Preparation and Characterization of Novel Stable Coamorphous System of Dasatinib with Oxalic Acid: Improved Solubility, Dissolution, and Stability

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Abstract:
Dasatinib used in the treatment of chronic myeloid leukaemia, has poor water solubility and pH-dependent dissolution, resulting in low or variable oral bioavailability. The strategy used to formulate a Co-amorphous system of dasatinib with oxalic acid were employed to convert crystalline dasatinib monohydrate into an amorphous form. Coamorphous system with oxalic acid got converted into a coamorphous system with solvent assisted grinding. These findings were confirmed by advanced solid state characterization techniques like DSC, PXRD, mDSC and PLM. MDSC analysis showed a single glass transition temperature for the systems, confirming homogeneous single-phase amorphous formation. Developed CAMs demonstrated enhanced solubility in purified water, SGF and FaSSIF media. The coamorphous system showed significant improvement in-vitro dissolution at pH 4.0 acetate buffer and pH 6.8 phosphate buffer. Intermolecular hydrogen bonds formation between dasatinib and oxalic acid, confirmed by FTIR, is the reasons that stabilize the system under accelerated temperature and humidity conditions. These results indicate the efficacy of co-amorphous technology as a solution to biopharmaceutical limitations of dasatinib.

Keywords: Co-amorphous system, Dasatinib monohydrate, Solubility, Stability, Solid state characterization, powder dissolution

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Introduction

Bioavailability of drug is mainly dependant on its solubility and permeability. High solubility accelerates the availability of free drug in solution state and will be absorbed immediately as compared poorly soluble drug [1]. Several strategies have been reported in literature to improve the solubility of drug such as amorphization, microemulsion, particle size reduction, etc. Among these reported techniques amorphization has been widely explored and proven as best approach. However, the amorphous form has its own limitations such as instability during storage due to high internal energy and recrystallization to more stable crystalline form [2-4].

To overcome the stability challenges associated with amorphous form, coamorphous system is being widely explored as viable option due to ease of manufacturing and better control over the physicochemical properties of drug. Coamorphous system involves mixing another pharmacologically relevant drug or small molecular weight excipients such as carboxylic acids, amino acids, sugars and

nicotinamide along with drug [5-7]. Due to molecular interaction and the intimate mixing during preparation of coamorphous system, the stability and recrystallization challenges can be addressed [8, 9].

In this research, a new co-amorphous formulation of dasatinib with oxalic acid was designed and thoroughly studied in terms of their solubility and dissolution capabilities. Specifically, the major goal of this work was to evaluate the possibility of novel coamorphous formulation of dasatinib and Oxalic acid using solvent-assisted grinding and whether this approach would influence solubility and dissolvability of the drug. The stability of the obtained formulation was then tested under open air conditions at 60 °C and 40 °C/75 % RH for 4 weeks.

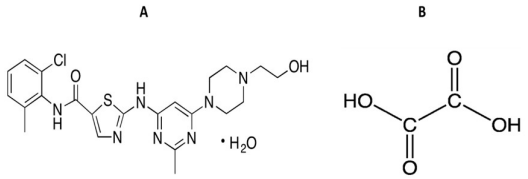

Fig.1. Chemical structure of dasatinib (a) and Oxalic acid (b)

2. Materials and Methods

2.1 Materials

Dasatinib monohydrate was kindly provided as a gift sample by MSN Laboratories, Hyderabad, India. Oxalic acid was purchased from Sigma-Aldrich (USA). Trifluoroacetic acid was procured from Sisco Research Laboratories Pvt. Ltd. (India). Methanol and acetonitrile were procured from Honeywell International India Pvt. Ltd. Deionized water was obtained from a Milli-Q ultrapure water system (Millipore, USA) and was used for the preparation of all buffer solutions. F3 powder was procured from Biorelevant, India.

2.2 Preparation of Coamorphous system of dasatinib and Oxalic acid by solvent assisted grinding

Solvent assisted grinding was employed to evaluate the coamorphous system of dasatinib with studied coformer. A mixture of drug and co-former was dispensed and gently triturated for about 5 min in mortar-pestle to break the lumps, if present any. After 5 min of dry grinding, few drops of methanol added such that it forms sticky, soft mass. Sticky mass triturated vigorously for 10, 20 and 30 min to evaluate the co-formability of dasatinib with respective co-former. Formulation showed crystalline impurities in PXRD when the trituration is not provided for adequate time.

Most of the methanol got evaporated during the trituration process, and complete removal of residual solvent was ensured by subjecting the sieved final product to vacuum drying after trituration. The samples at various timepoints were analysed by powder X-ray diffractometry (PXRD) after vigorous trituration, for residual crystalline impurities. Based on the analytical data, the trituration time was optimized to achieve complete amorphization. Following the trituration, the obtained solids mass was passed through a 40 µm sieve to produce powders of consistent particle size, which were then dried under vacuum. Finally, samples were packed in a suitable air tight container and stored in the refrigerator (2-8 °C) to avoid temperature-induced recrystallization until further characterization.

2.3 Impact of trituration time on amorphization

The effect of trituration time was assessed by analysing the samples with PXRD at different trituration durations (10 min, 20 min and 30 min). To ensure the complete amorphization, samples were analysed by PXRD, as the presence of trace crystalline impurities may further aggravate the recrystallization [10].

2.4 Powder X-Ray Diffractometry (PXRD)

PXRD was employed to understand the solid-state characteristics of as such dasatinib and coamorphous system. Nearly 15-20 mg of solid sample was spread uniformly on to the sample holder and the measurements were carried out using PANanalytical X-ray diffractometer with HiScore Plus software. Cu Kα radiation of $\lambda = 1.5406$ Å was the radiation source used for PXRD analysis over the range of $2\theta = 2–40°$. For sample analysis, PXRD was operated at accelerating voltage of 40 kV and a filament current of 40 mA.

2.5 Differential Scanning Calorimetry (DSC) and modulated DSC (m-DSC)

Thermal characterization was performed using differential scanning calorimetry (DSC), a very powerful technique for detecting material properties as a function of temperature. DSC analysis was performed using a TA Instruments DSC 2500 operating with TRIOS 5-7.0 software. The system was calibrated for heat flow and temperature using a high-purity Indium standard. About 3-5 mg of the dasatinib monohydrate was weighed into aluminium pans and carefully crimped. Heat was applied to the sample to determine thermal events. Heating was carried out at a rate of 10 °C/min up to 300 °C to investigate changes in the sample with respect to heat flow.

MDSC was performed to identify the glass transition event. The sample was equilibrated at 25.00 °C, followed by temperature modulation of ±1.000 °C with a period of 60.0 s. Subsequently, the temperature was ramped at a rate of 2.00 °C/min up to 350.00 °C.

2.6 Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of as such dasatinib and coamorphous formulations were recorded using an FTIR multiscope spectrophotometer (PerkinElmer, Buckinghamshire, UK) equipped with Spectrum v3.02 software to identify functional groups and evaluate possible intermolecular interactions between the drug and co-former. Absorption spectra

were recorded in the wavenumber range of 450–4000 cm^{-1}.

2.7 Polarized light microscopy (PLM)

PLM was used to check crystallinity in dasatinib monohydrate and developed coamorphous formulation. Small amount of sample was placed on a clean glass slide and examined under Olympus BX51 polarized light microscope which contains crossed polarizers and a red compensator (U-TP530). Images were taken at 10× magnification using transmitted light. If crystalline impurities are present, it appears as bright birefringent regions against the dark background, which makes it very easy to distinguish between crystalline and amorphous parts in samples [11].

2.8 High performance liquid chromatography (HPLC)

The method of high-performance liquid chromatography (HPLC) was adopted from literature sources and verified before applying it for the quantification of dasatinib in the developed formulation [12]. The method was found to perform excellently when used to quantify dasatinib in the formulations. Linearity was observed in the calibration graph, with the value of correlation coefficients (R^2) being near unity.

The analysis were done using the Waters HPLC system (Separation Module 2695), which was fitted with a photodiode array detector, an autosampler, and a column oven with data collection using the Empower 3 software. The samples were diluted appropriately with the selected diluent before being injected into the HPLC system.

2.9 Assay of Co-amorphous system

An accurately weighed quantity of the co-amorphous system, equivalent to 100 mg of dasatinib, was prepared in triplicate and transferred to a 100 mL volumetric flask. The volume was adjusted to 100 mL with diluent (acetonitrile: water, 50:50 v/v), and the contents were sonicated until complete dissolution was achieved. The resulting solution was further diluted appropriately with the same diluent and subjected to HPLC analysis for quantification of dasatinib.

2.10 Saturation solubility of optimized Co-amorphous system (Purified water, FaSSGF and FaSSIF)

The saturation solubility of dasatinib monohydrate, physical mixture and coamorphous formulation was evaluated by dispersing an excess quantity of each sample in different pH buffers along with water. For the determination of saturation solubility in different media, the solid was maintained excess in all samples at all timepoints.

For solubility determination, nearly 20 mg equivalent of as such dasatinib, physical mixture and coamorphous formulation was dispersed in 5 mL of respective buffer. The mixtures were transferred into sealed containers and placed in a shaking water bath (LAUDA, H20 SW), where they were maintained at 37 ± 0.5 °C with continuous agitation at 200 RPM to reach equilibrium. At pre-specific time intervals (Initial, 2 h, and 6 h), samples of about 500 µL were withdrawn and subjected to centrifugation to separate any undissolved material. From the resulting supernatant, 100 µL of the clear solution was carefully collected, appropriately diluted with the respective medium/diluent, and then quantified for drug content using a HPLC method. All the measurements were done in triplicate to ensure the reproducibility.

2.11 Powder dissolution in pH 4.0 acetate buffer

Accurately weighed quantities of as such dasatinib, physical mixture and coamorphous formulation equivalent to 50 mg of dasatinib were individually filled into size 3 hard gelatin capsules and subjected to dissolution testing. The dissolution study was carried out using a Electrolab EDT-08LX (Electrolab India Pvt. Ltd., India) dissolution apparatus (USP Type II) dissolution apparatus operated at a paddle rotation speed of 75 RPM. The dissolution medium consisted of 900 mL of pH 4.0 acetate buffer maintained at 37 ± 2°C throughout the study. The pH 4.0 acetate buffer was prepared by dissolving 9 g of sodium acetate trihydrate in approximately 4000 mL of purified water, followed by the addition of 117 mL of 2 N acetic acid with continuous stirring. The pH was adjusted to 4.0, if required, using dilute acetic acid or sodium hydroxide solution, and the final volume was made up to 6000 mL with purified water. Nearly 5 mL of samples were withdrawn at predetermined time intervals of 10, 15, 30, 45, and 60 minutes and immediately replaced with fresh buffer after withdrawal. The withdrawn samples were filtered through 0.45 µ polyvinylidene fluoride (PVDF) syringe filters and analysed for drug content using a suitable analytical method. All the measurements were done in triplicate to ensure the reproducibility.

2.12 Powder dissolution in pH 6.5 phosphate buffer

Crystalline dasatinib is reported to have very poor solubility at pH above 6.5 (<0.001 mg/mL) [13]. Hence the powder dissolution of as such dasatinib and coamorphous formulation at pH 6.5 buffer was performed to understand any improvement in the solubility due to amorphization. Dissolution behaviour of as such dasatinib monohydrate, physical mixture and coamorphous formulation was investigated using an Electrolab EDT-08LX dissolution apparatus (Electrolab India Pvt. Ltd., India), employing the USP apparatus II (paddle method). The dissolution medium consisted of 500 mL phosphate buffer (pH 6.5), prepared by mixing 1250 mL of KH_2PO_4 solution with 290 mL of 0.2 N NaOH, then making up to 5 L and adjusting the pH to 6.5. The temperature was maintained at 37 ± 0.5 °C throughout the study. An accurately weighed quantity of as such dasatinib, physical mixture and coamorphous formulation (equivalent to 50 mg of dasatinib) introduced into the dissolution vessels.

The paddle rotation speed was initially set at 75 RPM. Samples were withdrawn at predetermined time intervals (10, 20, 30, 45, and 60 min), passed through 0.45 µ polyvinylidene fluoride (PVDF) syringe filters to remove undissolved particles, and analysed using an HPLC method. All the measurements were done in triplicate to ensure the reproducibility.

2.13 Physical stability

Physical stability of the CAMs was systematically evaluated under varied storage conditions. Samples were kept in open glass vials in a humidity chamber (Newtronic Lifecare Equipment Pvt. Ltd., India) maintained at 40 ± 2 °C / 75 ± 5% RH, in a Stericell SC55ECO hot air oven (BMT Medical Technology s.r.o., Czech Republic) for 60 °C, and under refrigerated conditions (2–8 °C).

At defined time intervals (2 and 4 weeks), samples were withdrawn and characterized using PXRD and DSC to investigate potential alterations in solid-state properties. Chemical purity of the 1-, 2- & 4-week exposed samples was determined by a suitable HPLC method. Additionally, powder dissolution studies were performed on samples collected at the 4-week to evaluate any changes in drug release performance.

3 Results and Discussion

3.1 Preparation of Co-amorphous system

Co-amorphous systems are a powerful yet unexplored approach for getting a stable amorphous stage of crystalline drugs. Solvent-assisted grinding is best suited for early screening of conformers and one of the viable techniques to scale up from lab scale to large scale with the least possible usage of solvents [6, 14]. A solvent-assisted grinding method was employed for preparation of co-amorphous system of dasatinib with Oxalic acid. The developed coamorphous system was characterized with advanced characterization tools such as DSC and PXRD evaluating the complete amorphization.

The best trituration time was achieved using PXRD analysis at varying timepoints in order to achieve complete amorphization. The co-amorphous formulation exhibited crystalline impurities at less than 30 minutes of trituration time and complete amorphization was achieved after 30 min of trituration only.

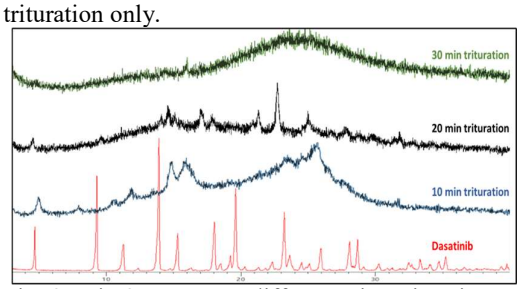

Fig. 2.: Fig 2: PXRD at different trituration time of dasatinib and oxalic acid (1:1 molar ratio)

3.2 PXRD

As depicted in fig 3, as such dasatinib showed characteristics Bragg's peaks at 2θ values like 4.7, 9.31, 12.39, 13.9, 15.33, 16.3, 18.06 19.62, 23.23, 25.95, 28.09° in its diffraction pattern, which was in line with the literature report [15]. These characteristic peaks were persistent with slightly reduced intensities in case of physical mixture of crystalline dasatinib. As confirmed in Fig 2, the developed coamorphous system showed the hollow pattern in PXRD, which confirms the complete amorphization, without any crystalline impurities.

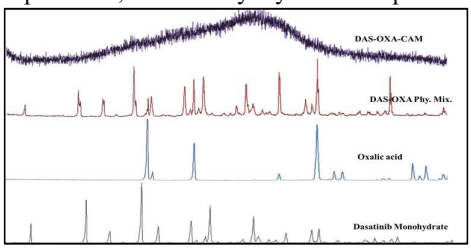

Fig 3.: PXRD overlay of as such dasatinib monohydrate, oxalic acid, physical mixture and coamorphous system

3.3 DSC and m-DSC

DSC was performed to study the thermal behaviour of dasatinib monohydrate. The DSC thermogram showed two distinct endothermic peaks. The first broad endothermic peak was observed at 149.48 °C, which corresponds to the loss of bound water from the crystal lattice of dasatinib monohydrate. A second sharp endothermic peak was observed at 287 °C, indicating the melting of dasatinib monohydrate. As reported by Kong et.al. the sharp nature of this peak indicates the crystalline nature of the drug and the stable baseline confirms its thermal stability up to the melting point [16].

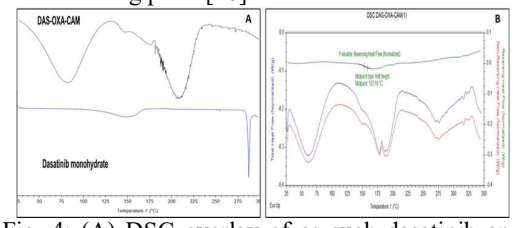

Fig. 4: (A) DSC overlay of as such dasatinib and coamorphous formulation & (B) Modulated DSC of coamorphous formulation

3.4 FTIR

The FTIR spectrum of dasatinib monohydrate matches with the literature reported characteristic peaks at 3418, 3200, 2946, 1620, 1582, 1513, 1456, 1310, 773 and 591 cm^{-1}, which correspond to N–H stretching vibration, O–H stretching, C–H (alkyl) stretching, C=O stretching, C=C (aryl) stretching, C–O stretching and C–Cl stretching, respectively. The FTIR spectra confirms the identity of pure form of dasatinib monohydrate [17, 18].

The FTIR spectrum of developed coamorphous formulation showed broadening and reduced intensity of the N–H/O–H stretching band of dasatinib monohydrate, indicating involvement of these groups in intermolecular interactions. a shift of

the C=O band from 1714 cm^{-1} to 1576 cm^{-1} was observed. A shift of this magnitude (~138 cm^{-1}) is characteristic of deprotonation of the carboxylic acid group and formation of a carboxylate anion (COO^-), indicative of proton transfer from oxalic acid to the piperazine nitrogen of dasatinib. As reported in literature, when a carboxylic acid undergoes salt or co-amorphous interaction with a basic drug such as dasatinib, the acid carbonyl stretching frequency disappears and two new stretching frequencies corresponding to the asymmetric and symmetric carboxylate anion (COO^-) appear at lower wavenumbers, typically lowered by approximately 100 cm^{-1} relative to the original C=O frequency [19]. The asymmetric COO^- stretching vibration typically appears in the range of 1540–1650 cm^{-1}, while the protonated COOH group absorbs at 1690–1750 cm^{-1}. These spectral changes collectively confirm the formation of strong ionic hydrogen bonding interactions between the carboxylate group of oxalic acid and the protonated piperazine N–H of dasatinib in the co-amorphous system [20].

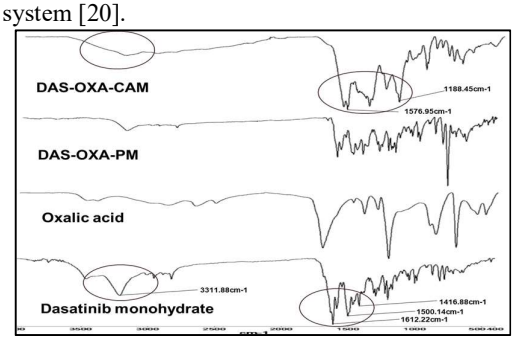

Fig.5: FTIR of dasatinib monohydrate, oxalic acid, DAS-OXA-PM and DAS-OXA-CAM

3.5 Polarized Light Microscopy

Polarized light microscopy (PLM) experiment was intuitively performed to evaluate presence of crystalline impurities in coamorphous systems. In Fig.6-A and 6-C, birefringence phenomenon was obviously observed in as such dasatinib, due to crystalline nature of dasatinib. Whereas the absence of birefringence for coamorphous system (Fig.6-B and 6D) confirms the complete amorphization of dasatinib. Under the polarized microscope, crystalline dasatinib showed a birefringence pattern against dark and bright background. The complete absence of birefringence pattern under polarized microscope confirming the amorphous nature. The PLM observations were found to be in good agreement with the PXRD and DSC data of coamorphous system.

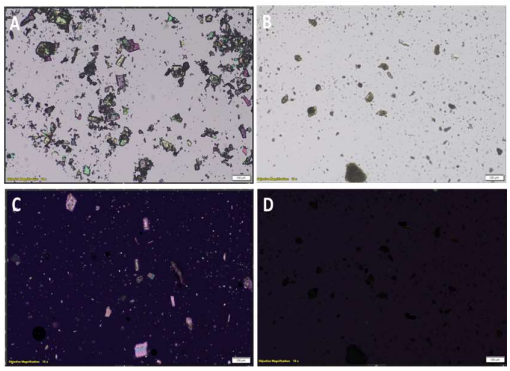

Fig. 6: PLM images under bright background- (A) as such dasatinib and (B) Coamorphous formulation & under Dark background- (C) as such dasatinib and (D) coamorphous formulation

3.7 HPLC analysis of Dasatinib

HPLC method was adopted from the already published article in a domain. Gradient method showed the elution of dasatinib at around 7.5 min, with stated method conditions [21]. Method was found to be suitable to detect the elution without interference from diluent or buffers. The method stated above was subsequently used for quantification of dasatinib in assay, solubility, and powder dissolution studies.

3.8 Assay of Coamorphous system

Assay of the developed CAM was done with a validated HPCL method to estimate the potency of developed coamorphous system. Assay of the developed coamorphous system was observed to be 99.25% by HPLC, which confirms homogeneity of drug content in developed coamorphous system.

3.9 Aqueous Solubility of Coamorphous system

Solubility is the key prerequisite for bioavailability, especially for BCS class-II drug candidates. Dasatinib is a weakly basic molecule, whose solubility is reported to be pH-dependent and poorly insoluble in water [22]. The saturation solubility of the drug in water is important, and it can be correlated with the in-vivo behaviour of the drug. Hence the solubility of as such dasatinib, physical mixture and coamorphous formulation was evaluated up to 6 hr in purified water, SGF and FaSSIF. As shown in Figure 7, coamorphous system consistently exhibited the highest solubility across all time points in all the media's. The physical mixtures demonstrated minimal improvement over pure dasatinib monohydrate due to acidic microenvironment. These findings highlight the enhanced solubility achieved through co-amorphization, with oxalic acid, relative to both the physical mixtures and the as such drug. Solubility of coamorphous system was maintained throughout the evaluated time points, without any significant drop during the course of study (up to 6 hr). Co-amorphous system showed nearly 160-folds improvement in the aqueous solubility as compared to as such dasatinib, which can be correlated with the complete amorphization. Amorphous form will

always have better solubility than crystalline counterpart due to higher thermodynamic free energy and lower lattice energy barrier [5, 23, 24].

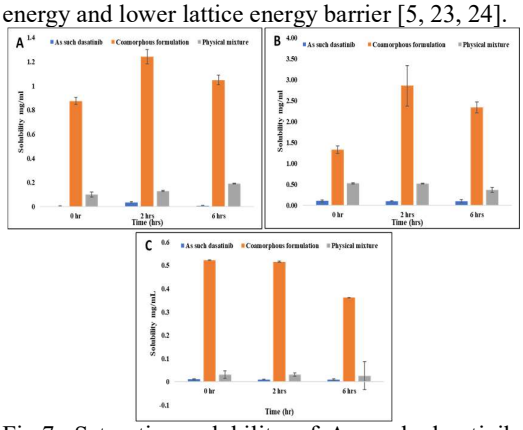

Fig.7: Saturation solubility of As such dasatinib, Coamorphous formulation and Physical mixture in (A) Purified water, (B) SGF and (C) FaSSIF media

3.10 Powder dissolution in pH 4.0 acetate buffer

A powder dissolution test was performed under sink conditions in purified water along with the crystalline drug and the physical mixture to investigate the dissolution behaviour of the co-amorphous formulations. As depicted in Fig.8-A, the coamorphous system showed the complete release of nearly 93.9% at 60 min timepoint, compared to 12.5% and 5.7%, respectively for crystalline counterpart and physical mixture. Co-amorphous system exhibited significantly faster dissolution compared to those of crystalline dasatinib and their physical mixtures in pH 4.0 acetate buffer in the presence of surfactant. This enhancement can be attributed to the amorphization due to molecular-level mixing of dasatinib with Oxalic acid, a highly water-soluble co-former, which reduces the solvation energy required for dasatinib molecules to enter the aqueous phase. Furthermore, the absence of lattice energy in the disordered amorphous state removes the energy barrier required for disrupting the crystalline structure. Collectively, these factors have contributed to faster dissolution and improved solubility of coamorphous system over the as such dasatinib. The significantly improved solubility of coamorphous system can be correlated to significantly better solubility in water.

3.11 Powder dissolution in pH 6.5 phosphate buffer

Dasatinib is reported to pH dependant solubility and shows rapid precipitation during stomach to intestine transition. Hence the dissolution was performed pH 6.5 phosphate buffer to understand the behaviour of coamorphous system along with as such dasatinib at harsher intestinal pH. As showed in Fig.8-B, the coamorphous formulation showed nearly 36.8% dissolution as compared to 4.8% and 5.3% for as such dasatinib and physical mixture. With the significantly improved (~ 8-fold) dissolution profile, coamorphous formulation showed higher release under harsher pH condition. These results were in good agreement with the saturation solubility data of coamorphous formulation in FaSSIF media.

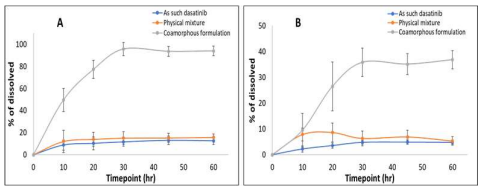

Fig. 8: Dissolution data of as such dasatinib, physical mixture and coamorphous formulation in (A) pH 4.0 acetate buffer and (B) pH 6.5 phosphate buffer

3.11 Physical stability

The physical stability of the coamorphous formulation was evaluated by PXRD after storage in an open container under accelerated (40 °C/75% RH) and stress conditions (60 °C) for up to 4 weeks. The initial CAM exhibited a broad diffuse halo pattern, confirming its amorphous nature. This halo pattern was retained after 2 and 4 weeks under both storage conditions without the appearance of any distinct sharp diffraction peaks, indicating that the CAM remained physically stable and maintained its amorphous form throughout the study period.

The DSC thermograms of pure dasatinib monohydrate and coamorphous formulation stored under different conditions (40 °C/75 % RH, and 60 °C for 4 weeks) are presented in Fig.9-B. The DSC thermogram of freshly prepared coamorphous formulation did not show the characteristic melting endotherm of dasatinib monohydrate, indicating successful modification of the crystalline structure to amorphous system. Open exposed samples under all conditions did not exhibit any sharp melting endotherm up to 4 weeks, confirming retention of the amorphous state without recrystallization. The thermograms of stability exposed samples were largely similar to that of the initial coamorphous formulation.

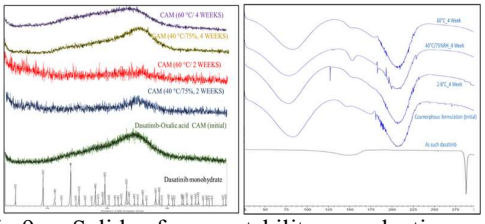

Fig.9: Solid form stability evaluation of coamorphous system by PXRD at 60°C (open exposure) and 40°C/75%RH (open exposure)

As specified in table 1, The chemical stability of coamorphous formulation was evaluated under refrigerated (2-8 °C), accelerated (40 °C/75% RH), and stress (60 °C) conditions at 1, 2 & 4 weeks. Developed coamorphous system showed minimal change in drug purity under refrigerated and high humidity stress conditions (40 °C/75% RH). However, a gradual decrease in the chemical purity

was observed under high temperature condition (60 °C) for developed coamorphous formulation.

Table 1: Chemical purity (%) data of stability exposed coamorphous formulation

Coamorphous formulation	Initial	Initial	99.85
	2–8°C	1Week	99.80
		2Week	99.77
		4Week	99.64
	40°C / 75% RH	1Week	98.94
		2Week	99.01
		4Week	98.60
	60°C	1Week	96.45
		2Week	96.12
		4Week	95.31

Finally, the dissolution of 4 weeks sample was performed in pH 4.0 acetate buffer, in comparison to freshly prepared coamorphous formulation. As depicted in Fig.10, the stability samples showed no sign of slow or incomplete release after 4 weeks of open exposure at high humidity and temperature, in comparison to fresh coamorphous formulation. This confirms the in-vitro behaviour of formulation remains unchanged during the course of stability duration.

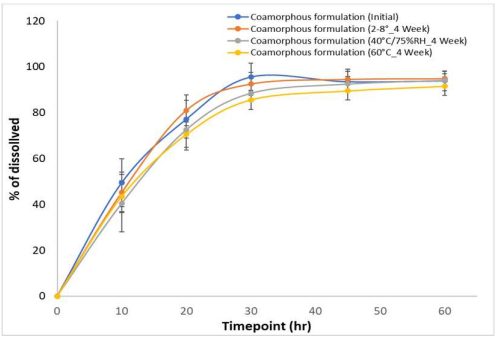

Fig. 10: Dissolution overlay of stability exposed coamorphous formulation

Conclusion

The novel coamorphous system of dasatinib with Oxalic acid at 1:1 molar ratio was developed with liquid assisted grinding technique. Methanol was selected as a solvent of choice by performing the qualitative solubility of dasatinib in different organic solvents. The grinding time required for complete solid form transformation was carefully evaluated by PXRD analysis of samples at different grinding time. The developed coamorphous system resulted in single Tg at nearly 150°C, which confirms the homogeneity of drug and coformer at selected molar ratio. FTIR data confirms the molecular interaction between drug and coformer, however the complete amorphization might have happened due to intimate mixing with solvent assisted grinding alongside molecular interaction. Solid form characterization i.e. DSC, m-DSC, PXRD and PLM showed solid form transformation of crystalline dasatinib in to complete amorphous system. Aqueous solubility of developed coamorphous system showed more than 160-fold improvement as compared to crystalline dasatinib. Developed coamorphous system showed significant improvement in the solubility in biorelevant media (FaSSIF and SGF) over as such dasatinib. Also, the powder dissolution of coamorphous system was observed to be significantly better as compared to crystalline dasatinib. Coamorphous system showed no signs of recrystallization at high temperature and humidity conditions up to 4 weeks. The outcome of this extensive study suggests the significance of development of stable co-amorphous system and role of small molecules for improvement of physicochemical properties of BCS class II and IV drugs. The relatively unexplored area of co-amorphization, has huge potential to overcome the solubility related challenges of poorly soluble molecules.

Authors contributions

All authors have contributed to the design of the study, carrying out of the experiments, data analysis, and preparation of the manuscripts.

Conflict of interest

The authors declare no conflict of interest.

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