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Original Article

ENHANCED SOLUBILITY AND DISSOLUTION BY SURFACE-MODIFIED SOLID DISPERSION OF ALECTINIB HYDROCHLORIDE

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ABSTRACT

Objective: Alectinib hydrochloride (AH), a poorly soluble drug, exhibits low solubility thereby very low bioavailability. The present study aims to develop and optimize surface-modified solid dispersion of AH (AH-SMSD) with enhanced solubility and dissolution using Soluplus® (SOL) and Gelucire 44/14 (GEL) as a polymer and surfactant, respectively.

Methods: Design of Experiments (DoE) was implemented to optimize the weight ratio of SOL (X1), and GEL (X2), keeping the drug weight constant to maximize the solubility (Y1) and dissolution (Y2). The optimized solid dispersion was subjected to solubility and dissolution in bio-relevant media and characterized using differential scanning calorimetry (DSC), Powder X-ray diffraction (pXRD), Fourier-transform infrared (FTIR), and scanning electron microscopy (SEM).

Results: A statistically significant model is obtained for solubility and dissolution through DoE. Formulation (F9) containing AH: SOL: GEL in weight ratios 1:5:5 showed a 547-fold increase in solubility. This solubility enhancement further translated into dissolution improvement with drug release of >80% in 15 min. The optimized formulation also showed improved solubility and dissolution in fasted-state bio-relevant media. DSC and pXRD showed a change in the crystallinity pattern of the drug. FTIR showed the existence of weak intermolecular interactions. Morphological evaluation through SEM demonstrated that the drug particles were dispersed to a hydrophilic carrier matrix, thus, transforming the hydrophobic drug into a hydrophilic form.

Conclusion: AH-SMSD with enhanced solubility and dissolution was successfully developed. The optimized formulation also showed improvement in the bio-relevant media and therefore has the potential to improve *in vivo* oral bioavailability (however, needs to be experimentally explored).

Keywords: Poor solubility, Soluplus, Gelucire, Surface-modified solid dispersion, Biorelevant media

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INTRODUCTION

Alectinib hydrochloride (AH) is a Food and Drug Administration (FDA) approved drug for the treatment of patients with Anaplastic Lymphoma Kinase (ALK+) non-small-cell lung cancer (NSCLC). AH is a highly selective ALK inhibitor that has demonstrated 10-fold potency over crizotinib. Currently, AH is used in patients with ALK+NSCLC who are intolerant to crizotinib [1, 2]. AH exhibits poor solubility, thus, presenting challenges for dissolution and clinical bio-availability [3]. The absolute bioavailability of AH has been reported as 37% under fed conditions. The impaired bioavailability of AH has been attributed to its low aqueous solubility in aqueous buffers and moderate *in vitro* permeability, which results in incomplete absorption of AH from the clinical formulation [2–5]. Interestingly, the solubility of AH is substantially higher in fed-state simulated intestinal fluid (FeSSIF) than in fasted-state simulated intestinal fluid (FaSSIF), thus, indicating a surfactant-oriented drug solubility [6]. This improved solubility led to an approximately 3-fold increase in systemic exposure of AH when co-administrated with a high-fat meal (fed state) as compared to a fasting state [3, 7]. Due to its poor bioavailability, the recommended dose of AH is quite high i.e., 600 mg (4 x 150 mg capsule) twice daily taken along with food to meet clinical efficacy [6, 7]. Thus, addressing the solubility concern is the first and foremost challenge for a formulator in the development of an immediate-release solid dosage form [8].

Various pharmaceutical techniques have been reported in the literature to address the solubility concern. Some of the key reported techniques are surfactant/micelle, co-solvency, self-emulsification, complexation, prodrug, salt/ionization/pH control, nanosuspension/nanocrystal, polymorphism, solid dispersion, etc. [9–16]. Of all reported techniques, the solid dispersion (SD) technique has proven to be a promising and industrially scalable technique to address the solubility and dissolution issues, with several approved products available in the market [14, 17]. The enhancement in solubility and dissolution in the SD system can be attributed to several factors, such as the transformation of crystal lattice into a highly disordered amorphous state, particle size reduction, improved wettability, etc. [18, 19]. A novel surface-modified solid dispersion (SMSD) has been discussed in the literature. This novel SMSD provides improved solubility and oral bioavailability of poorly water-soluble drugs. This is attributed to the surface modification of the hydrophobic drug to a hydrophilic form with the use of hydrophilic polymer and surfactant. Further, this SMSD does not show any crystalline change and, thus, offers excellent stability [20, 21].

Polymers in SD play a vital role in improving solubility and dissolution by inducing polymer-drug interactions, further stabilizing the SD, and preventing the recrystallization of the drug during its shelf-life [13]. It also helps to maintain super-saturation in the gastrointestinal (GI) tract, thereby resulting in improved bioavailability through SD. Soluplus® (SOL), a synthetic polymer with amphiphilic properties, has gained attention for its applicability in SD with extensive solubilization nature for poorly soluble drugs [22–25]. SOL as a polymer offers excellent biopharmaceutical wettability of drugs, preventing recrystallization and maintaining super-saturation in the GI tract with minimum toxicity [17, 26]. Several studies in the literature have reported that SOL can improve solubility, dissolution, and bioavailability for a variety of drugs, including diosgenin [26], lopinavir [27], and felodipine [28].

The introduction of surfactants for ternary SD resulted in enhanced *in vitro* dissolution and bioavailability of poorly soluble drugs by improving the wettability of drugs and preventing drug precipitation from a supersaturated state. Surfactants further facilitate the

inhibition of drug recrystallization by enhancing the miscibility between drug and carrier, therefore, stabilizing SD [18]. Gelucire 44/14 (GEL) is a semi-solid waxy amphiphilic excipient with surface-active properties that have been studied for solubility and dissolution enhancement of carbamazepine [29] and piroxicam [30], and bioavailability enhancement of piroxicam [31].

The present study focuses on developing and optimizing the SD formulation of AH with enhanced solubility and dissolution using the SMSD technique. Further, the performance of the optimized formulation was also evaluated for the drug release profile in bio-relevant media to foresee its performance *in vivo* conditions. Characterization of the optimized AH-SMSD was carried out using differential scanning calorimetry (DSC), Powder X-ray diffraction (pXRD), Fourier-transform infrared (FTIR), and Scanning Electron Microscopy (SEM) to investigate the possible reasons for solubility and dissolution enhancement.

MATERIALS AND METHODS

Materials

Alectinib Hydrochloride (AH) was provided by Sun Pharmaceutical Industries Limited (India). Polyvinyl caprolactam polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus® [SOL]), Copovidone (Kollidon® VA64), and Sodium lauryl Sulfate (Kolliphor® SLS) were kindly gifted by BASF (Germany). Plasdone™ K-29/32 was kindly gifted by Ashland (India). Hydroxypropyl cellulose (HPC-L) was provided by Nippon Soda Co. Lauroyl Polyoxyl-32 glycerides (Gelucire® 44/14 [GEL]) were provided by Gattefosse (France).

Formulation development

A systematic formulation development approach was taken for formulation development. It starts with screening suitable polymer and surfactant for SD and further optimizing the suitable ratio of polymer and surfactant to get maximum solubility and dissolution enhancement.

Carrier selection [Polymer/Surfactant]

Different SD carriers were screened to find suitable excipients for solubility enhancement. For screening the suitable carrier matrix, SD containing the drug to the carrier (SOL, GEL, Kollidon VA 64, Povidone K30, HPC-L, and SLS) in a 1:1 ratio was prepared and subjected to solubility studies in Simulated Gastric Fluid (SGF). The carrier that resulted in maximum solubility enhancement was selected as a suitable polymer and surfactant for further formulation development.

Optimization of AH-SMSD using design of experiments (DoE)

After the selection of a suitable polymer and surfactant, optimization of AH-SMSD for weight ratios of polymer and surfactant was carried out using design of experiments (DoE). Custom design with two factors and three levels was employed using JMP Statistical software version 9 (SAS Institute). The independent variables were the weight ratio for SOL (X1) and GEL (X2) at 0, 2.5 and 5 levels and 0, 5 and 10 levels, respectively, keeping AH weight ratio 1 constant. The dependent variables were solubility (Y1), and dissolution at 30 min (Y2). The experimental design suggested by JMP with independent variables (X1 and X2) along with their measured dependent variables (Y1, and Y2) has been summarized in table 1.

Preparation of solid dispersion

AH-SMSDs were prepared using the solvent evaporation method. Briefly, an accurately weighed quantity of carrier(s) was dissolved in acetone using a mechanical stirrer (RQ 124A, Universal Motors Ltd., Mumbai, India). Further, an accurately weighed quantity of AH was then added to the carrier solution and stirred for another 45–60 min. The obtained dispersion was then poured into petri-plates and dried at 40±2 °C in a vacuum oven (Remi, Mumbai, India). The dried samples were withdrawn, milled, and packed in the triple laminated bag.

Evaluation of solid dispersion

Solubility tests

The solubility tests of AH and AH-SMSDs were carried out in SGF pH 1.2. The excess amount of AH and AH-SMSDs samples was added to 25 ml of media. The suspension was kept at 37+1.0 °C for 24 h in a bio-shaker. Samples were withdrawn after 24 h and centrifuged at 4000 rpm for 10 min (REMI R-8C Laboratory Centrifuge). The supernatant was filtered through a 0.45 µm filter and subjected to HPLC analysis to determine the drug concentrations. Aliquots of 10 µl filtered samples were injected into a C18 column (250 x 4.6 mm, 5 µm, Waters). A gradient program consisting of mobile phases A and B was used for HPLC analysis. Mobile phases A and B consisted of pH 7 buffer and acetonitrile in 90:10 and 30:70 ratios, respectively. The flow rate and column temperature were maintained at 1.5 ml/min and 40 °C, respectively, during the analysis. A PDA detector was used to monitor the effluent at a wavelength of 230 nm [32].

In vitro dissolution tests

The drug release of all AH-SMSDs was studied in SGF pH 1.2 containing 0.25% Sodium lauryl sulfate (SLS), 900 ml, USP II apparatus (paddle), 100 rpm, 37.0±0.5 °C. AH-SMSD equivalent to 150 mg of AH-free base was used for dissolution studies. Samples were withdrawn at a predetermined time point and immediately replaced with fresh media. The withdrawn samples were filtered and injected into HPLC with a C18 column (250 x 4.6 mm, 5 µm, Waters). A gradient program consisting of mobile phases A and B was used for HPLC analysis. Mobile phases A and B consisted of water and acetonitrile and trifluoroacetic acid (TFA) in 700:300:0.5 v/v and 100:900:0.5 v/v, respectively. The flow rate and column temperature were maintained at 1.5 ml/min and 40 °C, respectively, during the analysis. A PDA detector was used to monitor the effluent at a wavelength of 230 nm [32].

Evaluation of optimized AH-SMSD in bio-relevant media

The optimized AH-SMSD formulation was further studied for its impact on solubility and dissolution in bio-relevant media. FaSSGF and FaSSIF media are reported to simulate the physiological condition of the stomach and proximal small intestine, respectively during the fasted state [33]. Studies in these media will help to understand the possibility of the improved *in vivo* oral bioavailability of the developed formulation. The solubility/dissolution samples were analyzed using HPLC parameters mentioned in the solubility tests and *in vitro* dissolution tests sections.

Preparation of FaSSGF media

HCl/NaCl solution was prepared by dissolving 19.990 g NaCl in about 9 L of purified water and the pH was adjusted to 1.6 by using HCl. The volume was made up to 10 L using purified water. 0.5597 g Simulated intestinal fluid powder was added to about 5 L of HCl/NaCl solution and then the volume was made up to 10 L using HCl/NaCl solution and thereafter it was used for dissolution studies.

Preparation of FaSSIF media

The preparation of FaSSIF starts with the preparation of blank FaSSIF. 6.186 g Sodium chloride, 4.47 g Sodium dihydrogen orthophosphate, and 0.348 g Sodium hydroxide were dissolved in 900 ml of distilled water. The pH of the obtained solution was adjusted to 6.5 by using 1 N NaOH or HCl, followed by a volume make up to 1000 ml using distilled water to get blank FasSSIF media. 2.240g Simulated intestinal fluid powder was dissolved in 500 ml of blank FaSSIF media to get a clear micellar solution. The volume of the solution was further made up to 1000 ml using blank FaSSIF media. The obtained solution was allowed to stand for 2 h and used thereafter [34]. The quantity of chemical reagents was adjusted as per the quantity of media required for the study.

Physicochemical characterization of optimized solid dispersion

Differential scanning calorimetry (DSC)

The optimized AH-SMSD and individual components were analyzed using a differential scanning calorimeter (STAR^e System DSC 3, Mettler Toledo). The instrument was calibrated using the Indium standard and Zinc. Experiments were performed to scan ranges from 30 to 400 °C at a heating rate of 10 °C/min at a nitrogen flow of 40 ml/min.

Powder X-ray diffraction (pXRD)

The powder X-ray patterns of optimized AH-SMSD and individual components were analyzed. pXRD of the samples was generated

using a PANalytical X'Pert PRO diffractometer. The instrument was equipped with a Copper anode (Cu Kα radiation, 40 kV voltage, 40 mA current). The samples were scanned with a step size of 0.02° at 0.01°/sec scan speed between 3° to 40° 2θ range.

Fourier Transform Infrared Spectroscopy (FTIR)

The FT-IR spectra of the optimized AH-SMSD and individual components were studied using a Perkin Elmer Spectrum ONE FT-IR spectrometer in the range of 4000-400 cm^{-1} using a resolution of 4 cm^{-1}.

Morphological study using Scanning Electron Microscope (SEM)

The morphologies of optimized AH-SMSD and individual components were characterized using SEM (Jeol, Model–JSM-6010LA, Japan). Before microscopic observation, all samples were exposed to platinum sputter-coating in argon.

RESULTS AND DISCUSSION

Carrier selection [Polymer/Surfactant]

Carrier selection was performed based on drug solubility studies. SOL and GEL showed higher solubility enhancement among various screened carriers at a 1:1 drug-to-carrier ratio (fig. 1). SOL exhibited 52-fold higher solubility, while GEL showed 23-fold higher solubility at 24 h, respectively, compared to the pure drug (1 µg/ml).

A study was further undertaken to assess the relationship between drug solubility and different concentrations of screened individual SD carriers-SOL (polymer) and GEL (surfactant). The varying weight ratio of individual SD carriers keeping the drug weight ratio constant (1:1, 1:5, 1:10) was further evaluated to select the right weight ratios of these two SD carrier combinations for DoE studies. A comparison of the drug solubility and carriers' concentration reveals higher linearity for GEL with R^2=0.994 as compared to SOL with R^2= 0.911 (fig. 2). A similar finding was observed where lapatinib ditosylate and carrier (SOL) concentration showed a linear relationship between solubility and carrier (SOL) concentration [15]. Further, GEL showed higher linearity for solubility above critical micellar concentration (CMC), indicating the solubilization is through micellization [35].

Solubility tests

One of the important factors that determine oral bioavailability is drug solubility [36, 37]. The poor aqueous solubility of the drug leads to incomplete absorption through the GI tract, thereby resulting in poor bioavailability [14]. One of the strategies to address the low bioavailability problem is to increase the apparent drug solubility and the dissolution rate [38]. To develop a formulation with maximum apparent solubility of the AH-SD, DoE was employed to optimize the weight ratio of SOL and GEL. The experimental design and the resultant experimental solubility data for AH-SMSD are elucidated in table 1. All AH-SMSD showed solubility enhancement as compared to pure AH. However, F7 and F9 with AH, SOL, and GEL in weight ratios 1:5:10 and 1:5:5 exhibited the highest solubility among the studied weight ratios.

The data (as a response) generated for each run of the suggested experimental design was analyzed using a fit model to achieve maximum solubility enhancement. A statistically significant model was obtained with a p-value<0.05 and R^2 of the regression plot (actual vs predicted) was close to 1 for the solubility response (Y1). As evident from table 2a, p-values for both SOL and GEL were less than 0.05 indicating that both excipients significantly impact the solubility of prepared AH-SMSDs. The surface profiler (fig. 3a) was generated during the custom design analysis through JMP software, showing a graphical representation of the correlation between dependent and independent variables. SOL showed a relatively linear relationship, while GEL showed a curvature effect for solubility at 24 h.

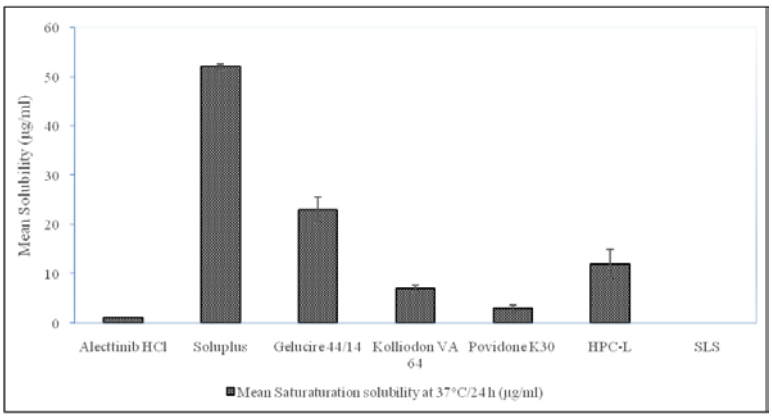

Fig. 1: Screening of solid dispersion carrier system using solubility studies of Alectinib hydrochloride in SGF [mean±SD, n=3]. HPC-L: Hydroxypropyl cellulose (L grade); SLS: sodium lauryl sulfate

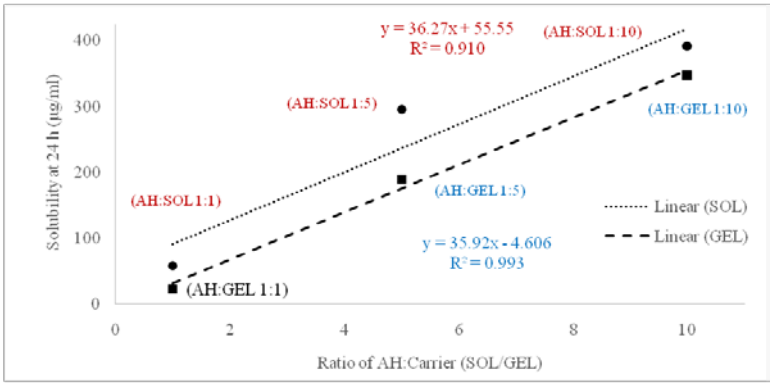

Fig. 2: Solubility of AH as a function of AH: Carrier solid dispersion. AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14

Table 1: Summary of AH-SMSD prepared as per the design of experiments suggested by JMP and their solubility and dissolution measurements

Formulation	AH	SOL [X1]	GEL [X2]	AH: SOL: GEL (Weight ratio)	Mean saturation solubility# (µg/ml)±SD at 37 °C/24 h [Y1]	Mean dissolution## (%)±SD at 30 min [Y2]
F1	1	2.5	0	1:2.5:0	208±33.7	75±9.8
F2	1	0	5	1:0:5	190±5.1	93±3.7
F3	1	0	0	1:0:0	1±0.0	45±3.1
F4	1	2.5	10	1:2.5:10	354±14.4	65±4.1
F5	1	5	0	1:5:0	296±33.2	89±1.0
F6	1	2.5	5	1:2.5:5	324±24.3	89±6.5
F7	1	5	10	1:5:10	547±91.1	83±7.4
F8	1	0	10	1:0:10	348±21.1	97±0.5
F9	1	5	5	1:5:5	547±124.4	94±2.5

AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14; AH-SMSD: Surface modified solid dispersion of Alectinib hydrochloride, #Simulated gastric fluid (SGF), n=3, ##900 ml, Simulated gastric fluid (SGF) containing 0.25% Sodium lauryl sulfate (SLS), USP-II, paddle speed 100 rpm, n=6

Table 2: Summary of parameter estimates for the design of experiments (DOE) suggested by JMP

a) Response: Solubility at 24 h

Term	Estimate	Std Error	t Ratio	p-value, Prob>|t|
SOL(0,5)	141.83333	26.00475	5.45	0.0121*
SOL*SOL	26.166667	45.04154	0.58	0.6020
GEL(0,10)	124	26.00475	4.77	0.0175*
GEL*GEL	-61.33333	45.04154	-1.36	0.2665
SOL*GEL	-24	31.84918	-0.75	0.5059

b) Response: Dissolution at 30 min

Term	Estimate	Std error	T ratio	P-value, Prob>|t|
SOL(0,5)	0.1666667	2.469568	0.07	0.9504
SOL*SOL	12.833333	4.277417	3.00	0.0577
GEL(0,10)	8.6666667	2.469568	3.51	0.0392*
GEL*GEL	-37.66667	4.277417	-8.81	0.0031**
SOL*GEL	-17	3.024591	-5.62	0.0111*

*p-value<0.05, **p-value<0.01, AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14

In vitro dissolution tests

Improvement in solubility is expected to result in an improved dissolution profile of the AH-SMSD. Accordingly, dissolution studies were carried out to investigate the improvement in the dissolution rate. The dissolution at 30 min, response (Y2), was analyzed using a fit model for the suggested experimental design to obtain maximum dissolution enhancement. A statistically significant model was obtained (p-value<0.05) with R^2 of the regression plots close to 1. As evident from table 2b, a significant impact (p-value<0.05) was observed on dissolution at 30 min (Y2) for individual GEL (X2), quadratic GEL (X2), and interaction factor for SOL (X1) and GEL (X2) for prepared AH-SMSD. However, SOL showed a quadratic relation with a p-value slightly higher than 0.05. The surface profiler (fig. 3b) showed a curvature effect for both SOL and GEL for dissolution at 30 min.

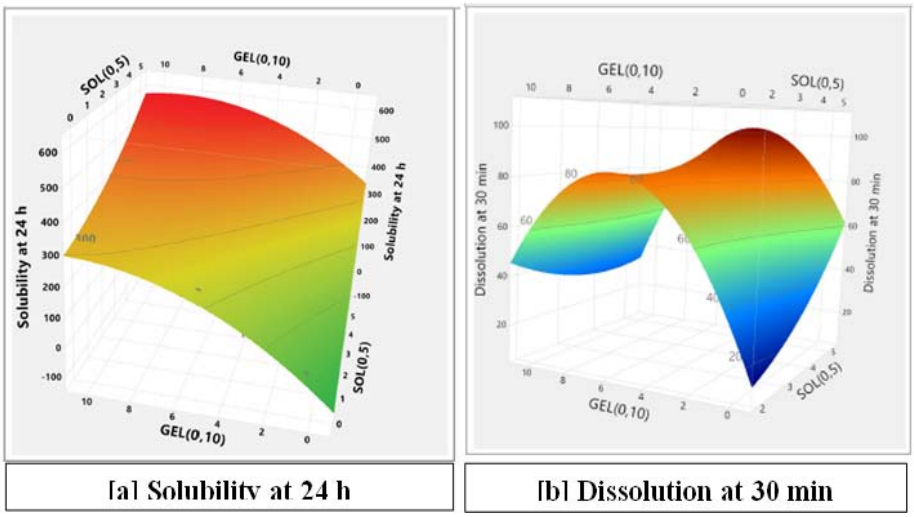

Fig. 3: Surface profiler for [a] Solubility at 24 h (Y1), and [b] Dissolution at 30 min (Y2) as a response generated by JMP software for different weight ratios of SOL (X1) and GEL (X2). SOL: Soluplus; GEL: Gelucire 44/14

As evident in fig. 4, AH (F3) showed the slowest and incomplete dissolution among all evaluated formulations. Formulations (F1 and F4) showed incomplete drug release while other formulations (F2, F5, F6, F7, F8, F9) showed complete drug release (>85% at terminal time point). Formulation (F9) containing AH: SOL: GEL at 1:5:5 weight ratio showed the fastest drug release with>80% drug release in 15 min. These findings suggest that an optimum quantity of polymer (SOL) is required to obtain the complete drug release and the inclusion of surfactant as ternary SD will maximize the dissolution rate. It supports the utility of developing ternary SMSD for AH, comprising SOL as a polymer and GEL as a surfactant. Moreover, the rapid release from formulation F9 (>80% in 15 min) may be due to the improved wettability of drug particles by the presence of surfactant (GEL), further supported by localized solubilization by amphiphilic polymer (SOL) [39–41]. In the solubility studies, both formulations F7 and F9 exhibited the highest solubility among the studied weight ratios. However, F9 showed the fastest dissolution profile, thus, further considered for characterization.

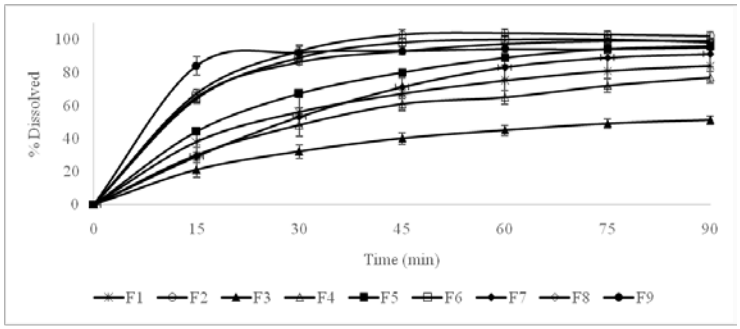

Fig. 4: Dissolution profile of Alectinib hydrochloride solid dispersions (AH-SD) in Simulated Gastric Fluid (SGF) containing 0.25% SLS [mean±SD, n=6]

Table 3: Saturation solubility of optimized formulation AH-SMSD (F9) in bio-relevant media as compared to alectinib hydrochloride

#	Formulation description	Mean saturation solubility [n=3] (µg/ml)±SD at 37 °C/24 h	
		FaSSGF	FaSSIF
AH	-	1±0.6	0±0.0
F9	AH-SMSD (AH: SOL: GEL 1:5:5)	290±63.5	559±87.0

AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14; AH-SMSD: Surface modified solid dispersion of Alectinib hydrochloride; FaSSGF: Fasted State Simulated Gastric Fluid; FaSSIF: Fasted State Simulated Intestinal Fluid

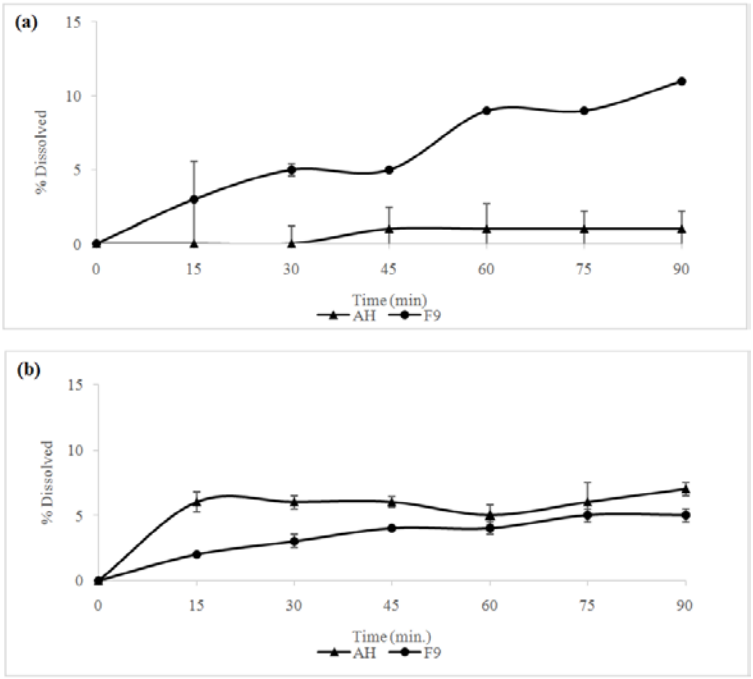

Fig. 5: Dissolution profile of the optimized AH-SMSD (F9) in bio-relevant media (a) FaSSGF–Fasted State Simulated Gastric Fluid (b) FaSSIF–Fasted State Simulated Intestinal Fluid in comparison of the pure drug (AH) [mean±SD, n=6]. AH: Alectinib hydrochloride; AH-SMSD: Surface-modified solid dispersion of Alectinib hydrochloride

Evaluation of optimized AH-SMSD in Bio-relevant media

AH showed low bioavailability in the fasting state; hence it becomes pertinent to study the performance of the optimized AH-SMSD in the bio-relevant media. Accordingly, the solubility of formulation F9 was studied in bio-relevant media–FaSSGF and FaSSIF. A remarkable increase in solubility for AH-SMSD (F9) was observed in bio-relevant media with 290-fold and 559-fold enhancement in FaSSGF and

FaSSIF, respectively [Table 3]. Further, the dissolution performance of the AH-SMSD formulation (F9) was studied in these bio-relevant media. A remarkable improvement in dissolution was observed for the optimized AH-SMSD (F9) as compared to the pure drug (AH) in FaSSGF (fig. 5a). Increased dissolution in FaSSGF media ensures the drug will be available in the solubilized form in the stomach, thereby, may enhance the bioavailability. However, observed dissolution in FaSSIF media is comparable for both AH and AH-SMSD F9 (fig. 5b), which is not aligned with the solubility observation. This may be due to the interaction of SOL micelles with bile and lecithin micelles. Similar results are reported in literature where SOL-based SD resulted in retarded solubilization for candesartan cilexetil [42] and dissolution for dolutegravir [43] in bio-relevant media.

Differential scanning calorimetry (DSC)

To further investigate the improvement in AH-SMSD solubility, the thermal behavior and changes in the crystallinity pattern of the AH and AH-SMSD were studied using DSC studies. AH and GEL are crystalline in nature, indicated by sharp melting peaks at 356.11 °C and 39.94 °C, respectively. While SOL does not show any endothermic peaks, indicating its amorphous nature. The optimized formulation, F9 showed the disappearance of the sharp melting peak of the drug, indicating a change in the crystallinity of the optimized AH-SMSD (fig. 6). It may be attributed to the transformation of the crystalline drug into an amorphous state [44] or the solubilization of AH in SOL and GEL. Similar results have been reported in another study wherein SD of lapatinib ditosylate (LB-DT) prepared by solvent rotary evaporation technique exhibited the disappearance of the drug peak in LB-DT, indicating the absence of crystallinity in the formulated solid dispersion [15].

Powder X-ray diffraction (pXRD)

To further understand the change in the crystallinity for the optimized AH-SMSD, pXRD was carried out. X-ray diffractive patterns of AH, SOL, GEL, and optimized AH-SMSD (F9) are depicted in fig. 7. The characteristic crystalline peak of AH was observed with major diffraction peaks at 8.45°, 8.70°, 11.97°, 14.02°, 16.76°, 18.80°, 18.99°, 20.20°, 21.49°, and 23.38°±0.2°θ. GEL exhibited two broad peaks at 18.92° and 23.24°±0.2°θ while SOL did not exhibit any crystalline peaks, indicating its amorphous nature. AH-SMSD containing AH: SOL: GEL 1:5:5 (F9) exhibited small low-intensity peaks at 14.02°±0.2°θ and 20.20±0.2°θ which are characteristic peaks of AH and broad peaks were observed at 18.79 and 23.38±0.2°θ that is common peak position to both AH and GEL. The disappearance of some of the characteristics peaks and reduction in the sharpness and height of the crystalline peaks of AH at 14.02°±0.2°θ and 20.20±0.2°θ of AH-SMSD (F9) confirm the change in the crystallinity of the AH when formulated by SMSD (F9) technique [45]. Similar findings have been reported in the previous study wherein the disappearance of characteristics peaks of kaempferol indicated a reduction in crystallinity after preparation of solid dispersion using Poloxamer 407 [46]. These results suggest that the enhanced solubility of AH was not due to the conversion of the crystalline drug into an amorphous state. It can be attributed to the reduction of crystallinity and the surface modification of hydrophobic drug (AH) by amphiphilic polymer (SOL) and surfactant (GEL) into a hydrophilic form [47].

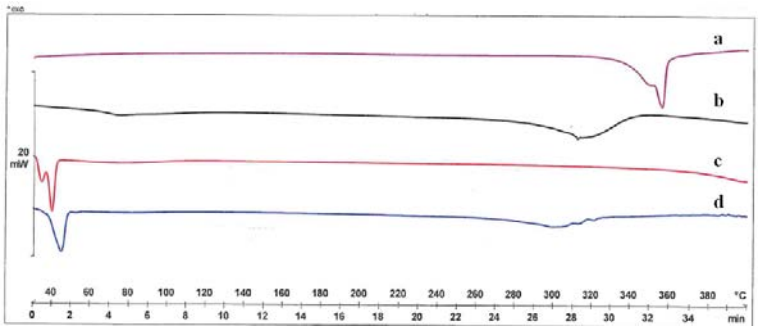

Fig. 6: DSC thermograms of (a) Alectinib hydrochloride (b) Soluplus (c) Gelucire 44/14 (d) AH-SMSD (F9)-AH: SOL: GEL in ratio 1:5:5. AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14; AH-SMSD: Surface modified solid dispersion of Alectinib hydrochloride

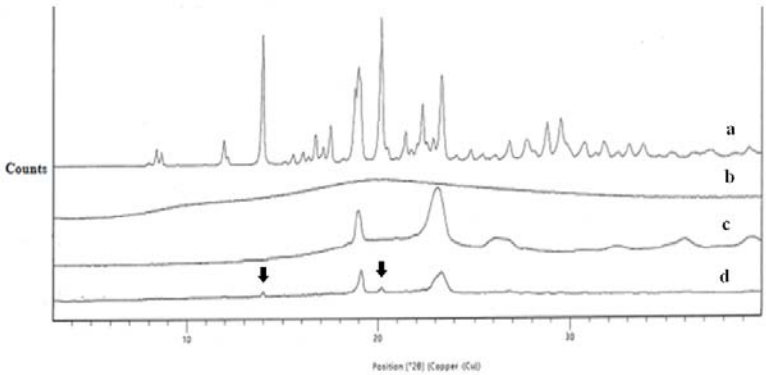

Fig. 7: PXRD spectra of (a) Alectinib hydrochloride (b) Soluplus (c) Gelucire 44/14/(d) AH-SMSD (F9) with AH: SOL: GEL in ratio 1:5:5. AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14; AH-SMSD: Surface modified solid dispersion of Alectinib hydrochloride

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR has been extensively used as a tool to investigate any specific interaction e. g., H-bond between drugs and carriers in SDs. Any interaction in the solid dispersion against the individual components is indicated by changes in the frequency, bandwidth, and intensity in FTIR spectra [48]. As evident from fig. 8, FTIR of AH, SOL, and GEL shows heavy overlapping IR peaks. AH, SOL and AH-SMSD (F9) showed peaks at 1632.06 cm^{-1}, 1639.93 cm^{-1}, and 1632.44 cm^{-1}, respectively, for the C=O bond. The formation of an H-bond reduces the carbonyl bond order indicated by the change in C=O stretching frequency. The IR peaks of the C=O bond for AH-SMSD (F9) were also observed in the same region, indicating that there is no direct evidence of H-bonding. This may be due to heavy

overlapping IR peaks in the same region. Further, AH, SOL, GEL, and AH-SMSD (F9) showed a peak at 3434.1 cm-1, 3462.97 cm-1, 3458.99 cm-1, and 3445.06 cm-1 for NH stretching. The shift and broadening of the peak for AH-SMSD (F9) in the NH region indicated intermolecular interaction. In our previous study, molecular docking studies showed that Van der Waals and hydrophobic interaction were the major interactions between AH and SOL [32]. Further, a hydrophobic interaction is expected between AH and GEL, resulting in the solubilization of a hydrophobic drug (AH) in hydrophobic long hydrocarbon chains of GEL. The above reasons may be attributed to enhanced AH solubility in the presence of SOL and GEL.

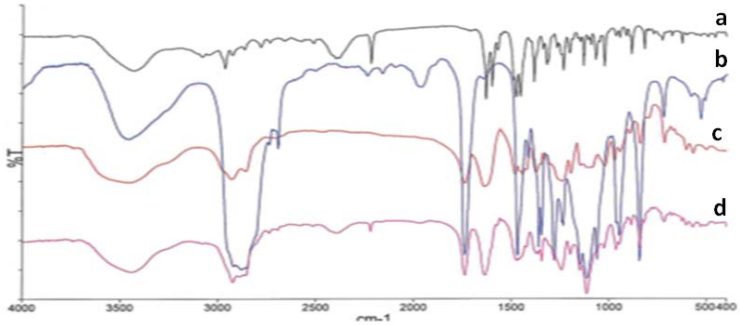

Fig. 8: FTIR spectra of (a) Alectinib hydrochloride (b) Soluplus (c) Gelucire 44/14 (d) AH-SMSD (F9) with AH: SOL: GEL in ratio 1:5:5. AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14; AH-SMSD: Surface modified solid dispersion of Alectinib hydrochloride

Morphological study of the AH-SMSD using Scanning Electron Microscope (SEM)

The morphological characteristics of the AH-SMSD were investigated through SEM to understand potential interaction, if any. The microphotographs from SEM of AH, SOL, and GEL showed fine agglomerated particles, irregular-shaped particles, and big indistinct particles, respectively (fig. 9a, b, c). AH-SMSD (F9) presents irregularly shaped particles with rough texture (fig. 9d), unlike conventional ternary amorphous solid dispersion. It indicates the drug particles are dispersed in the carrier matrix. Further, the polymer and surfactant might be attached to the hydrophobic surface of the drug, thus, resulting in the surface-modification of drug particles into a hydrophilic surface. Similar findings have been reported wherein SEM studies revealed the prepared SMSD showed rough and irregularly shaped particles with surface-attached hydrophilic carriers [49, 50].

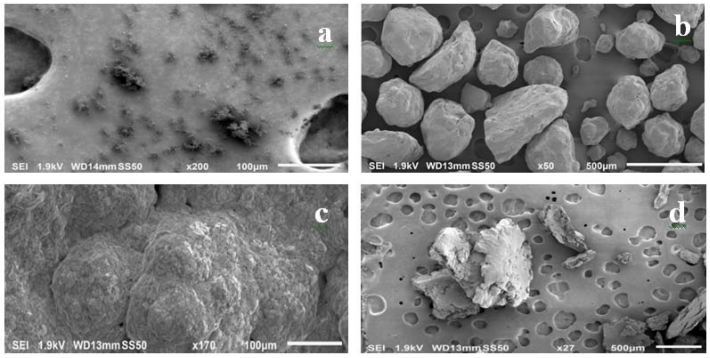

Fig. 9: SEM images of (a) Alectinib hydrochloride (b) Soluplus (c) Gelucire 44/14 (d) AH-SMSD (F9)-AH: SOL: GEL in ratio 1:5:5. AH: Alectinib hydrochloride; SOL: Soluplus; GEL: Gelucire 44/14; AH-SMSD: Surface modified solid dispersion of Alectinib hydrochloride

CONCLUSION

Alectinib hydrochloride is a poorly soluble drug that exhibits impaired bioavailability, thus, leading to a high dose recommendation to meet the therapeutic efficacy. Ternary AH-SMSD containing a combination of SOL and GEL were successfully developed and optimized using DoE. A significant improvement in both solubility and dissolution was observed for ternary AH-SMSD compared to the pure drug. Further, solubility analysis of the combination of SOL and GEL in the AH-SD in the DoE study suggests a synergistic improvement in AH solubility. A similar synergistic pattern was also observed in the dissolution enhancement for AH-SMSD (F9) containing a combination of SOL and GEL. The present study provides the merits and utility of using a combination of polymer (SOL) and surfactant (GEL) in ternary SMSDs for solubility and dissolution enhancement of a poorly water-soluble drug. Characterization of the AH-SMSD showed that solubility and dissolution enhancement may be accounted for a change in the crystallinity pattern of the AH. Furthermore, there was evidence of weak intermolecular interactions, as indicated by FT-IR. Also, the existence of hydrophobic interaction between AH and SOL was indicated by molecular docking studies in our previous study. There is the possibility of hydrophobic interaction between AH and GEL due to the hydrophobic drug and the long hydrocarbon chain of GEL. Morphological evaluation by SEM revealed that the drug particles are well dispersed within a hydrophilic carrier matrix, thus giving a rough and irregularly shaped particle. Optimized AH-SMSD (F9), a ternary SMSD, showed an improvement in solubility and *in vitro* dissolution in FaSSGF, a bio-relevant media. SOL is also reported as an absorption enhancer, thus, can further improve absorption [39]. Therefore, there are chances of improved *in vivo* oral bioavailability from the optimized AH-SMSD in the fasted state. These studies showed that ternary surface-modified solid dispersion of AH has a promising pharmaceutical application.

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ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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