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Formulation and Evaluation of Immediate Release Dasatinib Film Coated Tablet

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ABSTRACT:

This study focuses on the Formulation and Evaluation of Immediate Release Dasatinib Film Coated Tablet. Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Various formulations were prepared by direct compression technique using super disintegrants (cross carmellose sodium, sodium starch glycolate etc.) The main objective is to achieve immediate drug release profile for the developed formulation. Optimized formulation was selected and its in-vitro release profile should be comparable with the reference product (Sprycel). The Stability studies were performed on the optimized formulation. Formulation of tablets by direct compression method. Evaluation of formulated tablets by performing various tests. Dasatinib, Microcrystalline cellulose, Chemicals are used. The formulation and evaluation of immediate release Dasatinib film coated tablets for the treatment of Lymphoblast Phase chronic myeloid leukemia. this preformulating studies performed for the drug and excipients as per the standard procedure. Immediate release drug delivery is a conventional type of drug delivery. The optimized formulation was subjected to stability studies and it was found to be stable.

Keyword: Dasatinib, Cross Carmellose Sodium, Sodium Starch Glycolate , Crospovidone.

1.INTRODUCTION

1.1 Oral Drug Delivery[1]: Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered as most natural, uncomplicated, convenient and safe due to ease of administration, patient acceptibility and cost-effective manufacturing process.

1.2 Tablets[2]: Tablets are defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer (simplicity & economy of preparation, stability and convenience in packing, shipping and dispensing). Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size ,weight depending on the amount of drug substance present and intended method of administration.

1.3 Immediate Release Drug Delivery System: Immediate release drug delivery system is a conventional

type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features. These are the dosage forms in which ≥ 85% of labelled amount dissolves within 30 min[5]. However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release of the active drug which then becomes available in whole or in part, for absorption from gastrointestinal tract[6].

a.Dasatinib drug: Dasatinib is an orally available multikinase inhibitor indicated for the treatment of Philadelphia chromosome (Ph)-positive leukemias.[1,7] Ph is a chromosomal abnormality found in patients with chronic myelogenous leukemia (CML) and acute lymphocytic leukemia (ALL), where the ABL tyrosine kinase and the breakpoint cluster region (BCR) gene transcribe the chimeric protein BCR-ABL. BCR-ABL is associated with the uncontrolled activity of the ABL tyrosine kinase and is involved in the pathogenesis of CML and 15-30% of ALL cases.[5,6] Dasatinib also inhibits a spectrum of kinases involved in cancer, including several SRC-family kinases.[5]

1.3.1 Mechanism of drug release: On exposure to aqueous fluids, hydrophilic matrices take up water and the polymer starts hydrating to form a gel layer. Drug release is controlled by diffusion barriers/ by surface erosions. An initial burst of soluble drug may occur due to surface leaching. When a matrix containing a swellable glassy polymer comes in to contact with an aqueous medium, there is an abrupt change from a glassy to rubbery state associate with swelling process with time, water infiltration deep in to the case increases the thickness of the gel layer. The outer layer becomes fully hydrated and starts dissolving or eroding. When water reaches the center of the system and the concentration of drug falls below the solubility value, the release rate of the drug begins to reduce. At the same time an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

1.3.2 Advantages of immediate release drug delivery system: Release the drug immediately, More flexibility in adjusting the dose, It can be prepared with minimum dose of drug, There is no dose dumping problem

Immediate release drug delivery systems can be used in both initial stage and final stage of disease.

1.3.3 Super disintegrants in immediate release: These are especially important for an immediate release product where rapid release of dug substance is required. A disintegrant can be added to powder blend for direct compression.

Super disintegrants	Example	Mechanism of action	Special comment
Crosscarmellose	Crosslinked Cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation
Crosspovidone	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate	Crosslinked Starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix

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Table 1: List of Super disintegrants used in immediate release

2. EXPERIMENTAL METHODOLOGY:

2.1 Pre-Formulation Studies:

2.1.1 Preparation of standard calibration Curve of Dasatinib: 10 mg of Dasatinib was accurately weighed and dissolved in 10mlofacetate buffer pH 4(Stock Solution – I) to get a concentration of 1000 µg/ml. From the stock solution-I,1ml of aliquots was taken and suitably diluted with acetate buffer pH 4(Stock Solution-II) to get concentrations of 100µg/ml.from the stock solution- II, aliquots were taken and suitably diluted with acetate buffer pH 4 to get concentrations in the range of2to 14µg/ml. The absorbance of these samples were analyzed by using UV- Visible Spectrophotometer 315nmagainstreferencesolution acetate buffer pH 4.

2.1.2 Moisture Content: Take around 50ml of methanol in titration vessel of Karl Fischer titrator and titrate with Karl Fischer reagent to end point. In a dry mortar grind the pellets to fine powder. Weigh accurately about 0.5 g of the sample, transfer quickly to the titration vessel, stirr to dissolve and titrate with Karl Fischer reagent to end point.

Calculation: % Moisture content =(mg water/mg sample)*100

Where, mg water is the amount of water reacted with the Karl Fischer reagent .

mg sample is the weight of the sample analysed.

2.2 API and Excepient mixed in different ratios and subjected to FTIR Studies:

2.2.1 Drug – Excipient interaction studies: While developing a new formulation, it is necessary to check the drug compatibility with the carrier or excipient used and that the drug has not undergone any degradation when it passes through the various processes. Suitable evidential experiments are conducted to justify and prove the intactness of the drug in the formulations. Various methods, available for characterizing the products are: TLC, IR spectra, X-ray diffraction, scanning electron microscopy, diffuse reflectance spectroscopy and differential scanning calorimetry.

2.2.2 Infrared spectroscopy: Infrared spectroscopy is one of most powerful analytical technique when it comes to the determination of presence of various functional groups involved in making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring while in the processing of formulation. IR spectra of Dasatinib and its formulations were obtained by Bruker FTIR spectrometer in order to rule out drug-carrier interaction

occurring during the formulation process.

API and Excepient mixed in different ratios and checked for powder characterstics with the help of following methods:

2.2.3 Angle of Repose: Angle of repose is used to determine the flow properties of powders, pellets or granules. The method to find angle of repose is to pour the powder on a conical heap on a level, flat surface and measure the included angle with the horizontal[8].

Tan θ = h/r

Where, h = height of the heap, r = Radius of the heap

Angle Of Repose	**Powder Flow**
< 25	Excellent
25 – 30	Good
30 – 40	Possible
> 40	Very poor

Table 2: Angle of Repose

2.2.4 Bulk Density: Bulk density of a compound various substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring presieved powder into a graduated cylinder via a large funnel and measure the volume and weight.

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

2.2.5 Tapped Density: Tapped density is determined by placing a graduated cylinder containing a known mass of powder and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

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

2.2.6 Carr's Index: Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{(D_t - D_b) \times 100}{D_t}$$

Where D_t = Tapped density D_b = Bulk density

2.2.7 Hausner's Ratio: The Hausner ratio indicates the flowability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability. Hausner Ratio was calculated using the formula: Hausner's ratio = Dt/Db

Acceptable limits for flow properties

Compressibility Index	Flow Character	Hausner Ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25

21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very Poor	1.46 – 1.59
> 38	Very Very Poor	> 1.60

Table 3: Acceptable limits for flow properties

2.2.8 Sampling Schedule:

S.No	Condition	Duration
1	Initial	0 days
2	$55^0C \pm 2^0C$	14 days
3	40 ± 2^0C & 75 ± 5% RH	28 days

Table 4 : Sampling Schedule

2.3 Preparation of Dasatinib tablets: Sift Dasatinib monohydrate, croscarmellose sodium /sodium starch glycolate /crospovidone, lactose monohydrate, hydroxypropyl cellulose and microcrystalline cellulose (PH 102) through sieve no 40 and blend it for 2 min.

To this add magnesium stearate which is previously passed through sieve no 60 and blend for 1 min. Then compressed the above blend by using 12.5 mm round punch. Drug, MCC, Lactose monohydrate, HPC, Super disintegrants (CCS, SSG, CP) Sieved through Mesh no 40

↓

Blender in a blender

↓

Magnesium stearate is added (previously passed through # 60) Compressed into tablets (Tablet Compression Machine-8 station)

↓

Film Coating: 10% w/v coating solution of opadry white was used.

2.3.1 Preparation Of Coating Solution: Opadry white and water were weighed accurately.Opadry was dispersed in water under constant stirring and stirred for 45 mins. The solution was filtered and then it is used for coating.

2.4 Evaluation of tablets:

2.4.1 Weight variation test: It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there that should fall within prescribed limits. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and individual weight was compared with an average weight. Not more than one tablet fall outside this range. The difference of weight in tablet can lead to variation in d.

2.4.2 Hardness test: 10 tablets from each batch were selected and hardness was measured using Digital hardness tester to find the average tablet hardness or crushing strength.

Hardness of 4 kg is considered suitable for handling the tablets.

2.4.3 Tablet thickness: Thickness and diameter of formulation trials were measured using a Caliper,

Thickness Gauge. 10 tablets of each trial formulation were taken and measured individually at frequent intervals.

2.4.4Friability (%): Friability was determined by taking 20 tablets. Tablets samples were weighed accurately and placed in Friabilator after the given specification (4 min at 25 rpm). The tablets were weighed again and % friability was then calculated by

%F = {(W – W0)/W} x 100

Where,

% F = Friability of tablets in percent. W = Initial Wight of tablets.

WO = Final weight of tablets.

2.4.5 Disintegration Test: Disintegration test, measured using USP tablet disintegration test apparatus (ED2L, Electro lab, India) using 900 ml of distilled water at room temperature (37±2C). Disintegration time was measured for six tablets by inserting each tablet in each disk.

2.4.5 Dissolution Test: In vitro dissolution test was carried out by using USP type II (paddle) apparatus. 1000 ml of acetate buffer pH 4 with 1 % triton X-100 was used as dissolution medium and the paddle was rotated at 60 rpm at temperature (37°C ± 0.5°C). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analysed spectrophotometrically at λmax of the drug. (FDA method)

Medium : acetate buffer pH 4 with 1 % triton X-100

Temperature : 37°C ± 0.5°C Apparatus :

Time interval : 10, 15, 30 & 45 min.

Volume : 1000ml

USP type –II (paddle) RPM :60 RPM

2.4.6 Stability studies: The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

ICH Guide Lines For Stability Studies:

Study	Storage condition	Time period
Accelerated	40°C±2°C/75%±5% RH	6 months
Intermediate	30°C±2°C/65%±5% RH	6 months
Long term	25°C±2°C/60% ±5% RH	12 months

Table:5 ICH Guide lines for stability studies

3.RESULTS:

Physical characterization of API:

S.No:	Description	Result
1.	Appearance	Off-White to pale yellow powder
2.	Odour	Odourless

3.	Solubility	Practically insoluble in aqueous media, slightly soluble in ethanol and soluble in methanol and DMSO
4.	Water Content	2.8 %

Table:6 Physical characterization of API

3.1 Solubility Studies:

Ethanol - 3.4 mg/ml At pH 2.6 - 18 mg/ml

At pH 6 - 8 µg/ml At pH 7.4 - < 1µg/ml

Standard curve data of Dasatinib in acetate buffer pH 4 at 315nm

Conentration	**Absorbance**
0	0
2	0.006
4	0.016
6	0.026
8	0.037
10	0.046
12	0.057
14	0.067

Table 7: Standard curve data of Dasatinib

Compatibility Studies Results:

S.No	**Ingredients**	**Ratio**	**Description**		
			Initial	55°C (2weeks)	40±2°C /70±5 % RH (4weeks)
1	API(Dasatinib Monohydrate)	1	Off white	No change	No change
2.	Lactose Monohydrate	1	Off white	No change	No change
3	Micro crystalline cellulose	1	Off white	No change	No change
4	CrossCarmellose sodium	1	Off white	No change	No change
5	Sodium starch glycolate	1	Off white	No change	No change
6	Cross povidone	1	Creamy white	No change	No change
7	Hydroxy propyl cellulose	1	white	No change	No change
8	Magnesium stearate	1	Off white	No change	No change

9	Opadry white	1	White	No change	No change
10	API +Lactose monohydrate	1:5	Off white	No change	No change
11	API +Micro crystalline cellulose	1:5	Off white	No change	No change
12	API +Cross carmellose sodium	1:1	Off white	No change	No change
13	API + Sodium Starch glycolate	1:1	Off white	No change	No change
14	API+ Crospovidone	1:1	Off white	No change	No change
15	API + Hydroxy propyl cellulose	1:1	Off white	No change	No change
16	API+Magnesium Stearate	1:1	Off white	No change	No change
17	API + Opadry white	1:1	White	No change	No change

Table: 8 Compatibility studies

No Characteristic change in the colour of the powder and no additional degradation of the product were observed.

Caliberation curve of Dasatinib in acetate buffer 1.2N Hcl at 315nm

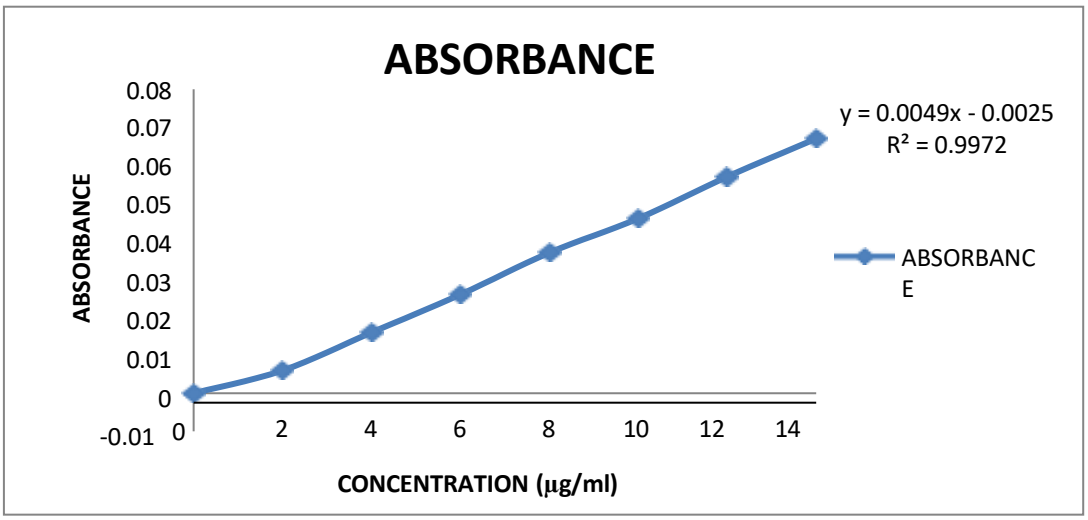


Figure 1: Caliberation Curve of Dasatinib

Various precompression parameters:

Formul Ation Code	Bulk Density (Gm/Ml)	Tapped Density (Gm/Ml)	Compressibi Lity Index(%)	Hausner's Ratio	Angle Of Repose
F1	0.484	0.547	11.51	1.13	21.63
F2	0.478	0.563	15.01	1.17	19.24

F3	0.472	0.528	10.6	1.11	20.42
F4	0.463	0.556	16.72	1.20	20.24
F5	0.456	0.574	20.05	1.24	20.42
F6	0.461	0.587	21.46	1.27	19.56
F7	0.447	0.593	24.62	1.32	21.72
F8	0.477	0.648	26.38	1.35	18.96
F9	0.468	0.604	22.51	1.29	22.35

Table 9: Various pre compressional parameters

Post Compressions Parameters:

Formulation code/ Parameters	Hardness (kg/cm^2)	Friability (%)	Weight variation	Disintegration time
F1	7.1	0.13	548.6	4min
F2	6.3	0.15	546.9	3.2min
F3	7	0.12	549.4	2.5min
F4	6.6	0.25	552.6	5min
F5	7	0.19	549.2	4.7min
F6	7.2	0.33	554.1	4min
F7	7.5	0.33	545.5	5.8min
F8	6.8	0.17	549.4	5.2min
F9	6.5	0.37	543.7	4.8min

Table 10: Post compressions parameterInvitro drug release of various formulations:

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	73.8	79.9	83.3	70.2	73.3	78.7	70.3	73.9	78.8
15	78.2	85.7	91.3	75.9	78.4	82.8	73.6	76.2	81.5
30	80.6	89.5	96.2	78.6	80.5	83.2	77.9	80.4	84.9
45	87.9	92.3	98.3	80.1	84.6	88.5	79.1	83.5	86.5

Table 11: Invitro drug release of various formulations

In vitro drug release profile of marketed product (Sprycel):

Time (Minutes)	Percentage Cumulative Drug Release
10	80.3%
15	89.5%
30	94.3%
45	97.6 %

Table 12: In vitro drug release profile of marketed product

Figure: 2 Comparison of cumulative percent drug release of formulations F1toF3

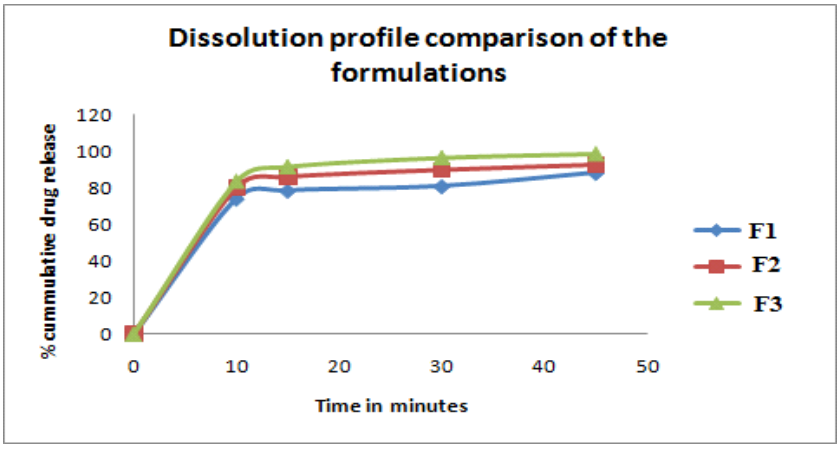
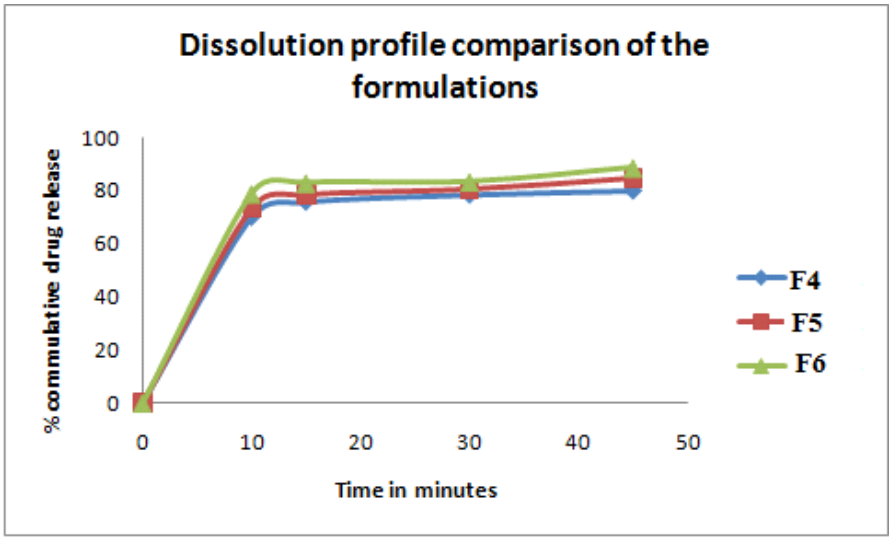


Figure:3 Comparison of cumulative percent drug release of formulations F4 to F6



Comparison of invitro drug release of innovator and formulation f3

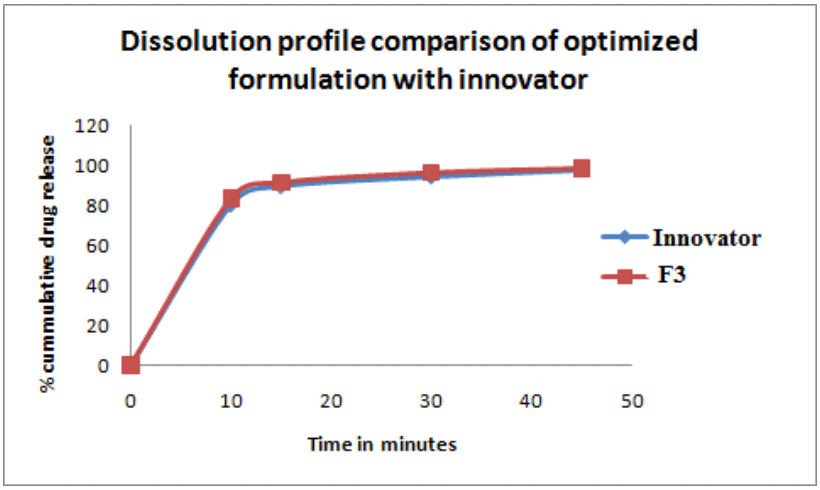
Time (Minutes)	Percentage Cumulative Drug Release	
	Innovator	F3
10	80.3%	83.3
15	89.5%	91.3

30	94.3%	96.2
45	97.6 %	98.3

Table 13: Comparison of invitro drug release of innovator and formulation f3 stability

Comparison ofcumulative percent drug release of innovator and formulation f3 stability

Figure :4 Comparison of cumulative percent drug release of formulations F7 to F9



Study data (Accelerated) of Trial F – 03:

S.No	Parameters	Specifications		Test Condition (Accelerated)			
				40 ± 2^{0}C & 75 ± 5% RH			
				0 Day	1 Month	2 Month	3 Month
1	Description	White to off- white round shape film coated tablet.		Comply	Comply	Comply	Comply
2	Moisture content	Not more than 6.0%		4.427%	4.326%	4.211%	4.143
3	Assay	Not less than 90% & Not more than 110%of labeled amount of drug.		97.9%	98.2%	98.8%	99.6%
4	Rela ted subst ance s by HPL C	Impurity A	Not more than 0.2%	Nodeviation	No deviation	No deviation	No deviation
		Impurity B	Not more than 0.2%	0.006%	0.007%	0.007%	0.007%
		Single max impurity	Notmore than 0.5%	0.059%	0.064%	0.067%	0.072%
		Total impurity	Notmore than 2%	0.065%	0.071%	0.074%	0.079%

5	Dissolution	Not less than 80% of labeled amount of dasatinib dissolved in 30min	97.8%	97.2%	96.2%	96.1%

Table:14 Stability Study data

4. DISCUSSION:

The present investigation was undertaken to formulate and evaluate immediate release dasatinib film coated tablets for the treatment of lymphoid blast phase chronic myloid leukaemia. For the development and formulation of immediate release tablets by direct compression method were carried out with combination of various approved excipients.All the experimental formulation batches have been subjected to various evaluation parameters viz average weight, thickness, hardness, fraibility, disintegration, dissolution.

4.1 Pre Compression Parameters: The bulk density of precompression blends was found to be in the range of 0.3 to 0.5. The tapped density in the range of 0.5 to 0.7. Carrs index values were in the 11-15% good,Hausner's ratio in the range 1.1-1.18 all the above values found to be within the prescribed limits according to IP.Thus ensuring good flow property to the formulation blends. The angle of repose was found to be within the limits. Angle of repose values were in the range of 18.96 to 22.35.

4.2 Post Compressions Parameters:

4.2.1 Hardness and Fraibility:- Hardness of the tablet formulation found to be in the range7kp.

The fraibility values were found to be in the range of 0.12% which were found to be according to IP limits and thus ensuring good mechanical strength of all the formulations.

4.2.2 Uniformity Weight: All the prepared immediate release tablets of dasatinib were evaluated for weight variation.The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed limits.

4.2.3 Disintegration Time: All The prepared immediate release tablets of dasatinib were evaluated for disintegration.The disintegration of all optimized the tablets found to be uniform with low values of standard deviation.

4.2.4 Invitro Dissolution: In-vitro dissolution was performed in 1.2N Hcl. The dissolution results showed gradient increase with the increase in concentration of the super-disintegrants. croscarmeellose sodium acts as a best super-disintegrant agent, among all the formulations F3 was found to show best results with 98.3% release within 45 minutes, followed by F1, F2, F4, F5, F6, F7, F8, F9 with values of 87.9%, 92.3%, 80.1%, 84.6%, 88.5%, 79.1%, 83.5%, 86.5%.

4.2.5 Stability studies: Stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the sample analyzed there is no deviation. All parameters and specifications are within limts.

5. SUMMARY:

The topic for the present study is "formulation and development and evaluation of Dasatininb Film coated tablets". Introduction is presented in chapter-1, which gives details about immediate release and its mode and choice of drugs for the treatment of Lymphoid blast phase chronic myeloid leukemia. The chapter

also gives overview about immediate release tablets and their methods of development. The aim of the study present in chapter -2 is to formulate and evaluate immediate release Dasatinib Film coated tablets. The literature of review is presented in chapter-3 which provides an extensive detail of the related research work providing to the present study. Drug profile is presented in Chapter-4, which gives details about the mechanism of action, pharmacodynamics, pharmacokinetics, dose and administration, precautions and side-effects of the selected drug. Excipients profile is chapter- 5, which gives details about the different excipients used in the formulation development.

Materials and methods is present in chapter- 6, which gives information about list of chemicals, equipments used for the study. This chapter also gives information about the methods involved in the development of formulation. Experimental investigation is presented in chapter- 7, which gives information about formulas developed int he formulation of immediate release tablets and the comparative evaluation of the developed formulation with that of the innovator product.

Results and discussion is presented in chapter-8, which deals with the complete information regarding physical and chemical analysis of the present study with the suitable tablets, graphs and figures.

6. CONCLUSION:

The formualation and evaluation of immediate release Dasatinib film coated tablets for the treatment of Lymphoblast Phase chronic myeloid leukaemia. In this preformulaiton studies performed for the drug and excipients as per the standard procedure. The concept of immediate release tablets containing Dasatinib. Immediate release drug delivery is a conventional type of drug delivery. various formulation trails of dasatinib tablets were conducted using three super disintegrants like Croscarmellose sodium, sodium starch glycolate and crospovidone These three super disintegrants were used at three different concentrations like 2.5%, 3.5% and 4.5%.

Based on the above results, the optimized formulation was found to be formulation containing crosscarmellose sodium at 4.5%. The optimized formulation was subjected to stability studies and it was found to be stable.

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