/v/v* ,was prepared, mixed and sonicated to degas used as mobile phase.

Preparation of diluent:

Prepared a mix of Water: Methanol in the ratio of (20:80%*v/v*) mixed and used as diluent.

Preparation of Standard solution for Apremilast:

Accurately weighed and transferred 75 mg of Apremilast as working standard into a 100 mL volumetric flask. Added about 70 mL of diluent and sonicated for 10 min to dissolve. The solution was cooled to room temperature and made up to mark with diluent and mixed well.

Further 4 mL of stock solution of Apremilast was pipette out and transferred to 50 mL volumetric flask and made volume up to mark with Diluent.

(Concentration of Apremilast: 60 ppm)

Preparation of Test Solution:

Weighed and Transferred 5 intact tablet of Apremilast into 250 mL volumetric flask. Added about 200 mL of diluent, sonicated for 25 minutes with intermittent shaking allow to cool and dilute up to the mark with diluent and mixed well, allowed to settle for 15 min. centrifuge this solution at 3000 RPM for 10 min. Further transferred 5 ml of centrifuge stock solution into 50 ml volumetric flask dilute up to the mark with diluent and mixed well, filtered through 0.45µ Nylon membrane syringe filter and injected

(Concentration of Apremilast: About 60 ppm)

Column	YMC pack C18 (150 x 4.6mm) 5µ
Flow Rate	1.0 mL/min
Injection Volume	20 µL
Wavelength	234 nm
Column Temp.	30°C
Auto sampler Temp.	20°C
Run time	8.0 min.
Retention Time	3.3 min.
Needle wash	Water : Methanol (90:10 v/v)
Seal wash	Water : Methanol (10:90 v/v)

Estimation of Apremilast in tablet dosage form by proposed method:

Procedure:

Separately injected equal volumes of Blank (diluent), 1ststandard solution (six replicates), 2ndstandard solution (two replicates) and sample solution (single injection). Record the chromatograms and measure Peak areas.

The amount of drug estimated in sample weight was calculated using formula.

$$\% \text{ Assay} = \frac{AT}{AS} \times \frac{\text{WS}}{100} \times \frac{4}{50} \times \frac{250}{SW} \times \frac{5}{50} \times \frac{\text{P}}{100} \times \frac{100}{LC} \times AW$$

Where,

AT: Average peak area of Apremilast in the chromatogram of sample solution.

AS: Average peak area of Apremilast in the chromatogram of standard solution.

WS: Weight of Apremilast standard in mg.

SW: Weight of sample in mg.

P: % Potency of Apremilast standard on as is basis.

AW: Average weight of sample in mg.

LC: Label claim of Apremilast in mg(30 mg).

7.

Dissolution method: -

In vitro dissolution study was carried out for optimized formulation of Apremilast Tablet and reference product in OGD media (Buffer pH 6.8 with 0.15% SLS). The temperature of the dissolution medium was maintained at 37 ± 0.5°C and the drug concentration was determined by HPLC method.

Procedure:

Preparation of Dissolution Media: Weigh and transfer 34.05 gm of Sodium dihydrogen orthophosphate monohydrate in 10 litre of water, mixed well. Adjust pH 6.8 with diluted Sodium hydroxide. Add 15 gm of Sodium lauryl sulfate mixed well. Sonicated to dissolve. Degas the media

Mobile phase preparation:

Measure and transferred Water, methanol and Triethylamine in the ratio 30:70:2 *v/v/v* ,was prepared, mixed and sonicated to degas used as mobile phase. respectively, mix and degas

Chromatographic Condition:

Retention Time	4.5 min.
Needle wash	Water : Methanol (90:10 v/v)
Seal wash	Water : Methanol (10:90 v/v)

Column	YMC pack C18 (150 x 4.6mm) 5µ
Flow Rate	1.0 mL/min
ection Volume	20 µL
Wavelength	234 nm
olumn Temp.	35°C
o sampler Temp.	25°C
Run time	10 min.

Dissolution Parameter:

Apparatus	USP TYPE II (Paadle)
Media	Buffer pH 6.8 with 0.15% SLS
Speed	50 RPM

Temperature	37◦C (± 5◦C)
Media Volume	900 mL
Time Point	5, 10, 15, 20, 30, 45 and 60 minutes
Tolerances	Not less than 85% (Q) of the labeled amount of drug is Dissolved in 30 minutes

Preparation of Standard Stock Solution:

Weight accurately about 55.0 working standard Apremilast and transfer into 50 ml volumetric flask. Add 5 ml of methanol, sonicate to dissolved and make up the volume up to mark with media. Transfer 3.0 ml of standard stock solution to 100 ml volumetric flask and dilute up to the mark of media. (Concentration of Apremilast: 33 ppm)

Preparation of Sample Solution: Set the dissolution apparatus as per parameter. Place one tablet in each dissolution vessel and carry out the dissolution. Withdraw 10.0ml of solution as per as the set intervals of time and replenish the same with fresh 10.0 ml dissolution media. Inject the filtered aliquot in chromatographic system.

Procedure:

Table 6.11: Inject 20µl of solution as per sequence below

Sr. No.	Description	No. of injection
1	Blank	1
2	Standard solution	6
3	Sample solution	1
4	Bracketing Standard Solution	1

Calculation:

Calculate the % release of Apremilast present in the tablet as given below:

% Content		AT		WS		3		900		P
	=	-----	x	-----	x	-----	x	-----	x	-----
		AS		50		100		1 Tablet		LC

Apremilast

Where,

AT : average peak area of Apremilast in chromatogram of sample solution

AS : average peak area of Apremilast in chromatogram of standard solution

WS : weight of Apremilast standard in mg

P : % potency of Apremilast standard on as is basis

LC : label claim of Apremilast per tablet in mg

Dissolution profile comparison:

Comparative dissolution profile is used for demonstrating the equivalence of any change in the formulation of drug.

Dissimilarity factor (f1)

Dissimilarity factor describe the relative error between two dissolution profiles. It approximately gives the error between curves reference profile are identical and increase proportionally with the dissimilarity between the two profiles.

Dissimilarity factor (f1) was calculated from the following equation

$$f_1 = \left\{ \frac{\left\{ \sum_{t=1}^{n} |Rt - Tt| \right\}}{\sum_{t=1}^{n} Rt} \right\} \times 100 \quad \text{(7}$$

Where, n = number of time point

R_t = % dissolved at time t of reference product

T_t = % dissolved at time t of test product

Dissimilarity factor (f1) should be between 0 to 15

S

imilarity factor (f2) The resulting dissolution profile was compared to the targeted profile by means of the food drug administration (FDA) recommend model-independent approach utilizing the similarity factor (f2). This similarity factor is algorithmic reciprocal square root transformation of the sum of squared errors, and it serves as measure of the similarity of two respective dissolution profiles.

Similarity factor(f2)=50 log {[1+1/nΣ(Rt−Tt)2]−0.5×100}nt=1 …… (8)

Where

Rt and Tt = % of drug which was dissolved at each time point for the test and reference products respectively.

n = number of time points considered.

FDA has set a standard of f2 value between 50-100 to indicate similarity between two dissolution profiles.

RESULT AND DISCUSSION

7.1 Physiochemical properties of drug:-

7.1.1 Organoleptic properties:

Table 7.1: Organoleptic properties of API

Properties	Observation
Colour	White to off white
Taste	Bitter
Odour	Odourless
Appearance	Powder

7.1.2 Melting point determination:-

Melting point of API was found to be, which is in range as given in literature (156-160ºC). Hence the drug can be stated as pure.

Table 7.2: Melting point determination

Sr.No.	Melting point [˚C] (observed)	Average [˚C]
1	158	158
2	157	
3	158	

7.1.3 Solubility:-

The solubility of the received sample of API was examined in various solvents (aqueous and organic). It is an only qualitative analysis. The results thus obtained were as follows-

Table 7.3: Details solubility of API

Sr.No.	Solvent	Solubility
1	Alcohol and DMSO	Freely soluble
2	water	Very slightly soluble

7.1.4 Particle size determination:-

Sample of API was analyzed by using Malvern particle size analyzer, particles were found in following size ranges

Table 7.4: Particle size determination

Sr.No.	Diameter	Particle size(µm)
1	D05	11.9
2	D04	49.6
3	D01	140.5

7.1.5 Loss on drying:-

Loss on drying was carried out by using halogen moisture analyzer and it was found to be 0.63% at 105ºC

7.3. BCS solubility study:-

Table 7.7: BCS solubility data of API in different media

Sr.No	Media	mg/250ml
1	Purified Water +0.15% SLS	505.2
2	0.1N HCl+0.15% SLS	725.0
3	pH 6.8 phosphate buffer+0.15% SLS	937.1
4	pH 4.5 Acetate buffer+0.15% SLS	794.3
5	pH 7.5 phosphate buffer+0.15% SLS	915.7

7.4 Micrometrics properties evaluation:

Table 7.8: Micrometrics properties of API

Sr.No	Parameters	Results	Flow properties
1	Bulk density(g/ml)	0.56	-
2	Tapped density(g/ml)	0.89	-
3	Carr's index (%)	37.18	Very Poor
4	Hauser's ratio(HR)	1.58	Very Very poor

7.5 Drug-excipients compatibility result:

1 Physical compatibility:

7.9: Result of physical compatibility of Drug

Sr.No.	API/ Excipients Name with Grade	Drug:Excipients Ratio	Condition	Observations on appearance	Assay (%)
01	API	1	Initial	White	99.8
02	API +Microcrystalline Cellulose	1:1	Initial	White	99.8
03	API + Lactose Monohydrate	1:1	Initial	White	99.8
04	API + Sodium starch glycolate	1.1	Initial	White	99.8
05	API +Croscarmellose sodium	1:1	Initial	White	99.8
06	API + Sodium lauryl sulfate	1:1	Initial	White	99.9
07	API + Magnesium stearate	1:0.5	Initial	White	99.8
08	API + Hypromellose 603	1:0.5	Initial	White	99.9
09	API + Opadry White	1:0.5	Initial	White	99.8
10	API + All excipient	1:1	Initial	No colour change	99.8

Conclusion:

No loss in assay was observed in any of these mixtures at Initial open condition hence degradation products not produce in open condition are within specification. There is no incompatibility with the selected excipients.

7.6 Pre compression parameter: -

Table 7.11: Evaluation of lubricated blend

Formulation. no	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio
F1	0.600	0.745	19.40	1.24
F2	0.610	0.750	19.90	1.23
F3	0.605	0.748	20.03	1.24
F4	0.612	0.776	22.31	1.25
F5	0.622	0.789	22.72	1.23
F6	0.618	0.768	20.31	1.24
F7	0.609	0.765	21.58	1.26
F8	0.601	0.760	21.63	1.27
F9	0.597	0.762	21.65	1.27

Conclusion:

In the above table characteristic of the powder blend from F1 to F9 is given. From values of Compressibility index and Hauser's ratio we can conclude that blend of the above formulation have passable flow properties and compressibility index.

7.7 Post compression Parameter:

Table 7.12: Evaluation of Post compression Parameter.

F. No	Weight Variation (mg)	Hardness(N)	Thickness(mm)	Disintegration Time	Friability (%)	Assay (%)
F1	181 (171-189)	91	3.56	2min 53sec	0.5	97.8
F2	185(174.8-193.2)	90	3.62	2min 51sec	0.6	98.3
F3	190(180.5-199.5)	86	3.84	2min 30sec	0.5	98.9
F4	200(190-210)	85	3.97	2min 20sec	0.6	98.7
F5	176(166.25-183.75)	86	3.37	2min 28sec	0.4	99.1
F6	175(166.25-183.75)	91	3.36	3min 05sec	0.5	98.1
F7	180(170.05-187.05	89	3.54	2min 46sec	0.5	99.4
F8	181(171.95-190.05	87	3.56	1 min 31sec	0.4	100.01
F9	180(171.95-190.05	87	3.55	1 min 32sec	0.4	99.9

Conclusion:

From among all the eight comparison batches with the variable Disintegrants formulation batch no F8 was found to be satisfactory as compared to other formulation. In this the thickness, hardness and disintegration time of prepared tablet was found to be satisfactory as that of Marketed Formulation tablet. In friability test the maximum weight loss should be not more than 1%. The result revealed that the tablets passed the friability test.

7.8. In vitro Dissolution Study:

7.8.1 Comparative dissolution profile of reference product with optimized batch (F8) in 0.1 N HCl + 0.15% SLS

Table 7.15. %Comparative dissolution profile of innovator with all Formulation batches in Buffer pH 6.8 with 0.15% SLS

Media	900ml of 0.1 N HCl at 100 rpm in USP Type I apparatus (Basket)									
Time	% Drug Release									
	Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
5	23	5	8	10	20	21	18	20	22	23
10	48	24	27	31	42	42	39	42	49	48
15	64	48	52	56	62	60	54	58	66	66
20	81	59	61	69	75	76	67	74	82	83
30	96	71	75	78	82	80	74	85	97	98
45	99	79	84	87	90	89	81	91	99	100
60	100	80	86	93	92	93	89	96	100	100

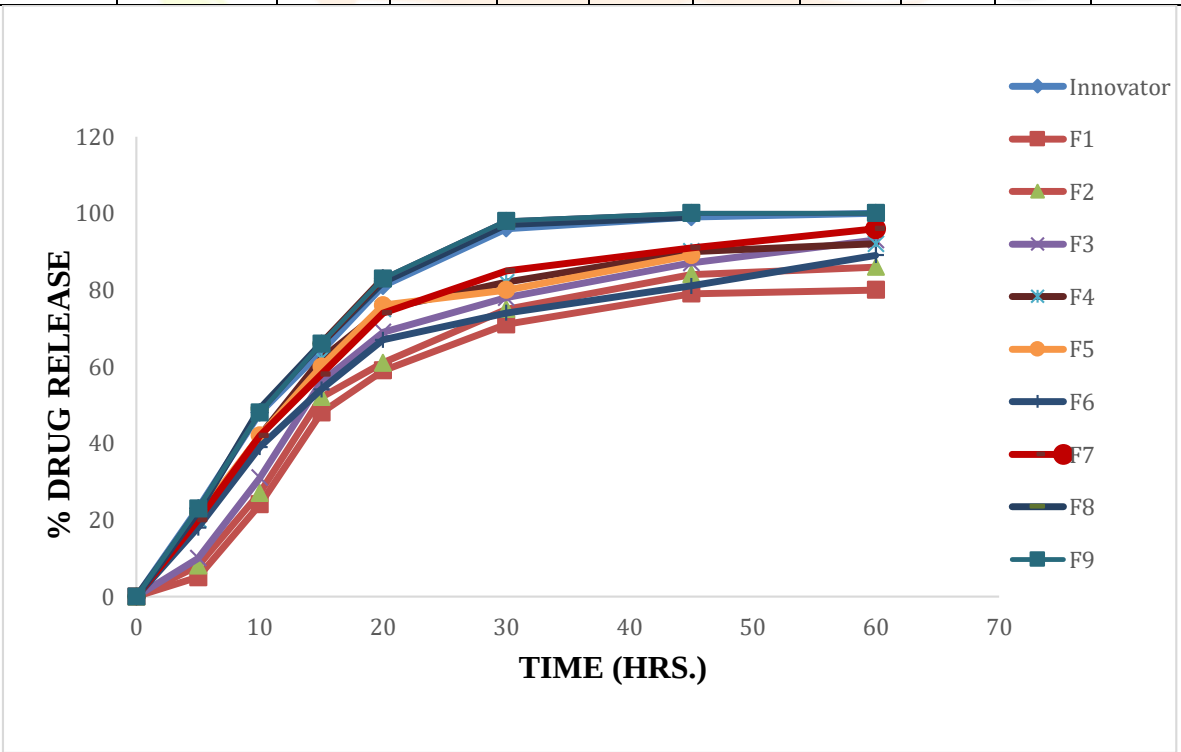

Figure 7.5: Comparative dissolution profile of all the formulation batches with reference product in OGD media

7.8.2 Comparative dissolution profile of reference product with optimized batch (F8) in 0.1 N HCl + 0.15% SLS

Table 7.16: Comparative dissolution data in OGD media (0.1 N HCl + 0.15% SLS)

Condition	**900ml of 0.1 N HCl + 0.15% SLS at 50 rpm in USP Type II apparatus (Paddle)**	
Time	**% Drug Release**	
	Innovator	**F8**
0	0	0
5	18	20
10	41	43
15	58	60
20	79	81
30	91	92
45	95	95
60	98	97

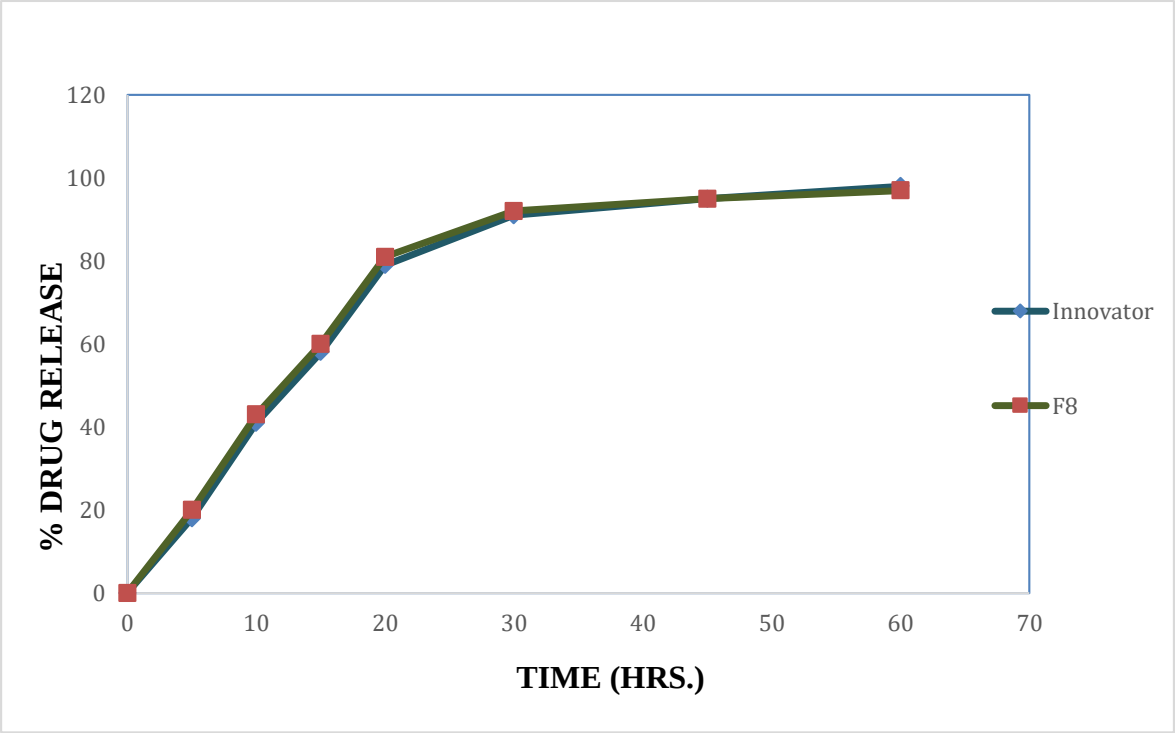

Figure 7.6: Comparative dissolution profile Reference product with optimized batch (F8) in 0.1 N HCl + 0.15% SLS

Conclusion: Dissolution of formulation batch (F8) complies as per reference product in 0.1 N HCL + 0.15% SLS dissolution media

7.8.3 Comparative dissolution profile of reference product with optimized batch (F8) in pH 4.5 Acetate Buffer + 0.15% SLS

Table 7.16: Comparative dissolution data in OGD media (pH 4.5 Acetate Buffer + 0.15% SLS)

Condition	**900ml of pH 4.5 Acetate Buffer + 0.15% SLS at 50 rpm in USP Type II apparatus (Paddle))**	
Time	**% Drug Release**	
	Innovator	**F8**
0	0	0
5	21	20
10	45	46
15	65	63
20	80	81
30	93	92
45	96	96
60	99	98

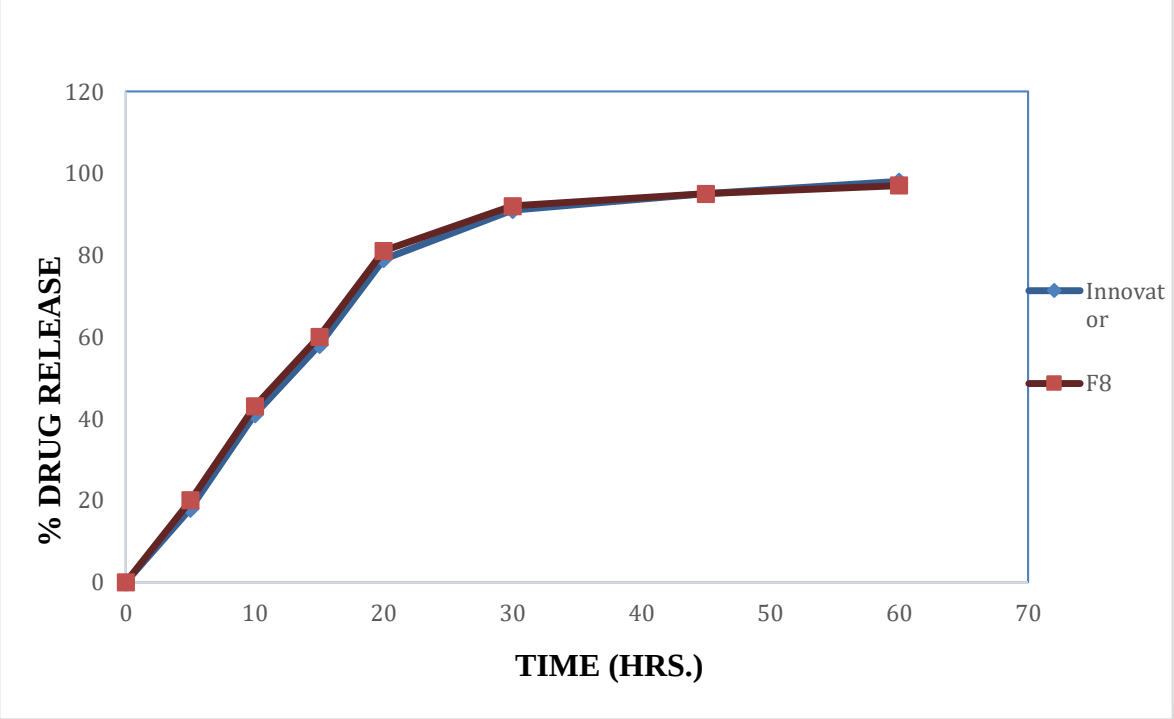

Figure 7.6: Comparative dissolution profile Reference product with optimized batch (F8) in pH 4.5 Acetate Buffer + 0.15% SLS

Conclusion: Dissolution of formulation batch (F8) complies as per reference product in pH 4.5 Acetate Buffer + 0.15% SLS dissolution media

. RESULT AND DISCUSSION

7.1 Physiochemical properties of drug:-

7.1.1 Organoleptic properties:

Table 7.1: Organoleptic properties of API

Properties	Observation
Colour	White to off white
Taste	Bitter
Odour	Odourless
Appearance	Powder

7.1.2 Melting point determination:-

Melting point of API was found to be, which is in range as given in literature (156-160ºC). Hence the drug can be stated as pure.

Table 7.2: Melting point determination

Sr.No.	Melting point [˚C] (observed)	Average [˚C]
1	158	158
2	157	
3	158	

7.1.3 Solubility:-

The solubility of the received sample of API was examined in various solvents (aqueous and organic). It is an only qualitative analysis. The results thus obtained were as follows-

Table 7.3: Details solubility of API

Sr.No.	Solvent	Solubility
1	Alcohol and DMSO	Freely soluble
2	water	Very slightly soluble

7.1.4 Particle size determination:-

Sample of API was analyzed by using Malvern particle size analyzer, particles were found in following size ranges

Table 7.4: Particle size determination

Sr.No.	Diameter	Particle size(µm)
1	D05	11.9
2	D04	49.6
3	D01	140.5

7.1.5 Loss on drying:-

Loss on drying was carried out by using halogen moisture analyzer and it was found to be 0.63% at 105ºC

7.3. BCS solubility study:-

Table 7.7: BCS solubility data of API in different media

Sr.No	Media	mg/250ml
1	Purified Water +0.15% SLS	505.2
2	0.1N HCl+0.15% SLS	725.0
3	pH 6.8 phosphate buffer+0.15% SLS	937.1
4	pH 4.5 Acetate buffer+0.15% SLS	794.3
5	pH 7.5 phosphate buffer+0.15% SLS	915.7

7.4 Micrometrics properties evaluation:

Table 7.8: Micrometrics properties of API

Sr.No	Parameters	Results	Flow properties
1	Bulk density(g/ml)	0.56	-
2	Tapped density(g/ml)	0.89	-
3	Carr's index (%)	37.18	Very Poor
4	Hauser's ratio(HR)	1.58	Very Very poor

7.5 Drug-excipients compatibility result:

1 Physical compatibility:

7.9: Result of physical compatibility of Drug

Sr.No.	API/ Excipients Name with Grade	Drug:Excipients Ratio	Condition	Observations on appearance	Assay (%)
01	API	1	Initial	White	99.8
02	API +Microcrystalline Cellulose	1:1	Initial	White	99.8
03	API + Lactose Monohydrate	1:1	Initial	White	99.8
04	API + Sodium starch glycolate	1.1	Initial	White	99.8
05	API +Croscarmellose sodium	1:1	Initial	White	99.8
06	API + Sodium lauryl sulfate	1:1	Initial	White	99.9
07	API + Magnesium stearate	1:0.5	Initial	White	99.8
08	API + Hypromellose 603	1:0.5	Initial	White	99.9
09	API + Opadry White	1:0.5	Initial	White	99.8
10	API + All excipient	1:1	Initial	No colour change	99.8

Conclusion:

No loss in assay was observed in any of these mixtures at Initial open condition hence degradation products not produce in open condition are within specification. There is no incompatibility with the selected excipients.

7.6 Pre compression parameter: -

Table 7.11: Evaluation of lubricated blend

Formulation. no	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio
F1	0.600	0.745	19.40	1.24
F2	0.610	0.750	19.90	1.23
F3	0.605	0.748	20.03	1.24
F4	0.612	0.776	22.31	1.25
F5	0.622	0.789	22.72	1.23
F6	0.618	0.768	20.31	1.24
F7	0.609	0.765	21.58	1.26
F8	0.601	0.760	21.63	1.27
F9	0.597	0.762	21.65	1.27

Conclusion:

In the above table characteristic of the powder blend from F1 to F9 is given. From values of Compressibility index and Hauser's ratio we can conclude that blend of the above formulation have passable flow properties and compressibility index.

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Table 7.12: Evaluation of Post compression Parameter.

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F4	200(190-210)	85	3.97	2min 20sec	0.6	98.7
F5	176(166.25-183.75)	86	3.37	2min 28sec	0.4	99.1
F6	175(166.25-183.75)	91	3.36	3min 05sec	0.5	98.1
F7	180(170.05-187.05	89	3.54	2min 46sec	0.5	99.4
F8	181(171.95-190.05	87	3.56	1 min 31sec	0.4	100.01
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Conclusion:

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7.8. In vitro Dissolution Study:

7.8.1 Comparative dissolution profile of reference product with optimized batch (F8) in 0.1 N HCl + 0.15% SLS

Table 7.15. %Comparative dissolution profile of innovator with all Formulation batches in Buffer pH 6.8 with 0.15% SLS

Media	900ml of 0.1 N HCl at 100 rpm in USP Type I apparatus (Basket)									
Time	% Drug Release									
	Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
5	23	5	8	10	20	21	18	20	22	23
10	48	24	27	31	42	42	39	42	49	48
15	64	48	52	56	62	60	54	58	66	66
20	81	59	61	69	75	76	67	74	82	83
30	96	71	75	78	82	80	74	85	97	98
45	99	79	84	87	90	89	81	91	99	100
60	100	80	86	93	92	93	89	96	100	100

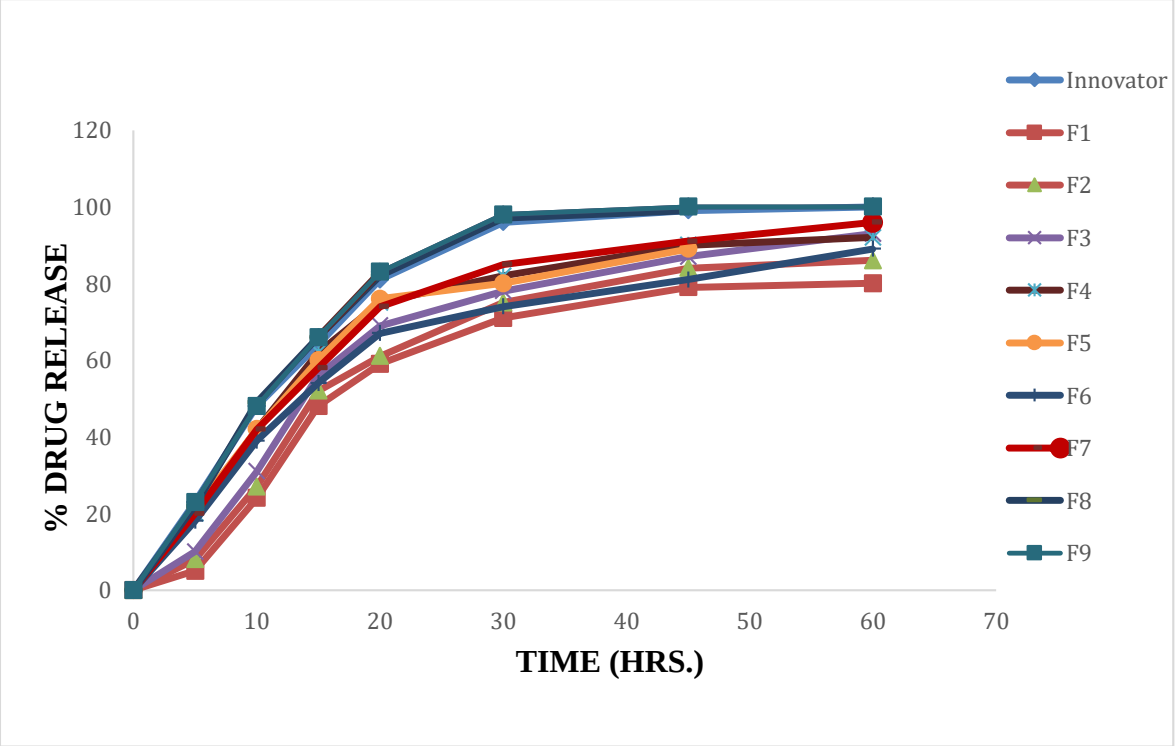

Figure 7.5: Comparative dissolution profile of all the formulation batches with reference product in OGD media

7.8.2 Comparative dissolution profile of reference product with optimized batch (F8) in 0.1 N HCl + 0.15% SLS

Table 7.16: Comparative dissolution data in OGD media (0.1 N HCl + 0.15% SLS)

Condition	900ml of 0.1 N HCl + 0.15% SLS at 50 rpm in USP Type II apparatus (Paddle)	
Time	% Drug Release	
	Innovator	F8
0	0	0
5	18	20
10	41	43
15	58	60
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45	95	95
60	98	97

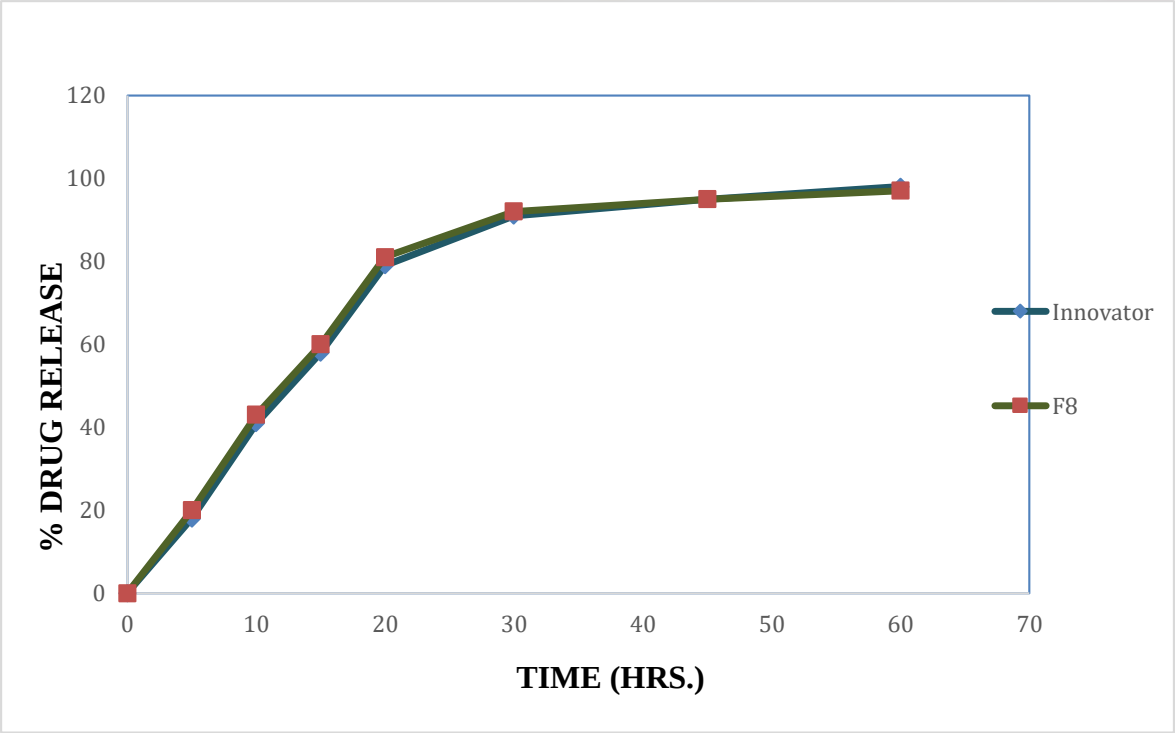

Figure 7.6: Comparative dissolution profile Reference product with optimized batch (F8) in 0.1 N HCl + 0.15% SLS

Conclusion: Dissolution of formulation batch (F8) complies as per reference product in 0.1 N HCL + 0.15% SLS dissolution media

7.8.3 Comparative dissolution profile of reference product with optimized batch (F8) in pH 4.5 Acetate Buffer + 0.15% SLS

Table 7.16: Comparative dissolution data in OGD media (pH 4.5 Acetate Buffer + 0.15% SLS)

Condition	900ml of pH 4.5 Acetate Buffer + 0.15% SLS at 50 rpm in USP Type II apparatus (Paddle))	
Time	% Drug Release	
	Innovator	F8
0	0	0
5	21	20
10	45	46
15	65	63
20	80	81
30	93	92
45	96	96
60	99	98

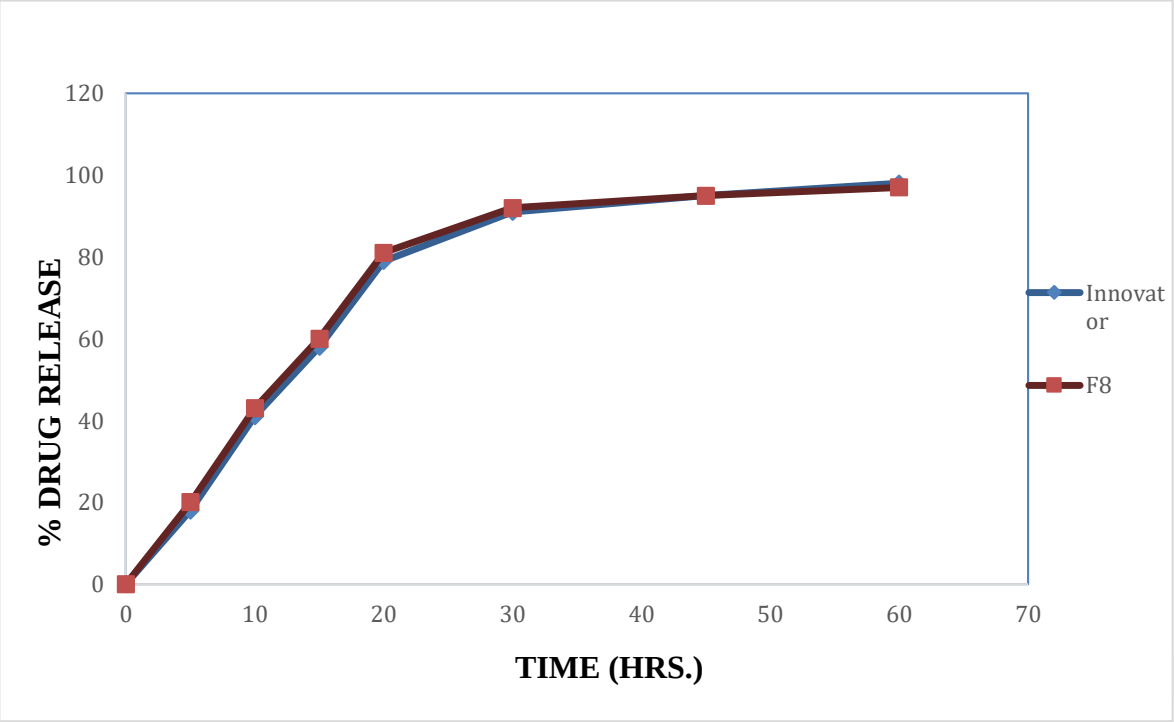

Figure 7.6: Comparative dissolution profile Reference product with optimized batch (F8) in pH 4.5 Acetate Buffer + 0.15% SLS

Conclusion: Dissolution of formulation batch (F8) complies as per reference product in pH 4.5 Acetate Buffer + 0.15% SLS dissolution media

SUMMARY AND CONCLUSION

The research work was aimed with formulation, development and evaluation of immediate release tablet of "Anti- Psoriatic Arthritis" i.e. Apremilast was formulated a stable as well as robust dosage form.

The basic objective was to develop a generic version of Apremilast tablets in line with the innovator. A generic version of IR tablets was developed that is safe, efficacious and to get the comparable dissolution profile and also bioequivalent to the reference product. The task of developing the IR tablet of Apremilast by using super disintegrant and solubility enhancer because to achieve the bioavailability within the short period.

The drug powders were subjected to preformulation studies. The preformulation characteristics are within the pharmacopoeia specification. The preformulation studies were carried out and the results were found to be satisfactory. The drug and excipients compatibility were carried out by HPLC method and physical observation showed there was no interaction between them. The drug assay was carried out by HPLC method. The various formulation of Apremilast were prepared by using Direct compression method, being direct compression involve few steps, offers commercial advantages and easy of manufacturability. The tablet was formulated by using excipients such as lactose monohydrate, MMC PH102, Cross carmellose sodium, Sodium starch glycolate, Sodium lauryl sulfate, hypromellose and Magnesium stearate. The blend ready for compression was evaluated for bulk density, tapped density, compressibility index and hausner's ratio. It was found that blend had compressibility index from 19 to 22% and hausner's ratio from 1.22 to 1.27 which indicate that blend ready for compression.

Total five formulations were prepared using different concentration of MCC PH102, Cross carmellose sodium, Sodium lauryl sulfate and Sodium starch glycolate. The tablets were evaluated for weight variation, thickness, hardness, disintegration time, friability, drug release and assay. The weight of tablets found within limit. The thickness of tablets varied from 3.80 ± 0.21mm. The

designation time vary according to the concentration of excipients. The assays of different batches were found between 97-100% indicating uniformity in drug content within tablet.

All nine formulations were evaluated for in vitro drug release in pH 6.8 phosphate buffer with 0.15% SLS, over a period of 60 min using USP type II (Paddle) dissolution apparatus at 50 RPM. The dissolution profiles of the batches were compared with that of innovator product. Among all seven batches F8 batch –showed comparable in vitro dissolution profile to that of innovator product. The multimedia dissolution was performed by using 0.1 N HCL and pH 4.5 acetate buffer. From the result it was observed and it was satisfied for improving dissolution rate to that of reference product. It was found that the release rate of tablet influenced by the solubility enhancer and super disintegrant. The samples were evaluated initially which showed no change in physical appearance, assay and drug release which indicate the tablet was stable.

Immediate release tablet prepared by direct compression showed comparable dissolution result with innovator. Form the above result it can be concluded that batch F8 showed comparable result with innovator, batch F9 Taken as a reproducible batch and also shows improvement in dissolution rate by using solubility enhancer and super disintegrant that means improving dissolution ultimately improvement in bioavailability. Hence Anti-Psoriatic Arthritis drug i.e., apremilast can be successfully formulated as an immediate release tablet.

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