An approach to improve the dissolution profile and solubility of dasatinib by solid dispersion using Soluplus and polaxomer.

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ABSTRACT:

Dasatinib is the first choice oral drug in the treatment of chronic myloeid leukemia for patients who are resistant to imatinib. new scientific findings have shown its potential in the treatment of CML in paediatric age, where its pharmacokinetic parameters, in particular, absorption and elimination time, were comparable with those in adult, with the same safety and efficacy profiles Based on this consideration, the purpose of this work is to make solid dispersion of dasatinib by using novel polymers. Physical Mixtures ,Solvent Evaporation and Hot Melt Extrusion techniques were used to prepare solid dispersion of Dasatinib with Soluplus and Polaxomer in the ratio of 1:3 and 1:5 respectively. The resultant solid dispersion were charecterised by Fourier Transform Infrared (FT-IR), Differential Scanning Calorimetry (DSC) techniques and its dissolution profile was studied at pH 7.4. In conclusion, this new inclusion complex could allow the development of a liquid and solvent free formulation to be administered both orally and parenterally, especially for Pediatric patients.

KEYWORDS: Dasatinib, chronic myloeid leukemia, Solid Dsipersion, Soluplus, Paediatric Patinrts, Liquid Formulation.

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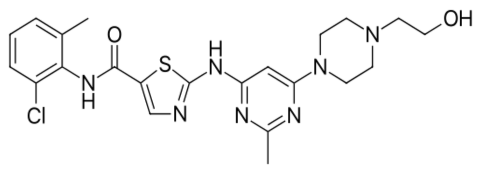
INTRODUCTION :

Dasatinib is an oral dual BCR/ABL and Src family tyrosine kinase inhibitor approved for use in patients with chronic myelogenous leukaemia (CML). The main targets of Dasatinib, are BCRABL, SRC, Ephrins and GFR. Dasatinib is used for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy. Until now, DAS was used exclusively for the treatment of adult patients, but new scientific findings have shown its potential in the treatment of CML in paediatric age, where its pharmacokinetic parameters, in particular, absorption and elimination time, were comparable with those in adult, with the same safety and efficacy profiles [4,5].However, in these clinical trials, the drug was administered to children in the form of tablets or crushed tablets dispersed in fruit juice. In fact, DAS, formulated as monohydrate and marketed under the name of Sprycel® by Bristol Meyer Squibb, is presented in the form of coated tablets with a dosage ranging from 20 to 140 mg of the active ingredient. No liquid formulation is available on the market, and this may be a problem for paediatric patients who may not be able to swallow the tablets.



Dasatinib

Fig. 1 Chemical structure of Dasatinib

Therefore, the purpose of this work was to prepare an aqueous formulation of this drug, evaluating the possibility of using an inclusion complex with Soluplus and polaxomer), as it is a molecule that is characterized by a low water solubility. Thus, in this work, we present an inclusion complex of DAS with Soluplus and Polaxomer. Subsequently, this complex was characterized by Fourier Transform Infrared (FT-IR), Differential Scanning Calorimetry (DSC), evaluation of the incorporation degree, and study of dissolution profiles at different pH values.

2. Results and Discussion

MATERIALS AND METHODS:

Materials

Dasatinib obtained as gift sample from Sun Pharmaceutical Ltd Baroda, Soluplus and Poloxamer (Alkem Laboratories Pvt. Ltd. Mumbai), Methanol (Research Lab. Fine Chemicals Pvt. Ltd. Mumbai), All other chemicals and materials were analytical grade and used accordingly.

Methods:

Calibration curve

10mg Dasatanib was weighed and dissolved in 10ml of methanol. From this stock solution, 1 ml was diluted to 10ml to make 100 mcg/ml solution. Initial dilutions were made of 1 ml in 10 ml with methanol to get 10 mcg/ml. Further dilutions were made with methanol and estimated spectroscopically.)

Fourier Transforms Infrared Spectroscopy

Fourier Transforms Infrared spectrophotometer was used to take Infrared spectrum measurements of Dasatinib and their solid dispersions. The Infra-red spectrum of dasatinib was recorded using IR spectrophotometer by the ATR method. The spectrum was scanned over a frequency range of 4000-400cm^{-1}. with a resolution of 2 cm^{-1}.

Differential Scanning Calorimetry

Differential scanning calorimetry or DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of the sample and reference is measured as a function of temperature. Samples (about 1.5mg) were weighed accurately and sealed in an aluminium pan and the DSC curves were determined at a 40-350^{0}C.

Preparation of Solid Dispersion:

Solid dispersions of Dasatinib with soluplus and Poloxamer407 were prepared at 1:3,1:5 ratios as described in detail below.

Physical mixture

A physical mixture of Dasatinib and both the polymers such as soluplus and poloxamer407 was made by homogeneously mixing for 1 hr in a mortar and pestle, passing through the appropriate sieve number, drying and finally storing in desiccator.

Solvent evaporation method

In this method the carriers are dissolved in methanol then drug is added with vigorous shaking and this solution is poured in porcelain dish and keep aside at R.T. for evaporation for 12 Hrs. After evaporation product collected and dried it on hot plate. The dried mass was pulverized and sieved through the mesh no.100.

Hot melt extrusion method

In hot melt extrusion method, the physical mixture of drug and carrier was prepared. This physical mixture is used for the process of extrusion.In this method the controlled temperature (45^{0}C) and speed of 45 rpm is provided and the physical mixture is feed through the hopper. Due to the temperature the polymers are melted and the mix with the particles of drug, then the extrudes are formed.

Characterization of Solid dispersion of Dasatinib:

Solubility studies

The solubility study of pure drug and formulations are performed by adding 10 mg drug and formulation equivalent to 10 mg drug are added in 2 ml distilled water and leave it for 48 hrs. in 10ml vials with shaking.

After 48 hrs. these solutions are centrifuged with laboratory centrifuge with 1000 rpm for 30 min.

After centrifugation process these formulations are filtered out using whatmann filter paper.

Further dilutions are made using distilled water and used for the UV spectroscopy.

Drug Content

The percentage drug content in solid dispersions was estimated by dissolving quantity of solid dispersion equivalent to 10 mg of Drug in 10 ml of methanol. The solutions were further diluted with distilled water and the absorbances were recorded at 323nm.

Dissolution Studies:

Dissolution studies are performed by employing following conditions

Moreover, dissolution studies have been performed at 37 °C in two different media: phosphate buffer 0.05M pH = 7.4.

DSC studies

FTIR studies

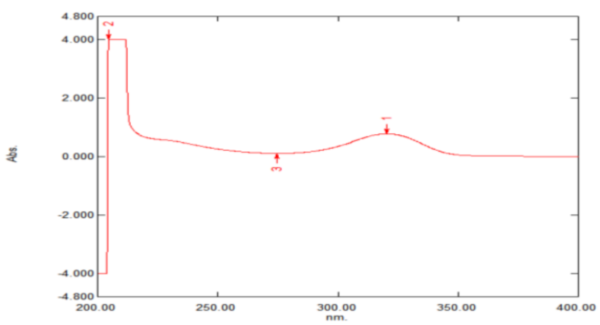
RESULT:

Determination of UV spectrum of Dasatinib

The UV spectrophotometer showed maximum absorption of Dasatinib at 323 nm in methanol

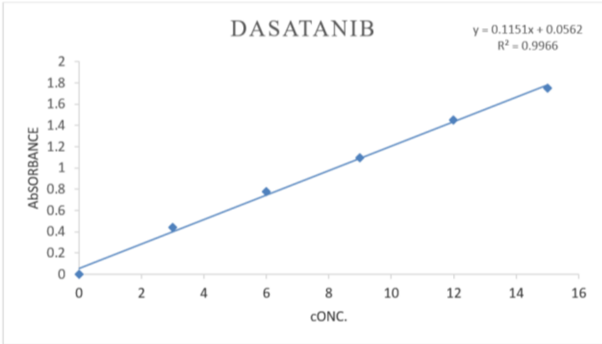
Determination of λmax of Dasatanib:

The UV spectrophotometer showed maximum absorption of Dasatanib at 323 nm in methanol.



Standard curve of Dasatanib:

Sr.No.	Conc.(μg/ml)	Absorbance (nm)
1.	0	0
2.	3	0.442
3.	6	0.779
4.	9	1.097
5.	12	1.449
6.	15	1.749



Percentage yield

Sr.No.	Formulation	% Yield
1	SH_1	71.4±0.9
2	SH_2	73.9±1.2
3	SS_1	84.6±2.5
4	SS_2	86.3±1.5
5	SP_1	94.2±3.5
6	SP_2	96.1±1.5
7	PH_1	77.1±1.9
8	PH_2	79.6±2.6
9	PS_1	85.9±4.5
10	PS_2	87.8±2.9
11	PP_1	94.1±1.2
12	PP_2	96.3±1.2

Solubility Studies

Solubility of solid dispersion is measured by UV spectroscopy (μg/ml)

Sr.No.	Formulation	Solubility(μg/ml)
1	SH_1	101.14
2	SH_2	103.09
3	SS_1	49.90
4	SS_2	51.07

5	SP_1	22.46
6	SP_2	24.68
7	PH_1	97.82
8	PH_2	100.14
9	PS_1	49.17
10	PS_2	50.19
11	PP_1	20.12
12	PP_2	22.97

The solubility studies of Dasatinib and its solid dispersions was performed by dissolving them in water and analyzed by using UV-Visible spectrophotometer. SH2 shows highest solubility as compared to pure drug and all other solid dispersions.

FTIR studies

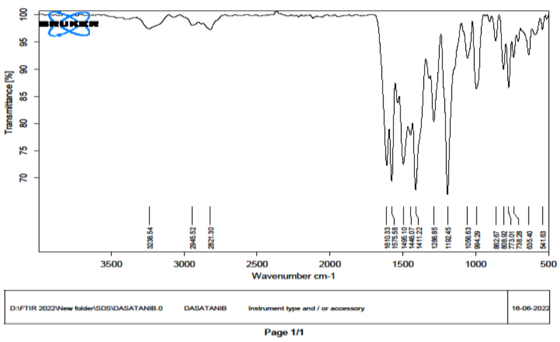


Fig. FTIR Spectra of Dasatanib

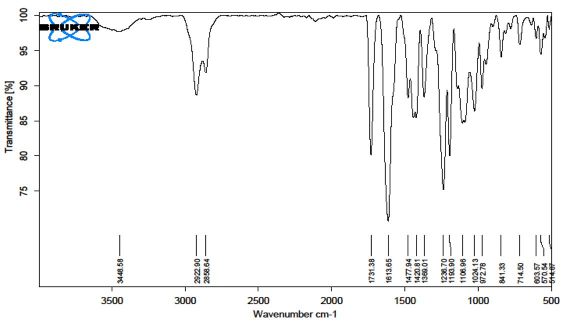


Fig. FTIR Spectra of Hot melt Extrusion of Dasatanib and Soluplus

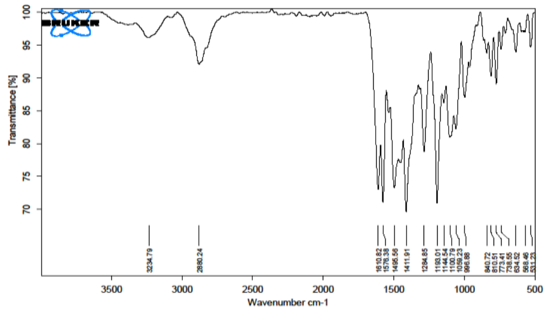


Fig. FTIR Spectra of Hot melt Extrusion of Dasatanib and Poloxamer

Drug content determination

The drug content of Solid dispersion of Dasatinib were assessed by dissolving them in 0.1N HCl, The % drug content was in the range of 97-99%, SH2 formulation shows a maximum drug content than the other formulation (Table 2).

Sr.No.	Formulation	% Drug Content
1	SH_1	97.61±0.32
2	SH_2	98.26±0.12
3	SS_1	97.49±0.55
4	SS_2	97.90±0.15
5	SP_1	96.90±0.63
6	SP_2	96.43±0.14
7	PH_1	97.11±0.86
8	PH_2	96.33±0.43
9	PS_1	95.14±0.75
10	PS_2	95.91±0.92
11	PP_1	97.17±0.45
12	PP_2	97.33±0.22

DSC studies:

DSC analysis was carried out using Shimadzu DSC-60 instrument. Dasatanib was placed in a platinum crucible and the DSC thermograms were recorded at a heating rate of 10^0C/min in the range 40^0Cto 350^0C. Nitrogen gas was purged at the rate of 30 ml/min. to maintain inert atmosphere.

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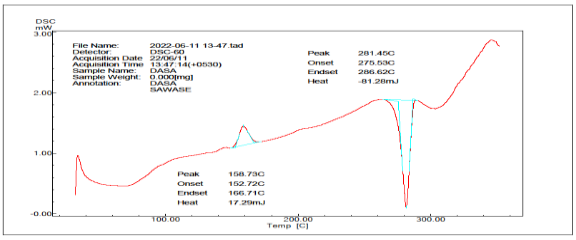


Fig. DSC Spectra of Dasatanib.

Table: DSC peaks of Drug Sample

Drug	M.P.	Peak	
		Onset	End set
Dasatinib	40^0-350^0C	275.53^0C	286.62^0C

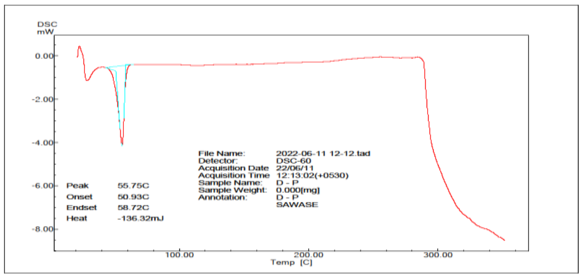


Fig. DSC Spectra of Dasatanib and Poloxamer407

In the thermogram of pure drug dasatinib we clearly see the crystalline nature and high degree of purity of the drug showing endothermic peak at 285^0C,

Preparation of solid dispersion of dasatinib with soluplus and polaxomer indicates the formation of amorphous nature.

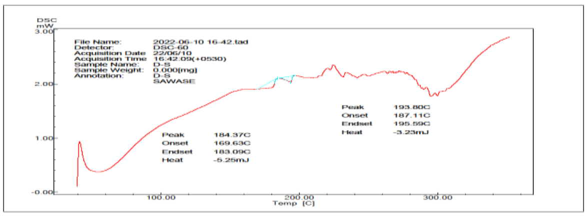
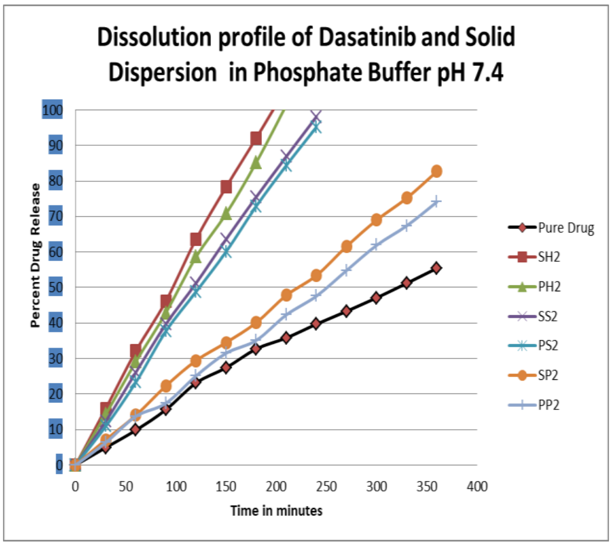


Fig. DSC Spectra of Dasatanib and Soluplus.

Dissolution studies

In-vitro drug dissolution studies in Phosphate Buffer pH 7.4 :

TIME	Pure API	SH2	PH2	SS2	PS2	SP2	PP2
0	0	0	0	0	0	0	0
30	4.9	15.9	14.3	12.3	10.9	7.1	6.3
60	9.8	32.1	29.1	26.1	23.3	14	13.7
90	15.6	46.2	42.9	39.7	37.7	22.3	17.4
120	23.1	63.6	58.6	51.2	48.8	29.4	25.1
150	27.4	78.3	70.8	63.6	60.1	34.5	31.5
180	32.7	92.1	85.2	75.5	72.9	40.1	35.1
210	35.8	106.3	101.4	86.9	84.4	47.8	42.3
240	39.7			98.1	95.2	53.4	47.6
270	43.3					61.6	54.8
300	47.1					69	61.9
330	51.2					75.2	67.4
360	55.4					82.7	74.1



The Solid dispersions were introduced into USP type–II (paddle) the conditions were maintained in same conditions as mentioned. The dissolution characteristics of the Dasatinib, Solid dispersions of Dasatinib with soluplus and poloxamer407 was observed .

It is clear that the Hot melt extrusion shows better dissolution profile than the pure drug at pH 7.4 value. As pure dasatinib has very low solubility at pH 7.4 this complex can overcome this low solubility problem of dasatinib and can be used for quantitative determination of drug via HPLC in the dissolution medium. The hydrophobic profile of drug causes drug to float on the surface hindering its dissolution, instaed the same dissolution medium shows better dissolution profile for drug soluplus inclusion complex prepared by hot melt extrusion. Therefore complexation with novel polymers such as soluplus and polaxomer can be used as an effective strategy for improving solubility profile of dasatinib at pH7.4

CONCLUSION:

By preparing solid sispersion pf dasatinib with novel polymers such as soluplus and polaxomer407 it is possible to say that dissolution profile of dasatinib complex at pH7.4 is increaded compare to the pure drug. This new inclusion complex can be used in the preparation of formulation which can be used orally for both paediatric and adult patients.

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