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Scaffolding of dasatinib bilayered sustained and immediate release tablets

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ABSTRACT

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, friability of 0.34and 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, 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 remaining drug release was sustained up to 12 hours and dasatinib immediate release with in a 20min since the tablet disintegrated within 2 minutes 12 seconds.

INTRODUCTION

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights.

The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of

administration lead to high levels of patient compliance[8]. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that50% of the population is affected by this problem, which results in a high incidence of ineffective therapy. These systems are described in terms of fronts. The following fronts are have been defined, with regard to anomalous release systems: the swelling front, the erosion front, and the diffusion front [1-12].

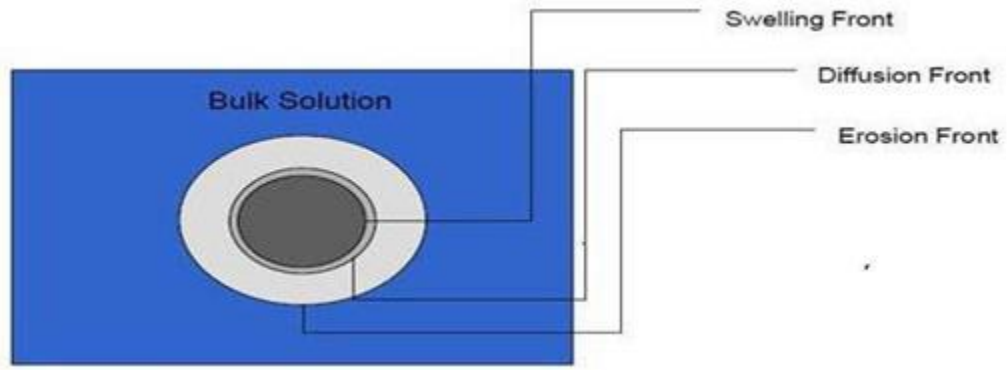

Fig 1. Scheme of particles dissolution

Thickness which determines the diffusion path length of the drug corresponds to the distance between the diffusion and erosion fronts [13-17]. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.

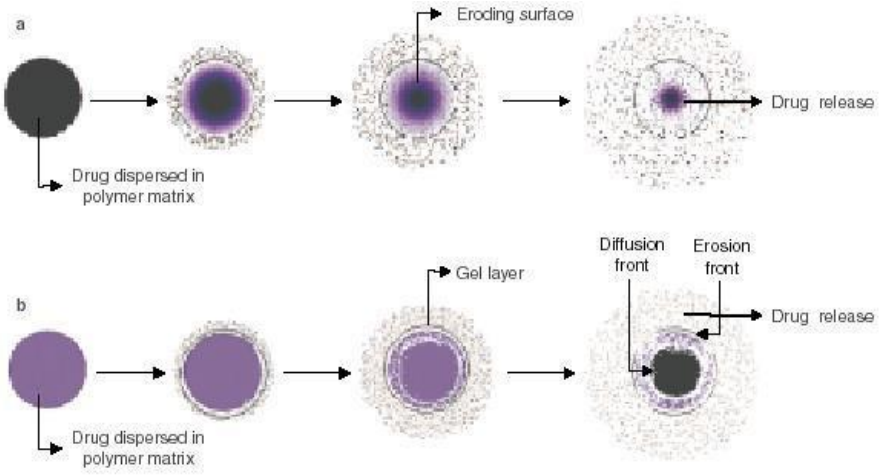

Fig.2. Schematic drug release from matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic, sellable polymer matrix.

MATERIALS AND METHODS

Dasatinib has been obtained from Chandra labs, HPMCK100M, Guargum, HPMCK15M, MCC and Iso propyl alcohol, are obtained from MYL CHEM Mumbai, All the other excipients used in the research are obtained from S.D Fine chem. LTD Mumbai.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentrations of Dasatinib (1-5 mcg/mL) solutions. The absorbances of above solutions were recorded at □max (315nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis) [17-22].

Drug -Excipient Compatibility Study

API and excipient are taken in the ratios above mentioned and mixed together in a polybag for 5 min. Each mixture is allotted sample code for identification. 4 sets of sample were allocated where each sample mixture is divided in to 1g in to its corresponding glass vial (USP Type I) at different conditions. All vials are properly sealed and loaded at respective conditions. The samples are to be checked for its Description, Related substance and water content by KF.

FORMULATIONS PERSPECTIVE

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 [23-26].

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% was 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

.

Table 2. Composition of Dasatinib immediate release tablets

F.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 weight	**180mg**	**180mg**	**180mg**	**180mg**	**180mg**	**180mg**	**180mg**	**180mg**	**180mg**

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 behavior, 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 postcompression parameters and *invitro*.evaluation of Matrix Tablets.

The quantitative evaluation and assessment of a tablets 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.

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 [27-31].

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.

RESULTS AND DISCUSSION

Characterization of Granules

The blend of sustained release tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 19). 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

.

Table 3. Physical Properties of Pre compression Blend for sustained release 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	0.214	0.251	14.74	1.17	Good
F2	31.24^0	0.308	0.364	15.38	1.18	Good
F3	32.05^0	0.276	0.322	14.28	1.16	Good
F4	33.97^0	0.341	0.388	12.11	1.13	Good
F5	34.97^0	0.341	0.388	12.11	1.13	Good
F6	25.32^0	0.445	0.49	9.183673	1.101124	Excellent
F7	26.45^0	0.489	0.56	12.67857	1.145194	Excellent
F8	25.65^0	0.71	0.813	12.66913	1.14507	Excellent
F9	27.65^0	.445	0.49	9.183673	1.101124	Excellent

The blend of immediate release tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 20). 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 4. Pre-compression parameters

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Flow property
F1	26.89^0	0.42	0.5	16	1.190476	Fair
F2	25.32^0	0.278	0.312	10.89744	1.122302	Fair
F3	28.92^0	.321	0.399	19.54887	1.242991	Fair
F4	28.45^0	0.325	0.4	18.75	1.230769	Fair
F5	33.45^0	0.38	0.445	14.60674	1.171053	Good
F6	32.49^0	0.214	0.251	14.74	1.17	Good
F7	31.24^0	0.308	0.364	15.38	1.18	Good
F8	33.05^0	0.276	0.322	14.28	1.16	Good
F9	34.97^0	0.341	0.388	12.11	1.13	Good

Table 5. Physical Properties of Pre compression Blend for immediate release formulations Post compression evaluation parameters for immediate release formulation

F.Code	Hardness (kg/cm^2) †(mm) ‡	Thickness	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 tablets are given in Table 20. 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/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 3.80±0.80 to 3.98±0.66mm. All the formulations satisfied the content of the drug as they contained 92 to 101 % of Dasatiniband good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table 6. Post compression evaluation parameters for sustained release formulations

DISSOLUTION STUDY (IR TABLETS)	PARAMETERS
Acidic Stage:	
Medium	: 0.1N HCL
Type of apparatus	: USP - II (paddle type)
RPM	: 50
Volume	: 900ml
Temperature	: 37ºC± 0.5
Time	: 60minutes

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

Table 7. Post compression parameters.

F.Code	Hardness (kg/cm^2) †(mm) ‡	Thickness	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	98.22±5.57

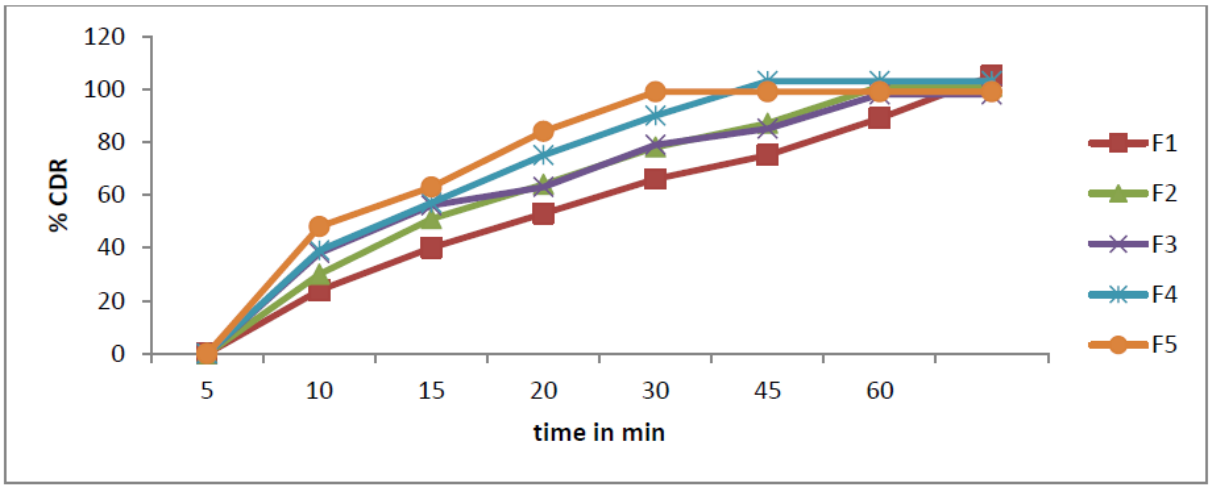

Fig 3. Dissolution graph for formulation F1-F2

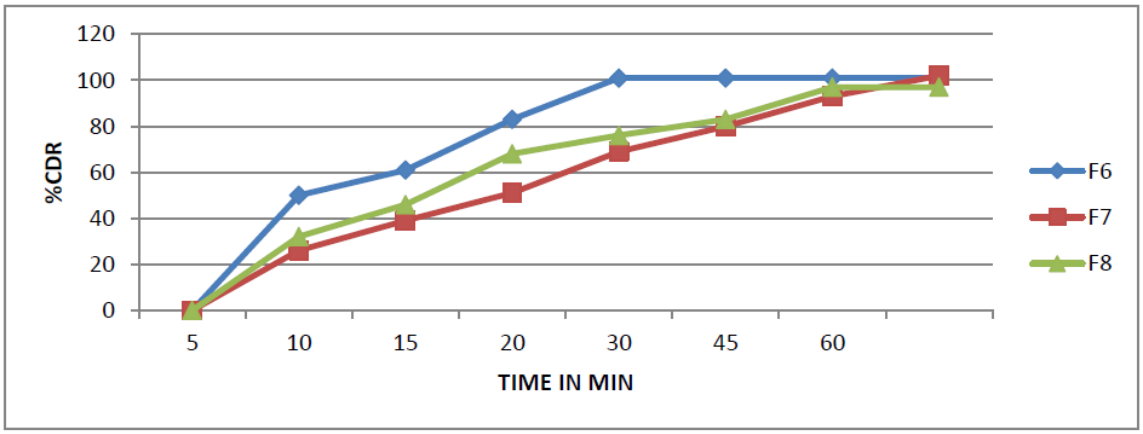

Fig 4. Dissolution graph for formulations F6-F9

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

In-Vitro Drug Release Studies for SR tablets

Table 8. Cumulative percentage drug release layer

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dissolution medium 0.1N HCL									
1	38	32	**28**	24	39	32	23	39	35
2	61	54	**50**	45	62	53	40.7	57	56

6.8pH phosphate74 buffer									
3	68	60	**53**	49.1	65	58	46	67	64
4	74	68	**60.8**	56	76	67	50	73	68
5	86	77	**70.4**	59.4	85	79	58.2	80	76
6	99.3	89	**78.5**	65./2	97.4	83	65.9	97	85
8		97	**84.3**	70.3		90	72.5	99.4	98.3
10		98	**90.7**	78.2		99.4	77.3		
12			**99.4**	84.5			89.5		

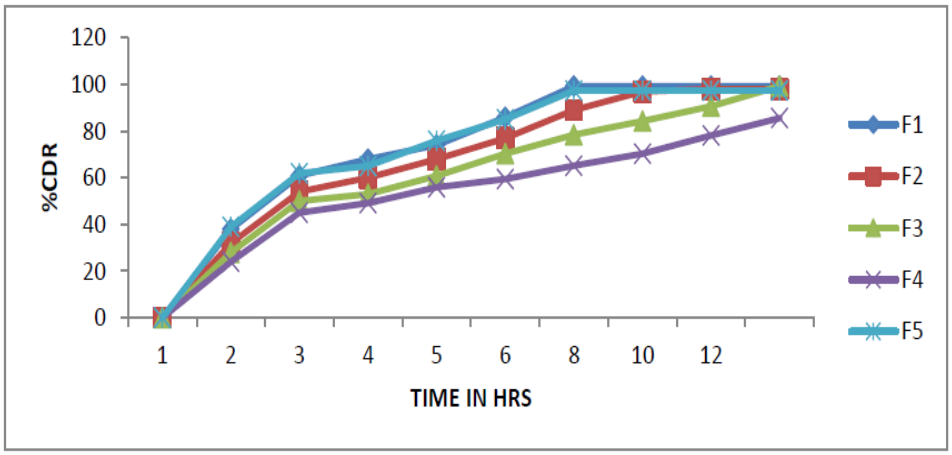

Fig 5. Dissolution graph for formulations F1-F5

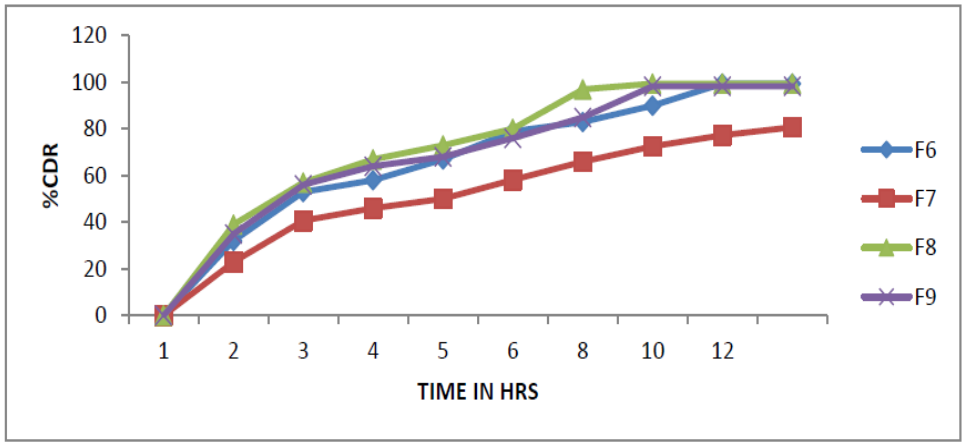

Fig 6. Dissolution graph for formulations F6-F9

In-Vitro Drug Release Studies

The results of release studies of formulations F1 to F9 are shown . 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 suautained up to 12hrs and followed marketed formulation.

Kinetic analysis of dissolution data

The release rate kinetic data for the F3 is shown in below table. As shown in Figures, 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.

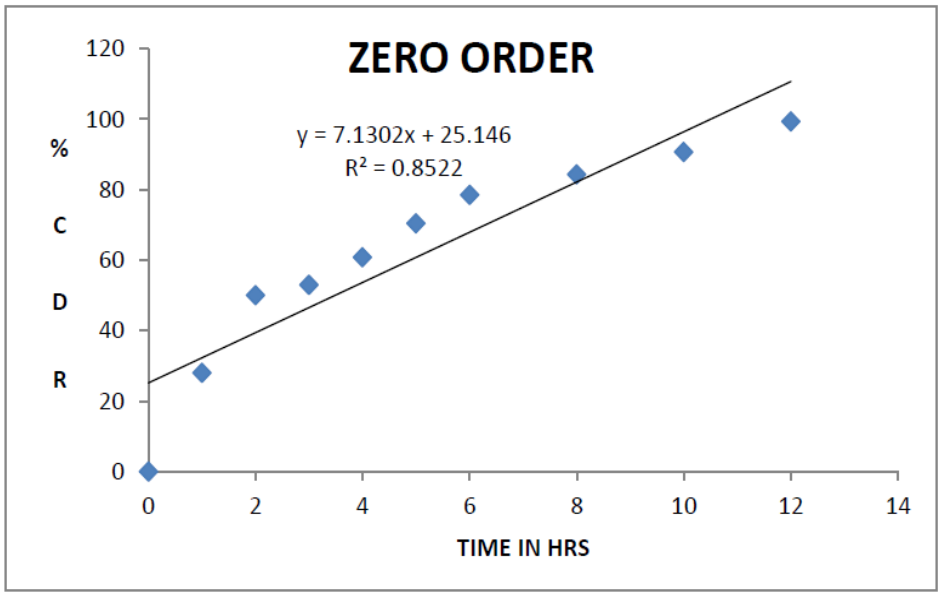

Fig 7. Zero order reaction

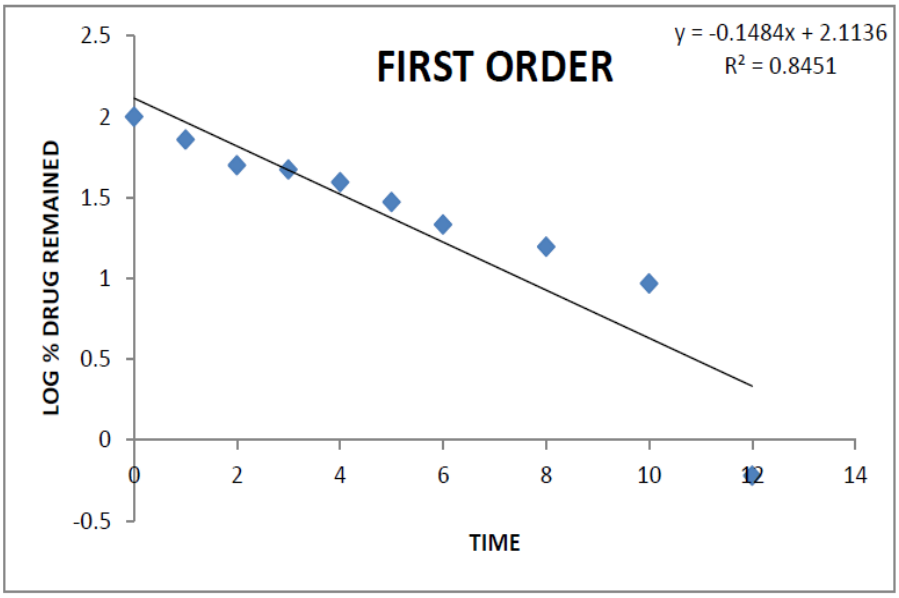

Fig 8. First order reaction

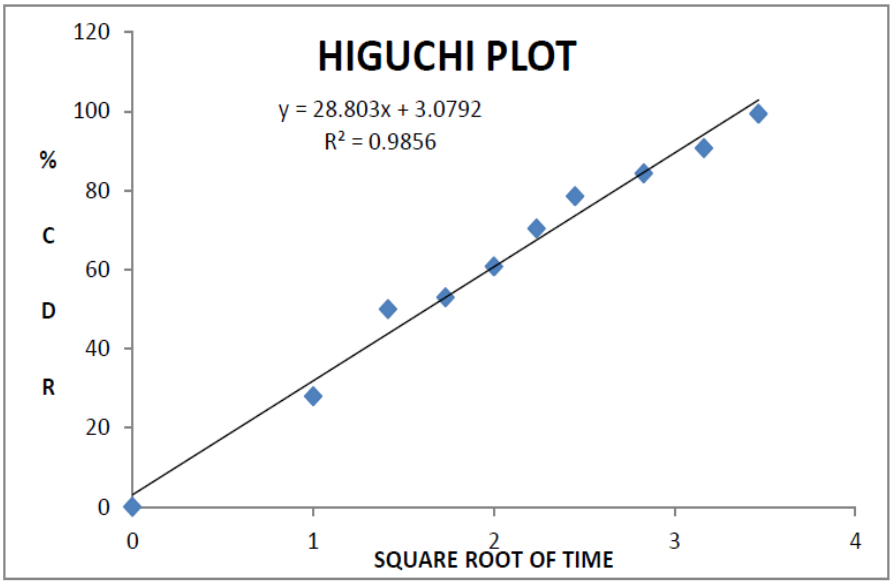

Fig 9. Higuchi plot

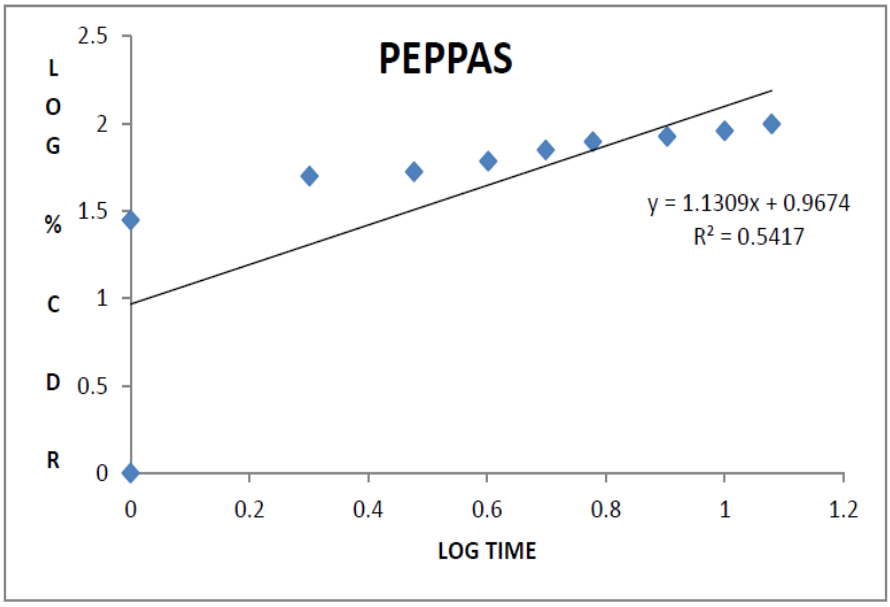

Fig 10. Peppas Model

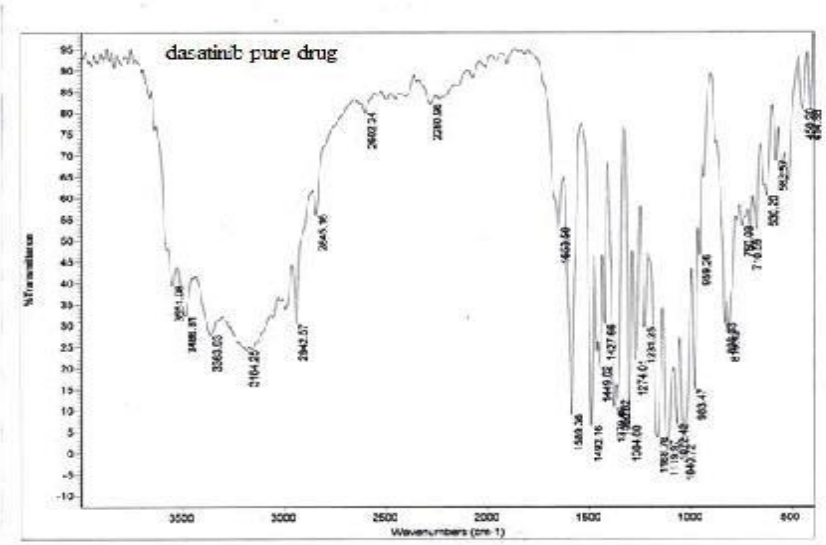

Fig 11. FTIR of Dasatinib pure drug

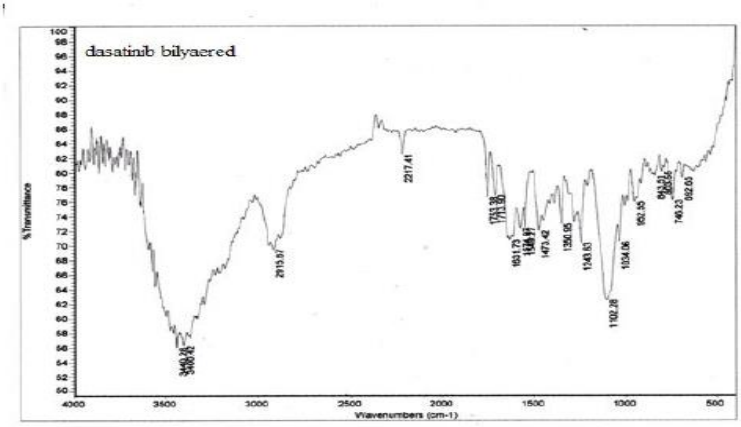

Fig 12. FTIR of Dasatinib bilayered optimized formulation

CONCLUSION

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, friability of 0.34and 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, average hardness of 7.6±0.40, average weight of 178±0.54, friability of 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 with in 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".

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