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Original Article

DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF DASATINIB USING SODIUM STARCH GLYCOLATE AS SUPER DISINTEGRANTS

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ABSTRACT

The present study was undertaken to develop immediate release (IR) tablets of Dasatinib a selective tyrokinase inhibitor (TKI) which is used in treatment of chronic myeloid leukaemia (CML) and acute myeloid leukaemia (AML).The tablets were prepared by wet granulation method using various excipients, drug and super disintigrants such as sodium starch glycolate (SSG). The prepared tablets were evaluated for pre compression parameters, post compression parameters, in vitro drug release study and stability study. Among the prepared formulations F5 Batch shows 91.32% drug release in 45minutes.The best formulation F5 batch indicates no significant changes from short term stability studies(at 40±2ºC/75±5% RH).Fourier Transform Infrared spectroscopy(FTIR) confirms no drug excipients interaction from various batches.

Keywords: Dasatinib, immediate release tablets, SSG, FTIR Spectroscopy.

INTRODUCTION

The advances in novel drug delivery systems for designing dosage forms like immediate release tablets for convenient to be manufactured and administered free side effects, offering immediate release and enhance bioavailability so as to achieve better patient compliance. Oral drug delivery systems [1] preferably tablets are most widely used dosage forms for being compact offering uniform dose and painless delivery. Solid oral delivery systems (especially tablets) is system of choice among all drug delivery system and they do not require special treatment and are therefore less expensive to manufacture, likewise immediate release tablets are more acceptable among all the tablets. Immediate release drug delivery system are based on single or multiple unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time. Immediate release drug delivery [2] is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. For immediate release tablets the drug is intended to be released rapidly after administration, or the tablet is dissolved and administered as a solution.IR tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features such as special coatings and other techniques. In pharmaceutical industries, manufactures of generic tablets are usually focused on the optimization of the excipients mixture composition to obtain a product that meet established standard.

Dasatinib [3] is a selective tyrosine kinase inhibitor (TKI) used in treatment of chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). Dasatinib have become first line drug in the pharmacotherapy of patients with CML. This is because the drug possesses tolerability and safety advantages over the other tyrosine kinase inhibitors. Dasatinib at nanomolar concentrations inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Dasatinib is predicted to bind to multiple conformations of the ABL kinase. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines over expressing BCR-ABL. Dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene over expression.Dasatinib undergoes hepatic first pass metabolism [4] by the cytochrome P450 enzyme 3A4 and terminal elimination half life between 1.3 to 5 hrs after oral administration. Dasatinib is excreted mainly in faeces (85%) and urine (4%). In the present study IR tablets of Dasatinib were designed using wet granulation method using various excipients and sodium starch glycolate (SSG) as natural superdisintegrants with prime objective arriving of a cost effective product.

MATERIALS AND METHODS

Materials

Dasatinib was received as a gift sample from Natco Pharma. Pvt Ltd., Hyderabad,Telangana.Hydroxy Propyl Cellulose, magnesium stearate, talc, micro crystalline cellulose,and potassium dihydrogen-o-phosphate were procured from SD fine chem. Ltd Mumbai. Sodium hydroxide, SSG and methanol were procured from Qualigens fine chemicals Mumbai.

Drug excipient studies

Fourier Transform Infrared Spectroscopy (FTIR)

The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures. Then the peaks of optimized formulation were compared with pure drug and excipients.

Preparation of immediate release (IR) tablets

Accurately weighed quantities of ingredients mentioned in Table-1 were

passed through sieve no. 40 and magnesium stearate was passed through sieve no.60. All the ingredients lubricant magnesium stearate and talc (glidant) were manually blended homogenous by way of geometric dilution. The mixture was moistened with aqueous solution and granulated with sieve no.20 and placed in hot air oven at 60º C for sufficient 3-4 hrs. Then dried granules passed through sieve no.12 and blended with mgnesium stearate and talc. The homogenous mixture were placed into tablet punching machine(10 station rotary tablet machine, Clint India) getting tablet using deep concave punch.

Table 1: Composition of Dasatinib immediate release tablets

Ingredients(mg)	F1	F 2	F 3	F 4	F 5
Dasatinib	70	70	70	70	70
Micro Crystalline Cellulose	400	395	390	385	380
SSG	5	10	15	20	25
Hydroxy propyl cellulose	20	20	20	20	20
Magnesium Stearate	3	3	3	3	3
Talc	2	2	2	2	2
Total weight(mg)	500	500	500	500	500

EVALUATION OF GRANULES

Pre compression parameters of immediate release (IR) tablets:

Angle of repose

The angle of repose [5] of granules blend was determined by the fixed funnel method. The accurately weighed quantity of granules was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equation

$\tan\Theta = h/r$

$\Theta = \tan^{-1}(h/r)$

Where Θ is the angle of repose, h is the height of cone in cm and r is the radius of the cone base in cm.

Bulk density (e_b)

Bulk density [6] was determined by pouring the granules into a graduated cylinder in bulk density apparatus (Sisco,India). The bulk volume (V_b) and mass (m) of the granules was determined. The bulk density was calculated by using the following formula.

Bulk density (e_b)=Mass of granules(m)/Bulk volume of granules(V_b)

Tapped density (e_t)

The measuring cylinder containing known mass of granules blend was tapped 1000 times for a fixed time in bulk density apparatus (Sisco,India).The minimum volume occupied in the cylinder(V_t) and mass of the granules(m) was measured. The tapped density[7] was measured by using the following formula.

Tapped density (e_t)= Mass of granules(m)/Tapped volume of granules(V_t)

Compressibility index (Carr's index)

The compressibility index [8] determines the flow property characterstics of granules developed by Carr. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The Carr's index can be calculated by the following formula.

$\%\text{Carr's index} = e_t - e_b / e_t \times 100$

Where e_t is the tapped density of granules and e_b is bulk density of granules

Hausner's ratio

Hausner's ratio is used for the determination of flow properties of granules. The ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

Post compression parameters of immediate release (IR) tablets:[9]

Thickness

The thickness of individual tablets are measured by using vernier caliper which gives the accurate measurement of thickness.It provides information of variation of thickness between tablets. Generally the unit for thickness measurement is mm.The limit of the thickness deviation of each tablet is ±5%.

Hardness

The hardness of a tablet is associated with the resistance of the solid specimen towards fracturing and attrition [10]. The hardness of tablets can be determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability

Friability of tablets was performed in a Roche friabilator. Ten tablets were initially weighed (WI) together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed finally (WF).The percentage of friability was calculated using the following equation.

$$\%\text{Friability (F)} = \left(1 - \frac{WF}{WI}\right) \times 100$$

Where, WI and WF are the weight of the tablets before (initially weight) and after(final weight) the test respectively.

Weight Variation

The weight variation test [11] was done by weighing 20 tablets individually (Shimadzu digital balance), calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications.

Disintegration test

Six tablets along disc were introduced in each tube of basket of disintegration test apparatus (Lab care instruments). The basket was positioned into a beaker containing 900 ml of distilled water [11]and operated at 37 ± 2º C. The time of disintegration of tablet was recorded. The average time and standard deviation were calculated. Three trails were performed.

Drug Content

Drug content for immediate release (IR) tablet was done by the assay method. First the prepared tablet (70mg API) was crushed and added to 70ml of acetate buffer pH 4 with 1 % triton X-100. After 30 minutes the solution was filtered and from 70ml solution 1ml solution was withdrawn diluted up to 10 ml with acetate buffer pH 4 with 1 % triton X-100 producing 100 µg/ml. From this 10 ml solution again 1 ml of sample is withdrawn diluted upto 10ml with acetate buffer pH 4 with 1 % triton X-100 obtaining desired concentration 10µg/ml. This solution concentration for the drug content of formulations was calculated using calibrated standard curve equation $y=0.004x-0.002$.The drug content was determined at λmax315 nm by UV-spectrophotometer (ELICO164) against blank.

Diameter of tablet

The diameter of individual tablets is measured by using vernier caliper which gives the accurate measurement of diameter. It provides information of variation of diameter between osmotic pump tablets. Generally the unit for thickness measurement is mm.

In vitro dissolution studies:

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 (37ºC ± 0.5ºC).In specified time intervals (0,5,10,15,20,25,30,35,40,45min) an aliquot of 5ml samples of the solution were withdrawn from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. The samples were

filtered through filter paper of 0.45 µm. Absorbance of these solutions were measured at λmax 315nm using a UV/Visible Spectrophotometer (ELICO164). The drug release was plotted against time to determine the release profile of various batches.

Stability studies

Short term stability studies [12,13] on the above promising formulation (at 40±2ºC/75±5% RH for 3 months) were carried out for observing significance changes in physical appearance and drug content.

RESULTS AND DISCUSSION

Drug excipient studies

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the FTIR study it was found that the drug and excipients were compatible.

Pre-compression parameters of immediate release (IR) formulations

All the compressible excipients (Table-1) with drug by wet granulation method was prepared. This granules were evaluated for pre-compressionparameters(Table-2) such as angle of repose bulk density, tapped density, Carr's index and Hausner's ratio.

Table 2:Pre-compression parameters of IR formulations.

Formulation code	Angle of repose (degree)[a] ± S.D	Bulk density (gm/ml)[a] ± S.D	Tapped density (gm/ml)[a] ± S.D	Carr's Index (%)[a] ± S.D	Hausner's Ratio[a] ± S.D
F1	29.65±0.13	0.462±0.17	0.545±0.15	15.22±0.14	1.17±0.16
F2	28.73±0.12	0.483±0.11	0.536±0.09	9.88±0.06	1.10±0.08
F3	26.32±0.08	0.479±0.01	0.534±0.03	10.3±0.04	1.11±0.06
F4	25.43±0.11	0.481±0.04	0.529±0.05	9.07±0.05	1.09±0.04
F5	30.12±0.12	0.467±0.03	0.532±0.02	12.21±0.06	1.13±0.03

N.B.All values are expressed as mean± S.D, [a] n = 3.

The angle of repose was found in the ranges from 25.43 to 30.12 degrees,bulk density of pre-compression blends was found to be in the range of 0.462 to 0.483gm/ml, tapped density in the range of 0.529 to 0.545 gm/ml, the Carr's index values were in the range of 9.07 to 15.22%, and the Hausner's ratio was in the range between 1.09 to 1.17.

Post-compression parameters of IR formulations

The post compression parameters such as hardness, weight variation, drug content uniformity, friability and thickness have given below (Table 3).

Table 3:Post-compression parameters of IR formulations

Formulation code	Thickness (mm)[a] ± S.D	Hardness (kg/cm^2)[a] ±S.D	%Friability (%)[b] ± S.D	Average wt.of tablet(mg)[b] ± S.D	Disintegration time(min.)[c] ±S.D	%Drug content[a] ±S.D	Diameter (mm)[a] ±S.D
F1	4.01±0.01	5.8±0.12	0.31±0.03	500.18±1.16	4.1±0.03	97.92±1.32	12.13±0.02
F2	4.123±0.02	5.9±0.11	0.46±0.02	500.4±1.03	3.8±0.11	99.32±1.41	12.11±0.03
F3	3.961±0.03	6.1±0.16	0.44±0.03	500.3±1.02	3.6±0.15	98.64±0.98	12.13±0.07
F4	3.992±0.01	6.5±0.18	0.50±0.02	500.12±1.06	3.9±0.12	98.96±1.4	12.14±0.09
F5	4.094±0.02	6.3±0.13	0.57±0.01	500.11±1.04	3.5±0.02	99.71±1.5	12.12±0.06

N.B.All values are expressed as mean± S.D, [a] n = 10, [b] n = 20, [c] n = 3

The thickness of the tablet formulations was found to be in the range of 3.961to4.123mm. The hardness of the tablet formulations was found to be in the range of 5.8to6.5 kg/cm^2. The friability values were found to be in the range of 0.31 to 0.57%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed USP limits.The average weight of one tablet was found to be in range 500.11 to 500.4mg. The disintegration time was in range 3.5 to4.1min.The percent drug content of all the tablets was found to be in the range of 97.92 to 99.71% of the expected drug content which was within the acceptable limits. The diameter of the tablet formulations was found to be in the range of 12.11to12.14mm.

In vitro drug release study

In vitro drug release studies were performed in acetate buffer pH 4 with 1 % triton X-100. On the above promising formulation (F5) gives maximum amount of drug release comparing to other formulations. The Percentage of drug release of various batches were F1(76.79%),F2(78.83%),F3(80.1),F4(84.6) and F5(91.32%) respectively. The dissolution profiles of the above formulations are depicted in figure 1.

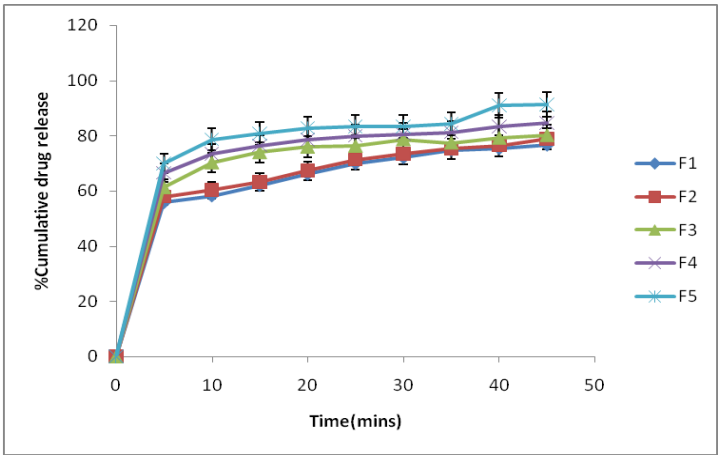

Figure 1: Comparative in vitro drug release study of Dasatinib IR batches.

Short-term stability studies

Short-term stability studies on the above promising formulation (at 40±2^{o} / 75±5% RH for 3 mo) have shown no significant changes in physical appearance, drug content.There were no appreciable changes in in vitro drug release up on storage at 40±2^{o} / 75±5% RH for 3 months period.

CONCLUSION

The study clearly demonstrates that immediate release (IR) tablets of Dasatinib could be successfully prepared by wet granulation method in a cost effective manner employing SSG. It was evident from the results that rate of drug release can be optimized using disintegrants for immediate release (IR) formulations. From the developed formulations the release of Dasatinib was best in F5 formulation i.e in-vitro drug release study. From the FTIR study, it was confirmed that the drug and excipients in the formulations were compatible with each other. Hence the availability of various technologies and the manifold advantages of immediate release (IR) tablets will surely enhance the patient compliance providing rapid onset of action.

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