IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND IN-VITRO EVALUATION OF DASATINIB BILAYERED TABLETS

[1]Asra Farooqi, [1]Damineni Saritha*, [1]K. Anupama, [2]P. Subhash Chandra Bose, [2]G. Ravi

[1]Department of Pharmaceutics, Sultan-ul-Uloom College of Pharmacy, Hyderabad-500034, Telangana State, India.

[2]Department of Pharmaceutics, MNR College of Pharmacy, Sangareddy-502294, Telangana State, India.

ABSTRACT

The Bilayered tablets containing Dasatinib SR and Dasatinib IR were successfully prepared by direct compression and wet granulation method respectively. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index The physiochemical evaluation results for the dry blend of all trials pass the official limits in angle of repose, compressibility index. The prepared blend for IR relaese were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation contains the average thickness of 2.58±0.66, average hardness of 4.6±0.57, average weight of 183±1.14 mg, friability of 0.34 and 100.24±1.25%. The prepared dry mixer for sustained release were also upheld the physiochemical properties of tablets such as thickness, weight variation, friability. The optimized formulation contains the average thickness of 3.80±0.80, average hardness of 7.6±0.40, average weight of 178±0.54, friability of 0.36. In the F3 trial, the optimized formulation was F3 trial which releases the dasatinib in sustained manner in 1st hour it releases 28 % but the remaning drug release was sustained up to 12 hours and dasatinib immediate release with in an 20min since the tablet disintegrated within 2 minutes 12 seconds.

Keywords: Dasatinib, compressibility index, sustained release.

INTRODUCTION

Drug delivery systems (DDS) are a planned device for increasing markets/indications, prolonging product life cycles and producing openings. Oral administration is the most principal route for systemic effects due to its easiness in absorption, pain, evading, tractability and most knowingly, patient compliance[1]. Solid oral distribution systems do not need germ-free circumstances and are therefore, less costly to manufacture. Patient compliance, high-precision dosing, and manufacturing competence make tablets the solid dosage form of choice. Excipients and apparatus choices will be eloquently affected should the solid dosage form equipment's change in response to the unprecedented shifts in the drug discovery such as genomics[2].

A solid dosage form is drug delivery system that comprises tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Amongst the various dosage forms oral solid dosage forms have superior importance and occupies a prime role in the pharmaceutical arcade[3]. Oral route of drug administration is

extensively acceptable and drugs administered orally as solid dosage form represents the chosen class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms[4].

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as Immediate release of special rate controlling features such as special coatings and other techniques. These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators[5].

The FDA defines an extended release dosage form as one that allows are duction in dosing frequency as compared to that presented by a conventional dosage form. An extended release dosage form makes the drug available over an extended period of time following administration. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance[6,7].

The main objective of the present study was to design and evaluation of bilayer tablets dasatinib, an attempt was made to develop bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

MATERIALS AND METHODS:

Dasatinib, HPMC K4M, Xanthum, Aerosol, Magnesium stearate, Lactose monohydrate, SSG, CP, CCS, Aerosol, Magnesium stearate, MCC, PVP and IPA

Experimental methods:

Sustained release formulations:

In the formulations prepared, the release retardants included were HPMC K100M, HMPC K 15M and Guargum, MCC were used as filler. Magnesium stearate MS) 1% were used as lubricants and PVP as binder. For preliminary studies to optimize the SR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 12 mm flat faced punch of 16 station Cadmach compression machine to get IR tablets. Nine formulation batches were made in order to achieve desired disintegration time and drug release. Formulation compositions of different sustained release batches are given in the (Table 1).

Table 1: Composition of desatinib sustained release tablets

F. Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
API (mg)	50	50	50	50	50	50	50	50	50
HPMC K100M	70	87.5	105	122.5	-	-	-	-	-
Guar gum	-	-	-	-	70	87.5	105	-	-
HMPC K 15M	-	-	-	-	-	-	-	105	122.5
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Mg. Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
PVP	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total (mg)	350	350	350	350	350	350	350	350	350

Immediate release formulations

In the formulations prepared, the release enhancers included were SSG, CP and CCS, MCC were used as filler. Magnesium stearate (MS) 1% were used as lubricants and PVP+IPA as binder. For preliminary studies to optimize the IR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 16 station Cadmach compression machine to get IR tablets. Nine formulation batches were made in order to achieve desired disintegration time and drug release. Formulation compositions of different immediate release batches are given in the (Table 2).

Table 2: Composition of Dasatinib immediate release tablets

Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
API	50	50	50	50	50	50	50	50	50
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
PVP	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
SSG	9	13.5	18	--	--	--	--	--	--
CP	--	--	--	9	13.5	18	--	--	--
CCS	--	--	--	--	--	--	9	13.5	18
Mg.stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Aerosol	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Total wt. (mg)	180	180	180	180	180	180	180	180	180

Preparation of Bilayer Tablets:

In order to prepare bilayer tablets, the dissolution test was conducted for both layers of IR/SR separately with the aim of selecting the best formulations. Based on dissolution behaviour, formulations of Sustained release optimized layer and Immediate release optimized layer were selected for bilayer tablet. First, sustained release layer was placed in the die cavity and punched with low compression force. Then the immediate release layer was placed in the die cavity and allowed for punching with optimum hardness of 6–8 kg/cm2 to form bilayer tablets. Compression was made by using 12 mm punches. The total weight of each bilayer tablet was adjusted to 530 mg, containing 5 mg of Enalapril in immediate-release layer and 10 mg of Enalapril in sustained release layer. Prepared bilayer tablets were evaluated for various post compression parameters and in vitro dissolution studies.

Evaluation of Precompression Blend:

Flow Properties:

Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free-standing surface of a powder heap and the horizontal[8].

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

where,

h = height of a pile (2 cm)

r = radius of pile base.

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup[8].

$$\text{Bulk density} = M / V_0$$

Where M= mass of the powder;

V0=bulk volume of the powder.

Limits:

It has been stated that the bulk density values having less than 1.2 g/cm^3 indicates good packing and values greater than 1.5 g/cm^3 indicates poor packing.

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was

observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed[8].

$$\text{Tap density} = M / Vr$$

Where M = mass of the powder,

Vr = final tapping volume of the powder.

Compressibility index and Hausner ratio:

The compressibility index and hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

$$\text{Compressibility index} = 100 \times \text{tapped density} / \text{bulk density}$$

$$\text{Hausner ratio} = \text{tapped density} / \text{bulk density}$$

Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio:

Table 3: Acceptance criteria of flow properties

S. No.	Flow properties	Angle of repose(θ)	Comp. Index (%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	> 66	>38	>1.6

Evaluation of Matrix Tablets

Evaluation of Tablets:

The quantitative evaluation and assessment of a tablet's chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and invitro-dissolution characters[9].

Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc[9].

Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by another device. Tablet thickness should be controlled within a ± 5% variation of standard value[10].

Weight variation test:

This is an in-process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form[11].

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 4: Limits for Tablet weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely linked to tablet hardness and intended to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator[11].

Method:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the

tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W1-W2) / W1 \times 100$$

W1 = Weight of tablets before test

W2 = Weight of tablets after test

***In vitro* Dissolution Studies:**

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 12 hr, at 100 rpm, 0.1 N HCl (pH 1.2) was used as a dissolution medium for first 2h followed by pH 6.8 phosphate buffer for further 10 hr. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug content in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer and cumulative percent drug release was calculated[12].

Kinetic Analysis of Dissolution Data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero-order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou et al., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K0\ t \qquad (1)$$

where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1\ t / 2.303 \qquad (2)$$

where, C0 is the initial concentration of drug and K1 is first order constant.

$$Q = K_H t_{1/2} \qquad (3)$$

where, KH is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\ t \qquad (4)$$

where,

Q_t is the amount of drug remained in time t,

Q_0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model), Log cumulative of % drug remaining vs. time (First order kinetic model), Cumulative % drug release vs. square root of time (Higuchi model) and cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law)[13].

Mechanism of drug release

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

where Mt / M∞ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

Drug-Excipient compatibility studies:

FTIR studies[14]:

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 - 400 cm^{-1}.

Differential scanning calorimetry (DSC):

The possibility of any interaction between the drug and the polymer during preparation of tablets was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10 °C/min conducted over a temperature range of 30 to 350 °C under a nitrogen flow of 50 mL/min[14].

RESULTS AND DISCUSSION:

Characterization of Granules:

The blend of sustained release tablets was characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 5). Angle of repose was less than 35° and Carr's index values were less than 21 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.19 for all the batches indicating good to excellent flow properties. The drug content was more than 90 % for all the granules of different formulations.

Table 5: Physical Properties of Pre compression Blend for SR formulations

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Flow property
F1	33.49	0.214	0.251	14.74	1.17	Good
F2	31.24	0.308	0.364	15.38	1.18	Good
F3	32.05	0.276	0.322	14.28	1.16	Good
F4	33.97	0.341	0.388	12.11	1.13	Good
F5	34.97	0.341	0.388	12.11	1.13	Good
F6	25.32	0.445	0.49	9.18	1.10	Excellent
F7	26.45	0.489	0.56	12.67	1.14	Excellent
F8	25.65	0.712	0.813	12.66	1.14	Excellent
F9	27.65	0.445	0.49	9.18	1.10	Excellent

The blend of immediate release tablets was characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 6). Angle of repose was less than 35° and Carr's index values were less than 16 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's

ratio was less than 1.25 for all the batches indicating good to excellent flow properties. The drug content was more than 90 % for all the granules of different formulations.

Table 6: Physical Properties of Pre compression Blend for IR formulations

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Flow property
F1	26.890	0.42	0.5	16	1.190476	Fair
F2	25.320	0.278	0.312	10.89744	1.122302	Fair
F3	28.920	.321	0.399	19.54887	1.242991	Fair
F4	28.450	0.325	0.4	18.75	1.230769	Fair
F5	33.450	0.38	0.445	14.60674	1.171053	Good
F6	32.490	0.214	0.251	14.74	1.17	Good
F7	31.240	0.308	0.364	15.38	1.18	Good
F8	33.050	0.276	0.322	14.28	1.16	Good
F9	34.970	0.341	0.388	12.11	1.13	Good

Physical Evaluation of tablets:

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the immediate release tablets are given in Table 7. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 178±0.54 and 185±0.83mg. The hardness of the tablets ranged from 4.3 ±0.44 to 4.6±0.60 kg/cm^2 and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from to 3.98±0.66 to 2.58±0.66 mm. All the formulations satisfied the content of the drug as they contained 90 to 103 % of Dasatinib and good uniformity in drug content was observed. Thus, all the physical attributes of the prepared tablets were found be practically within control.

Table 7: Post compression evaluation parameters for immediate release formulation

F. Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F1	4.3 ±0.44	2.54±0.17	180±1.48	0.36	98.25±1.37
F2	4.6±0.31	2.62±0.25	178±0.54	0.39	95.28±0.80
F3	4.6±0.40	2.50±0.80	179±0.41	0.43	99.12±2.47
F4	4.5±0.55	2.52±0.20	181±1.64	0.32	101.22±0.88
F5	4.6±0.57	2.58±0.66	183±1.14	0.34	100.24±1.25
F6	4.5±0.30	2.53±0.25	185±0.83	0.58	99.53±1.87
F7	4.6±0.57	2.65±0.71	183±0.67	0.54	96.28±1.99
F8	4.5±0.60	2.65±0.89	180±0.43	0.37	95.35±1.14
F9	4.6±0.45	2.53±0.69	182±0.57	0.58	98±1.57

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the sustained release tablets are given in Table 8. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 348±0.54 and 354±0.43mg. The hardness of the tablets ranged from 7.3 ±0.44to 7.6±0.40kg/cm2 and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from to 3.80±0.80to 3.98±0.66mm. All the formulations satisfied the content of the drug as they contained 92 to 101 % of Dasatinib and good uniformity in drug content was observed. Thus, all the physical attributes of the prepared tablets were found be practically within control.

Table 7: Post compression evaluation parameters for immediate release formulation

F. Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F1	7.3 ±0.44	3.84±0.17	352±1.48	0.32	92.25±1.37
F2	7.6±0.31	3.92±0.25	348±0.54	0.30	96.58±0.80
F3	7.6±0.40	3.80±0.80	349±0.41	0.36	99.32±2.47
F4	7.5±0.55	3.82±0.20	352±1.64	0.31	101.23±0.88
F5	7.7±0.57	3.98±0.66	349±1.14	0.34	99.54±1.25
F6	7.6±0.30	3.93±0.25	350±0.83	0.35	97.33±1.87
F7	7.5±0.57	3.85±0.71	352±0.67	0.32	96.68±1.99
F8	7.6±0.60	3.95±0.89	354±0.43	0.32	97.55±1.14
F9	7.7±0.45	3.83±0.69	352±0.57	0.30	98±5.57

Dissolution Study (IR Tablets):

The results of release studies of formulations F1 to F9 are shown in Figure 1. The release of drug depends only on the nature and amount of super disintegrants. As the percentage of super disintegrants increased the release also increased. Based on this F5 was optimised as the maximum drug release was observed with in 20min.

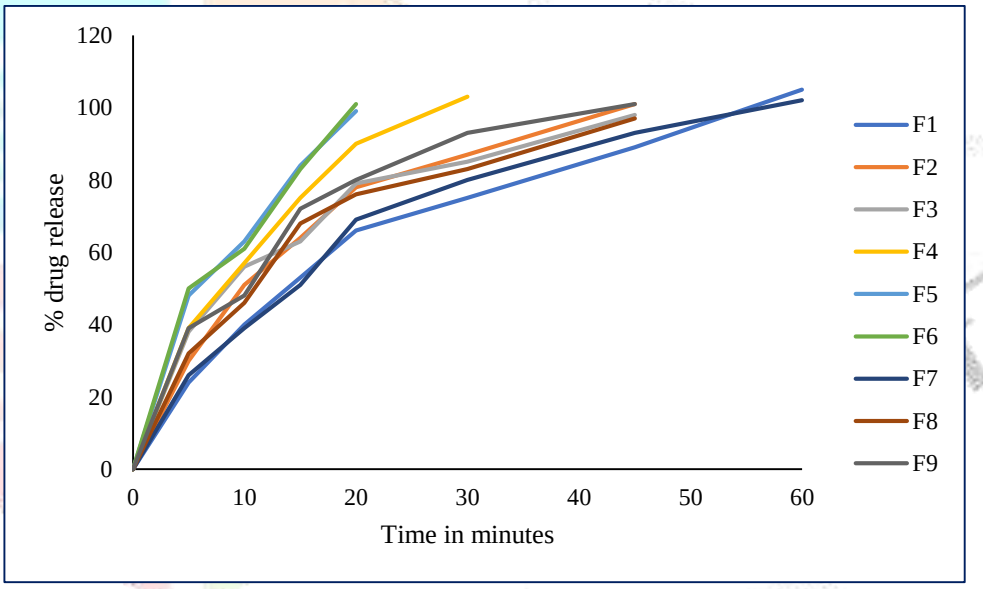

Figure 1: Drug release of IR tablets (F1-F9)

Dissolution Study (SR Tablets):

The results of release studies of formulations F1 to F9 are shown in Figure 2. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F1, F2, F5, F6, F8 and F9 were failed to sustain release beyond 10h. The formulation F3 was optimized because drug release was sustained up to 12hrs and followed marketed formulation.

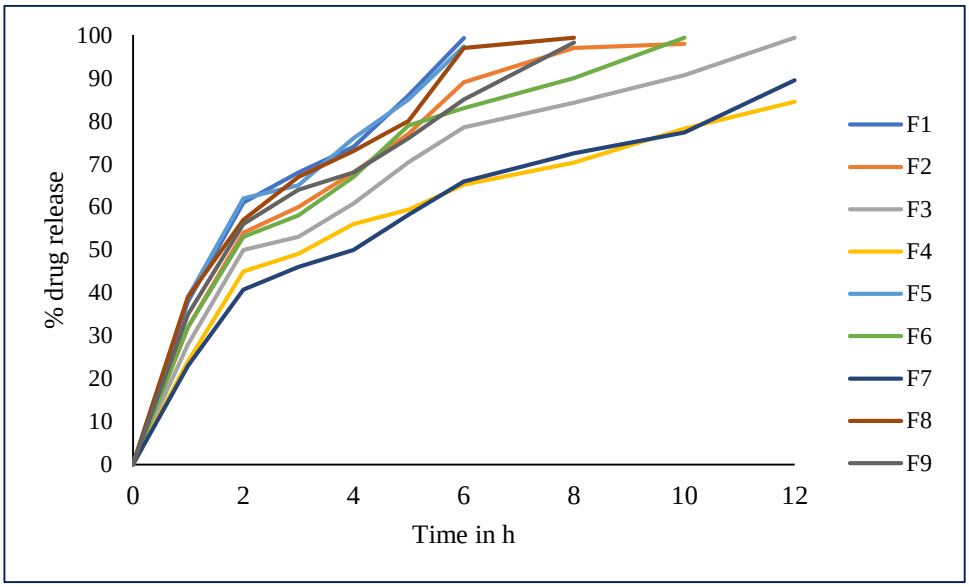

Figure 2: Drug release of SR tablets (F1-F9)

Kinetic analysis of dissolution data:

The release rate kinetic data for the F3 is shown in below table. As shown in Table 7, drug release data was best explained by zero order equation, as the plots showed the highest linearity (r^2 = 0.8521), followed by Higuchi's equation (r^2= 0.9856). As the drug release was best fitted in zero order kinetics, indicating that the rate of drug release is independent of time. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

Table 7: Kinetic analysis dissolution data for dasatinib

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.130237581	-0.148386652	28.80262917	1.130864595
Intercept	25.14578834	2.113566968	3.079176248	0.967376994
Correlation	0.923139266	-0.919266506	0.99279152	0.736026248
R^2	0.852186104	0.845050909	0.985635001	0.541734638

Bilayered Tablets:

Bilayered tablets were prepared using F5 formulation from immediate release tablets and formula of F3 formulations from sustained release tablets. The formula for formulation 10 i.e., bilayered tablets is depicted in Table 8 below.

Table 8: Formula for bilayered tablet (F10)

Bilayered formulation code F10	
Sustained Release Formula(F3)	
API (mg)	50
HPMC K100M	105
Guar gum	-
HMPC K 15M	-
MCC	204.5
Mg.stearate	3.5
PVP	17.5
Talc	3.5

Total weight	350 mg
Immediate Release Formula (F5)	
API	50
MCC	150.4
PVP	5.4
IPA	Q.s
CP	13.5
Mg.stearate	1.8
Aerosol	0.9
Total weight	180 mg
Total wt. of bilayered tablet: 530 mg	

Post compression parameters

Average weight: 530mg

Hardness: 8.2±0.031

Thickness: 5.5±0.023

Tooling: 16*8 mm modified capsule punch.

Dissolution study (Bilayered tablets):

Dissolution Medium for IR tablets:

Acidic Stage:

Medium : 0.1N HCL

Type of apparatus : USP - II (Paddle type)

RPM : 50

Volume : 900 ml

Temperature : 37ºC± 0.5

Time : 60 min.

In vitro dissolution for IR tablets were done in 0.1N HCL for 60 minutes.

Dissolution Medium for SR tablets

Acidic Stage:

Medium : 0.1N HCL

Type of apparatus : USP - II (Paddle type)

RPM : 50

Volume : 900 ml

Temperature : 37ºC± 0.5

Time : 2 hrs.

Buffer Stage:

Medium : 6.8 pH phosphate buffer

Type of apparatus : USP - II (Paddle type)

RPM : 50

Volume	:	900 ml
Temperature	:	37ºC± 0.5
Time	:	8 hrs.

In vitro dissolution for SR tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphate buffer for 8hrs.

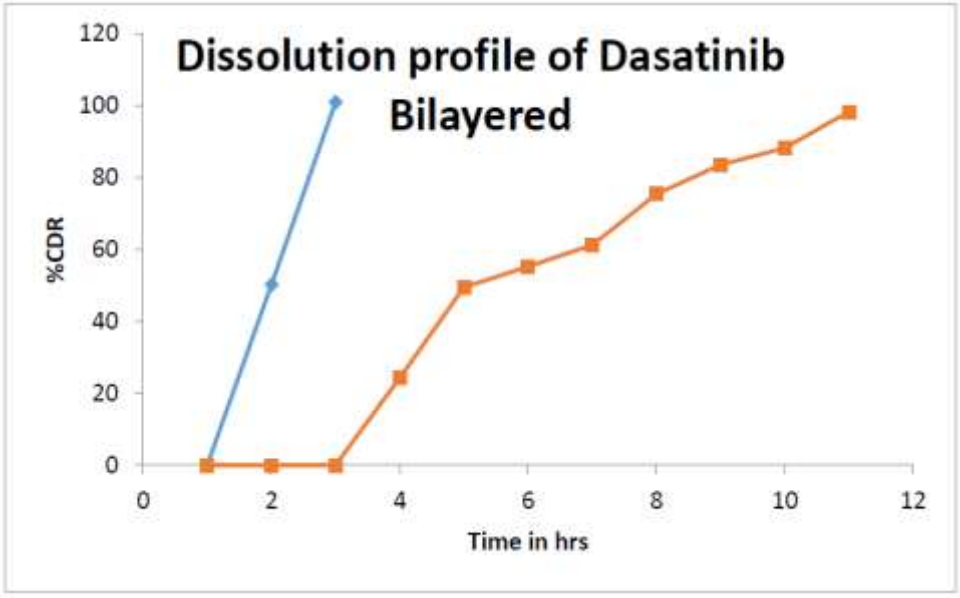

Figure 3: Dissolution graph for Dasatinib Bilayerd Tablets

Fourier transform infrared spectroscopy (FTIR)

FT-IR spectroscopic study was carried out to find out drug excipients interaction. The characteristic peaks between IR spectrum of pure drug and bilayered tablet were identified by absorption peaks at 2942.57 cm^{-1} (secondary amine N-H stretch), 2845.16 cm^{-1} (=C-H aromatic ring), 843.51 cm^{-1} (C-H bending), 1119.97 cm^{-1} (C-N stretch), 1589.36 cm^{-1} (C=O stretch) and 1274.01 cm^{-1} (C=C) stretch, aromatic ring. The principal peaks of pure drug and bilayered formulation were observed and indicated that no interactions had been observed an the FTIR graph was depicted in Figure 4.

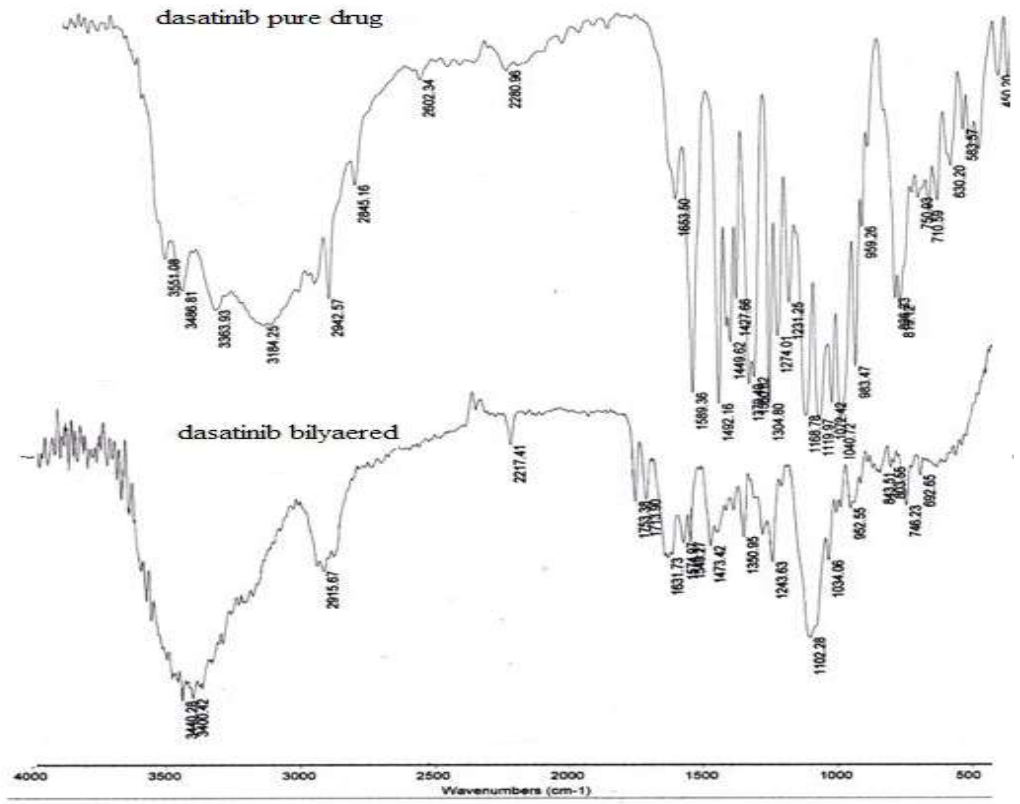

Figure 4: FTIR Spectra for A. Dasatinib pure drug and B. Dasatinib bilayer tablets

Differential Scanning Calorimetry (DSC)

DSC thermograms obtained for pure drug of dasatinib and for optimized formulation are shown in the figure**.** pure drug has shown all well-defined endothermic peak at corresponding to the melting point 116 ^{o}c of crystalline drug. Likewise, the optimized formulation has shown endothermic peaks at 143 ^{o}c representing the melting points. The endothermic peaks of pure drug and optimized formulations remains same. The validates that there is no morphological change in the drug form during the process.

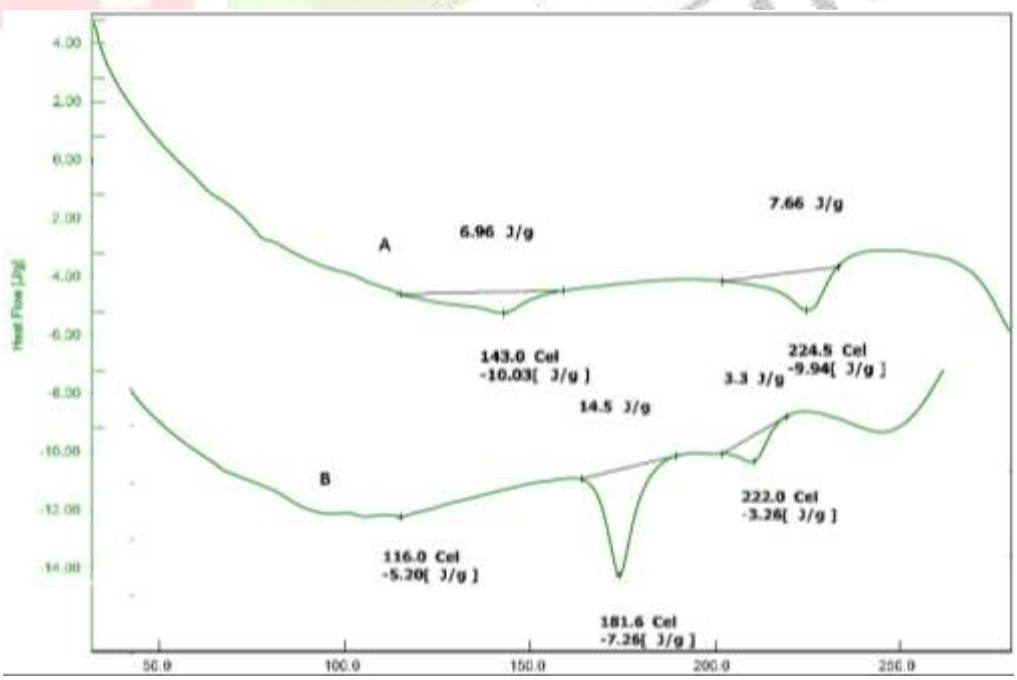

Figure 5: DSC Thermograms for A. Dasatinib pure drug and B. Dasatinib bilayer tablets

CONCLUSION:

The Bilayered tablets containing Dasatinib SR and dasatinib IR were successfully prepared by direct compression and wet granulation method respectively. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index. The physiochemical evaluation results for the dry blend of all trials pass the official limits in angle of repose, compressibility index. The prepared blend for IR release were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation contains the average thickness of 2.58±0.66 mm, average hardness of 4.6±0.57 kg/cm^2, average weight of 183±1.14 mg, friability of 0.34 % and 100.24±1.25%. The prepared dry mixer for sustained release were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation contains the average thickness of 3.80±0.80 mm, average hardness of 7.6±0.40 kg/cm^2, average weight of 178±0.54 mg, friability of 0.36 %. In the F3 trial, the optimized formulation was F3 trial which releases the dasatinib in sustained manner in 1st hour it releases 28 % but the remaining drug release was sustained up to 12 hours and dasatinib immediate release with in an 20min since the tablet disintegrated within 2 minutes 12 seconds. Hence it may be summarized that the trial F5 tablets prepared for immediate release layer and F3 formulation of sustained release layer might be a perfect and effective formulation to treat the hypertension.

REFERENCES:

1. Panda N, Reddy AV, Reddy GVS et.al. Formulation design and in vitro evaluation of Zolmitriptan immediate release tablets using primojel and AC-Di-Sol, J Pharm Sci and Res 7(8);2015:545-553.
2. Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery Systems Modern Pharmaceutics, 4thed; 2011;121:501-502.
3. Ahmed JA. A Review on immediate release tablet dosage form. Int. J. of Pharmacy and Pharmaceutical Research. 2 (3); 2015:1-17.
4. Sahoo CK, Sahoo NK, Sahu M, Alagarsamy V, Moharana AK, Sarangi DK, Satyanarayana K. Formulation and evaluation of orodispersible tablets of granisetron hydrochloride using plantago ovate as natural superdisintegrants. Indonesian J.Pharm.2016,27(1),35-43.
5. Sandip BT, Krishna Murthy T, Raveendra Pai M, Pavak RM, Pasula BC. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech. 2003;4(3):1-7.
6. Klingberg U, T Pavan P, Krishna RAV, Ravi KN. Bioequivalence, safety and tolerability of dasatinib tablets 140 mg in healthy adult volunteers under fasting conditions. J Global Trends Pharm Sci. 2016;7(3):3367–73.
7. Salsa T, Veiga F, Pina ME. Oral controlled-release dosage forms. I. Cellulose ether polymers in hydrophilic matrices. Drug Dev Ind Pharm. 1997;23:929-938.
8. Selim R, Mohiuddin AQ, Syed SH. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Pharmaceut Sci. 2003;6(2):282-291.
9. Sahoo CK, Sahoo NK, Sahu M, Moharana AK, Sarangi DK. Formulation and Evaluation of Orodispersible Tablets of Granisetron Hydrochloride Using Agar as Natural Super disintegrants. Pharm Methods. 2016;7(1):17-22

10. Shruti Chopra, Gayathri VP, Sanjay KM. Release modulating hydrophilic matrix systems of losartan potassium: Optimization of formulation using statistical experimental design. Eur J Pharm Sci. 2007;66:73-82.
11. Siepmann J, Kranz H, Bodmeier R, Peppas NA. HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanisms and predicting the release kinetics. Pharm Res. 1999;16:1748-1756.
12. Chinmaya KS, Venkata DR, Nalinikanta S, Kanhu CP, Uttam PP. Formulation and Evaluation of Immediate release Tablets of Dasatinib using Croscarmelose Sodium. Research J. Pharm. and Tech. 2017;10(3):833-8.
13. Hyder SA, Hasan ul SA, Sharma S. Formulation and optimization of immediate release tablet of rupatadine fumarate, Int. J. Pharma Prof. Res. 2011;2(3):345-350.
14. Srikanth PR, Alagarsamy V, Subhah CBP, Sarita D, Sruthi V. Formulation and evaluation of film coated dasatinib immediate release tablets. Int J Medical Biomed Studies. 2019;3(8):102-6.