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Enhancing the Dissolution of Oral Dasatinib Tablets Using Zein–Hydroxypropyl Methylcellulose Solid Dispersions

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ABSTRACT

Zein has been used in several pharmaceutical applications because of its unique composition. It is an amphiphilic molecule that is biodegradable, biocompatible, and has adhesive, matrix-forming, and film-coating properties, making it a promising pharmaceutical excipient. Zein-based formulations have been investigated in tablet-coating, nanoparticulate delivery systems, and controlled-release formulations. However, to date, very few studies have been performed on the inclusion of zein in solid dispersion formulations to enhance drug dissolution. This study aimed to improve the dissolution of the weakly basic and poorly soluble oral dasatinib (used as a model) using zein–hydroxypropyl methylcellulose (HPMC) solid dispersion to achieve rapid disintegration and dissolution in the gastric pH. Using the spray-drying technique, four solid dispersions were prepared with different zein, HPMC, and dasatinib ratios. Subsequently, five different tablets were directly compressed using the previously prepared solid dispersions along with basic excipients. Various in vitro characterization analyses were performed to predict their behavior in vivo. Particle size measurement, tablet weight variation and content assay, disintegration, and dissolution studies were also performed. The results indicated that zein solid dispersion improved the disintegration and dissolution of dasatinib in the gastric media by reducing the drug particle size and the formation of the dasatinib amorphous state. Moreover, the tablets exhibited desirable properties in terms of high drug content, friability, and tensile strength. In conclusion, tablets comprising zein–HPMC solid dispersion showed improved properties; however, including a higher ratio of zein in the solid dispersion adversely affected the disintegration and release properties of formulations.

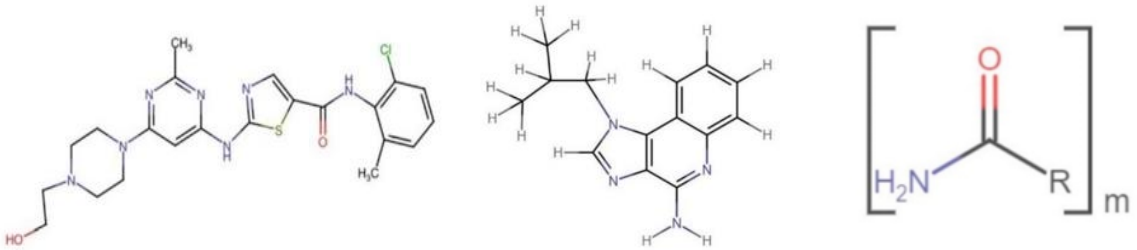
Key words: *Solid dispersion, Dasatinib, Zein, Bioavailability, Dissolution, Disintegration*

INTRODUCTION

An increasing number of oral chemotherapy agents has emerged in the last decade. This treatment approach is appropriate for schedule-dependent agents that may need to be administered daily for months or years, compared to intermittent, short-term conventional antiproliferative or cytotoxic agents that are often administered intravenously [1-3]. Many oral drug candidates have been reported to exhibit low solubility and poor bioavailability after dosing. Approximately 75% of the new drug candidates correspond to classes II and IV in the biopharmaceutical classification system (BCS) [3, 4]. Solubility is an essential factor to achieve the desired drug concentration in the blood for a therapeutic response [3-5]. Orally administered antitumor agents usually exhibit

pH-dependent solubility and are often characterized as BCS class II, that is, weak, basic drugs that dissolve in acidic pHs and precipitate in the small intestine [5, 6]. Unfortunately, the bioavailability of these agents is reduced by the co-administration of antacids to alleviate gastroesophageal reflux and gastric inflammation [4-6]. Examples of agents whose exposure is include imatinib, gefitinib, erlotinib, and dasatinib [5-8].

Dasatinib **(Figure 1a)** is a second-generation tyrosine kinase inhibitor that is administered to patients with imatinib-resistant chronic myeloid leukemia and is also used for treating other solid tumors [5-9]. Dasatinib exhibits anti-inflammatory properties, including T-lymphocyte inhibition, and can act as a senolytic agent by selectively eliminating senescent cells via the ephrin signaling pathways to delay cellular aging [7-9]. It is available as a commercial oral tablet and, since it is a BCS class II compound, it exhibits pH-dependent aqueous solubility ranging from 18.4 mg/mL to 0.008 mg/mL at pHs 2.6 and 6 [5-9]. This makes the drug susceptible to gastric degradation or emptying before absorption. Drug levels below the minimal effective concentration at the site of action can lead to treatment failure.



a) Dasatinib b) HPMC c) Zein

Figure 1. The chemical composition of a) Dasatinib, b) HPMC, and c) Zein.

Improving the solubility of poorly aqueous-soluble drugs is a challenge. To overcome this, the rate of absorption and extent of bioavailability should be improved, which can be achieved by controlling the rate of disintegration and dissolution [3-5]. Techniques such as complexation, micronization, spheronization, salt formation, and solid dispersion (SD) have been used to enhance the solubility of such drugs [1-6]. The latter refers to a group of solid materials that contain one or more active ingredients uniformly dispersed in a solid, inert, water-soluble carrier, or vehicle matrix [4-6, 10-12]. SD has been used for various poorly water-soluble drugs, such as prednisolone [11], nifedipine [12], ketoprofen [13, 14], docetaxel [15], regorafenib [16], and lapatinib [17].

Many materials have been employed as carriers to prepare solid dispersions, such as polymers (β-cyclodextrin, polyethylene glycols, polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC) **(Figure 1b)** [16-19], surfactants, sugars, and acids [10-19]. Such materials are often employed due to their low toxicity and melting point, fast solidification, and high aqueous solubility. However, water-soluble carriers used in SD usually formed a soft and wet mass that hardly produces tablets [20-22]. These carriers may counter the desired effect by decreasing the dissolution due to the increased viscosity at the boundary layer near the dissolving contact surface [20-22]. This problem can be attenuated by using water-insoluble hydrophilic carriers that deposit the drug on their surfaces. Upon contact with water, the carrier releases the drug immediately. Therefore, the selection of a suitable carrier matrix has a significant effect on the overall dissolution profile of the dispersed drug [20-23].

Protein-based carriers in pharmaceutical formulations provide several advantages such as biodegradability, biocompatibility, and availability of surface area for drug encapsulation [23, 24]. Zein is a natural protein extracted from maize seeds **(Figure 1c)**. The U.S. Food and Drug Administration has classified zein as "generally recognized as safe" because this prolamin protein is composed of 75% lipophilic and 25% hydrophilic amino acid residues [21-23]. This structure may be responsible for its insolubility in water alone; however, it is soluble in binary aqueous solvents that contain fewer aliphatic alcohols, such as ethanol or isopropanol [21-23]. This hydrophobic feature has allowed zein to be successfully employed in tissue engineering scaffolds, targeted and controlled drug delivery systems, and nanocarriers, particularly for poorly water-soluble drugs [20-25]. Various studies recommend using zein as an alternative tablet excipient to traditional matrix polymers that are produced by chemical modification or synthesis [20-29]. Nguyen *et al*. [23] studied the inclusion of zein in a solid dispersion system to improve the drug dissolution rate of poorly soluble prednisolone in low-pH media [11]. Another study investigated the role of surfactants in zein–HPMC solid dispersion [26]. The study found that the combination of zein–HPMC solid dispersion with surfactants improved drug dissolution by increasing wettability and crystal

changes. However, the comprehensive characterization of zein as an excipient in the aforementioned solid dispersion has not been explored.

In this study, we investigated the potential use of zein in an SD mixture that was directly compressed into tablets with other excipients and dasatinib as a drug model. This system within system (solid dispersion within a tablet) was developed to improve the dissolution of BCS class II oral chemotherapeutic agents.

MATERIALS AND METHODS

Materials

Dasatinib monohydrate was purchased from MedChem Express (Monmouth, NJ, USA); USP-compliant zein from Qingdao Sigma Chemicals Co., Ltd. (Qingdao, China); fasting-and fed-state simulated gastric fluid (FaSSGF and FedSSGF) media from Biorelevant (London, UK); and magnesium stearate, HPMC, ethyl cellulose (EC), and lactose from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals and solvents were obtained from Sigma-Aldrich (St. Louis, MO, USA), were of analytical grade, and were used without further purification.

Methods

Preparation of Zein–HPMC SDs

A spray drying-based solvent evaporation method was used to prepare SDs [26]. To evaluate the improvement in the dissolution rate of the SDs, different ratios of each polymer were used **(Table 1)**; this was to investigate the role of the different ratios in achieving a controlled release rate from the tablets. Zein (a hydrophobic polymer) was slowly dissolved in 90% ethanol, under magnetic stirring (LabTech, Seoul, Korea), to obtain a translucent solution. HPMC 4000 (a hydrophilic polymer) was slowly injected into hot water (60 °C) to form a swelling polymeric solution, which was then transferred to cold water (-4 °C) and mixed until a transparent solution was formed. Dasatinib was dispersed into the two solutions under continuous stirring for 30 min. Finally, all the components were placed in a mini spray dryer (Buchi, Flawil, Switzerland) at predetermined settings. The prepared solid mass of SD was stored in a desiccator until further use.

Table 1. Compositions of different powders used in SD preparation.

SD No.	Zein (mg)	HPMC (mg)	Dasatinib (mg)	Total (mg)	Ratio
SD1	30	-	20	50	3:0:2
SD2	-	30	20	50	0:3:2
SD3	15	15	20	50	1.5:1.5:2
SD4	20	10	20	50	2:1:2

Abbreviations: SD, solid dispersion; HPMC, hydroxypropyl methylcellulose; and mg, milligram.

Preparation of drug–excipient powder blends

Excipient powders were sieved using a vibratory sieve shaker (Preiser Scientific, St Albans, WV, USA; sieve No. 40 and 60) to reduce the particle size and eliminate any large, non-uniform particles outside the 150–426 µm threshold. They were then weighed separately on an electronic balance (Mettler Toledo, Columbus, OH, USA) according to the suitable tableting quantities required. The excipient powders were mixed using an automatic V-blender (ERWEKA GmbH, Langen, Germany) for 10 min and placed in the b290 mini spray dryer at predetermined conditions. Finally, the powder blends of SDs were added to the spray-dried co-excipients for 5 min. The compositions of all the blends are listed in **Table 2**.

Table 2. Compositions of the prepared dasatinib-zein SD tablets

	Formulations				
Component (mg)	F1	F2	F3	F4	F5
SD1 (zein + dasatinib)	80	-	-	-	-
SD2 (HPMC + dasatinib)	-	80	-	-	-
SD3 (zein + HPMC + dasatinib)	-	-	80	-	-
SD4 (zein + HPMC + dasatinib)	-	-	-	80	-
Ethylcellulose	7	7	7	7	9.5
Lactose	12.5	12.5	12.5	12.5	90

Magnesium stearate	0.5	0.5	0.5	0.5	0.5

Abbreviations: SD, solid dispersion; HPMC, hydroxypropyl methylcellulose

Particle size measurement

The particle size of each SD powder blend was determined using laser diffraction (Zetasizer Nano, Malvern, UK). Each spray-dried powder blend was added to a cuvette that was filled and mixed with phosphate-buffered saline. All measurements were performed in triplicate.

Tablet preparation

Tablets were directly compressed [20]. Briefly, the quantities of each component **(Table 2)** were obtained from the automatic V-blender, and the tablets were accurately weighed using the electronic balance (Mettler Toledo). The powders were compressed using an ERWEKA GmbH instrument (Germany) with a force of 60–80N and round punches. The lubricant magnesium stearate was added to the mixture in the final step.

Tablet hardness, thickness, and tensile strength

The dimensions of individual tablets were measured using a Vernier caliper (Swastik Scientific, Mumbai, India); the hardness of individual tablets (from the different formulations) **(Table 2)** was determined 24 h after compression (allowing for stress relaxation) using a tablet hardness tester (Horsham, Mecmesin, UK), which applies force from two oppositely situated metal anvils. The digital screen displayed the hardness required to break the tablets in kg/cm^2. The tensile strength (T) of each tablet was calculated using the formula:

$$T = \frac{0.0624\ X\ Hardness\ (P)}{Diameter(\mathrm{D}) X\ Thickess\ (L)} \quad (1)$$

Tablet friability

This test measured the friability of the tablets by determining the percentage weight loss during the rotations inside a Roche friabilator (Copley, Nottingham, UK) [30-33]. Twenty pre-weighed tablets were initially placed in the friabilator. The friabilator was then rotated 100 times over 4 min. Once finished, the tablets were gathered, dusted, and reweighed, and this value was considered the final weight. Percentage weight loss was calculated using the formula:

$$\text{Percentage of weight loss } = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \quad (2)$$

Tablet weight variation

For each formulation type **(Table 2)**, 20 tablets were randomly selected and weighed individually using the electronic balance (Mettler Toledo), from which the average weight was determined. The average weight was calculated, and the weight of the individual tablet was compared to the average weight. The upper and lower limits at % and double % differences were calculated and compared to the individual weights of the tablets.

Drug content analysis

A validated UV spectrophotometer was used to analyze the dasatinib content in the tablets [27]. First, a calibrated standard curve for dasatinib was used as the reference. A stock standard solution containing dasatinib was prepared by dissolving 100 mg of the pure drug in 250 mL acetic acid in a calibrated flask. The working solution (0.04% w/v) was used for spectrophotometric analysis (S-2150UV spectrophotometer, Dayton, NJ, USA). Briefly, different aliquots of the standard drug solution were transferred into calibrated flasks that contained 3 mL of acetate buffer (pH 4) and 1% Triton X-100 and mixed well. Absorbance was measured at 323 nm against a blank. The absorbance values were plotted against the drug concentrations to obtain a calibration curve. The tablets were then crushed and mixed thoroughly in 70 mL of acetate buffer (pH 4) and 1% Triton X-100 (Sigma-Aldrich). The resultant solution was filtered using filter paper (Hawach Scientific, Xi'an City, China), and 1 mL of the filtrate was collected and diluted to obtain the desired concentration of 10 µg/mL.

Tablet disintegration

Six tablets of each formulation **(Table 2)** were placed inside different tubes of a basket disintegration test apparatus (Caleva, Struminster, UK). The baskets were then placed inside beakers containing a suitable volume

of distilled water and FaSSGF and FedSSGF media at 37 ± 0.5 °C. The time required for full tablet disintegration was recorded.

In vitro dissolution studies

This experiment was performed using a USP dissolution tester apparatus II (PTWS 820-MA; Hainberg, Germany). The paddle was rotated at 60 rpm at 37 ± 0.5 °C. Each type of tablet presented in **Table 2** was exposed separately to 900 mL of FaSSGF and FedSSGF media, and distilled water was used as the control. Samples of 5 mL for each tablet type were withdrawn at predetermined intervals (starting from 0 min until 60 min) and replaced with fresh medium to maintain a constant dissolution volume. To filter the withdrawn samples, a Whatman filter paper grade 1 was used. The concentration of dasatinib was analyzed using spectrophotometry model S-2150UV (Dayton, NJ, USA), and expressed as a percentage of the drug dissolved.

Statistical analysis

The results were acquired in triplicate and analyzed using the student's *t*-test or one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison procedure, using Prism GraphPad version 7.3.1 for Windows (GraphPad Software, San Diego, CA, USA). The results are presented as the mean ± standard deviation (n = 6). Statistical significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

Preparation of Zein–HPMC SDs and excipients

Zein and HPMC were added to achieve a high degree of dasatinib dissolution in the gastric environment. HPMC also acts as a super disintegrant [17-19]. Spray drying has been used successfully to produce excipients with superior properties compared to physical mixtures. In this study, the excipients used were well-known components of most co-processed excipients; they are considered excellent and directly compressible excipients [20, 21]. Zein was used as the hydrophobic portion of SD, while HPMC was the hydrophilic portion and disintegrant. EC, lactose, and magnesium stearate were used as the binder, filler, and lubricant, respectively.

Particle size analysis

Drug particle size is known to notably affect drug dissolution rate, thus size reduction is important. **Table 3** shows the particle size distributions of the various preparations composed of zein SDs and zein SDs/excipients. The particle size distributions of the spray-dried powder blends were significantly smaller than those of the physical mixture. It was observed that the range of the physical mixtures of all the formulations was 262.4 ± 3.5 and 539.2 ± 0.5 µm, which was further reduced to 107.3 ± 3.1 and 190.5 ± 0.5 µm when the physical mixtures were spray dried. There was a significant difference (P=0.002) in favor of all the spray-dried preparations, regardless of the compositions.

Table 3. Particle size distribution of the zein SDs and zein SDs/excipients (mean± SD, N = 3)

Preparations	Particle Size (µm) Physical Mixture of Powder	Particle Size (µm) Spray-Dried Powder
F1	310.5 ± 1.4	190.5 ± 0.5*
F2	420.3 ± 1.2	107.3 ± 3.1*
F3	343.6 ± 3.4	129.3 ± 3.4*
F4	539.2 ± 0.5	152.9 ± 2.7*
F5	262.4 ± 3.5	160.2 ± 1.5*

*Mean P-value was found to be equal to 0.002 or less

Abbreviation: SD, solid dispersion

Tablet hardness, thickness, and tensile strength

The average hardness of the zein tablets was similar to the official range of hardness stated in the USP guidance, which is not less than 4 kg of pressure required to break a tablet [27, 28, 30, 34]. The average thickness of the dasatinib tablets was also following the USP guidelines. The tensile strength of the formulations showed an average of 1.02 ± 2.1 to 2.13 ± 3.1 MPa, as shown in **Table 4**.

Table 4. Zein SD tablets' hardness, thickness, tensile strength, and friability (mean ± SD, N =3)

Tablet	Hardness (kg)	Thickness (mm)	Tensile Strength (MPa)	% Friability
F1	2.9 ± 1.5	5.2 ± 0.3	1.02 ± 2.1	3.80 ± 1.55
F2	4.1 ± 0.5	5.2 ± 0.3	2.13 ± 3.1	1.20 ± 0.75
F3	3.4 ± 0.4	5.2 ± 0.3	1.83 ± 1.2	0.71 ± 0.15
F4	3.5 ± 0.2	5.2 ± 0.3	1.89 ± 2.1	0.82 ± 0.42
F5	3.7 ± 0.2	5.2 ± 0.3	1.42 ± 1.2	1.32 ± 0.45

Abbreviation: SD, solid dispersion

Tablet friability

Table 4 shows the average percentage of weight loss for each tablet type. Only the tablets containing HPMC alone or excipients were found not to be compliant with the permissible USP guidelines (less than 1%). In contrast, the F3 and F4 tablets were within the permitted USP range of friability, as reported previously [31-33].

Tablet weight variations and drug content assay

A weight variation test was performed to ensure tablet uniformity [31]. The weight variation test indicated that the average weight of the tablets was in accordance with the USP requirement that no more than two tablets out of 20 tablets should cross a ±10% deviation **(Table 5)**. Similarly, the zein SD tablets were within the range of the upper and lower limits, where the average weights of 20 tablets of F3 and F4 (containing dasatinib with different ratios of zein and HPMC) were 106.5 ± 0.41 and 103.7 ± 0.24 mg, respectively. This indicated a statistically significant difference between the two formulations in favor of F4 ($P < 0.02$). However, both formulations were within the allowable limits for tablet weight in accordance with the UPS recommendations.

Table 5. Zein SD tablets' weight variations and drug content (mean ± SD, N = 3)

Tablet	Weight (mg)	% Drug Content	Disinteg. Time (min) D.W.	Disinteg. Time (min) FaSSGF	Disinteg. Time (min) FedSSGF
F1	112.9 ± 0.32	90.16 ± 1.45	98.1 ± 2.95	60.2 ± 5.7	50.9 ± 3.1
F2	134.1 ± 0.11	92.14 ± 1.56	25.2 ± 5.67	41.6 ± 4.3	30.5 ± 2.2
F3	103.7 ± 0.24	94.11 ± 3.45	75.5 ± 3.30	40.3 ± 4.2	35.5 ± 3.6
F4	106.5 ± 0.41	93.21 ± 1.25	71.7 ± 5.70	50.5 ± 2.7	39.1 ± 2.9
F5	109.3 ± 0.51	4.20 ± 1.20	15.8 ± 2.30	10.5 ± 3.7	13.5 ± 3.3

[1] Abbreviations used in Table 5: Disinteg. Time, disintegration time; D.W., distilled water; FaSSGF, fasted-state simulated gastric fluid; FedSSGF, fed-state simulated gastric fluid.

Dasatinib content was measured using a validated UV spectrophotometer. The percentage drug contents of all the tablets (except F5, which contained no drug at all) were found to be in the range of 90.16 ± 0.45 to 94.11% of the expected drug content, which was within the acceptable USP limit [31, 32], as shown in **Table 5**.

Tablet disintegration assay

The disintegration behaviors of the produced tablets in the fasted and fed-state gastric media are shown in **Table 5**. Gastric media in both states (fasted and fed) were used because dasatinib is a weak base that dissolves well in acidic pHs and precipitates in the small intestine [5-9, 32, 33, 35]. All the tablets that contained zein required a longer time to disintegrate in distilled water compared to those that contained HPMC only (F2) or excipients only (F5). In contrast, the disintegration time was significantly reduced in the tablets containing zein and HPMC SDs, in both states of the simulated gastric media **(Table 5)**.

In vitro dissolution studies

In vitro drug dissolution studies were used to simulate the in vivo behavior of the tablets to predict the in vivo performance if the conditions of the studies are feasible [30, 33, 35]. The dissolution profiles of pure dasatinib and zein-HPMC-based SDs in different media are shown in **Figure 2**. In distilled water, the F1 tablets, which contained zein SDs (without HPMC), showed the lowest percentage release rate (approximately 15.2% ± 2.5). The same formulation showed a release rate that more than doubled over time (43.7% ± 8.3 and 47.7% ± 8.3, respectively) when placed in both gastric simulated media **(Figure 2a)**. In contrast, the F2 tablets containing

HPMC SDs alone showed increasingly higher percentages of release over time in all the media and reached an average of more than 90% by the end point of the experiment, as shown in **Figure 2b**. Meanwhile, the F3 tablets, which were composed of SD3 (zein and HPMC SDs in the ratio of 1.5:1.5:2) and dasatinib, demonstrated significantly improved release characteristics over time in both states of the gastric medium. The percentage of dasatinib release reached 76.70% ± 2.60, 76.70% ± 13.6, and 79.70% ± 10.45 in DW, FaSSGF, and FedSSGF, respectively, by the end of 60 min. Similar results were observed with the F4 tablets, which contained zein and HPMC SDs in the ratio of 2:1:2, and dasatinib, which achieved more than 80% drug release in both states of the gastric medium. Although the dissolution rate improved in the DW medium for all the formulations, a better dissolution rate was still observed in both states of the gastric medium.

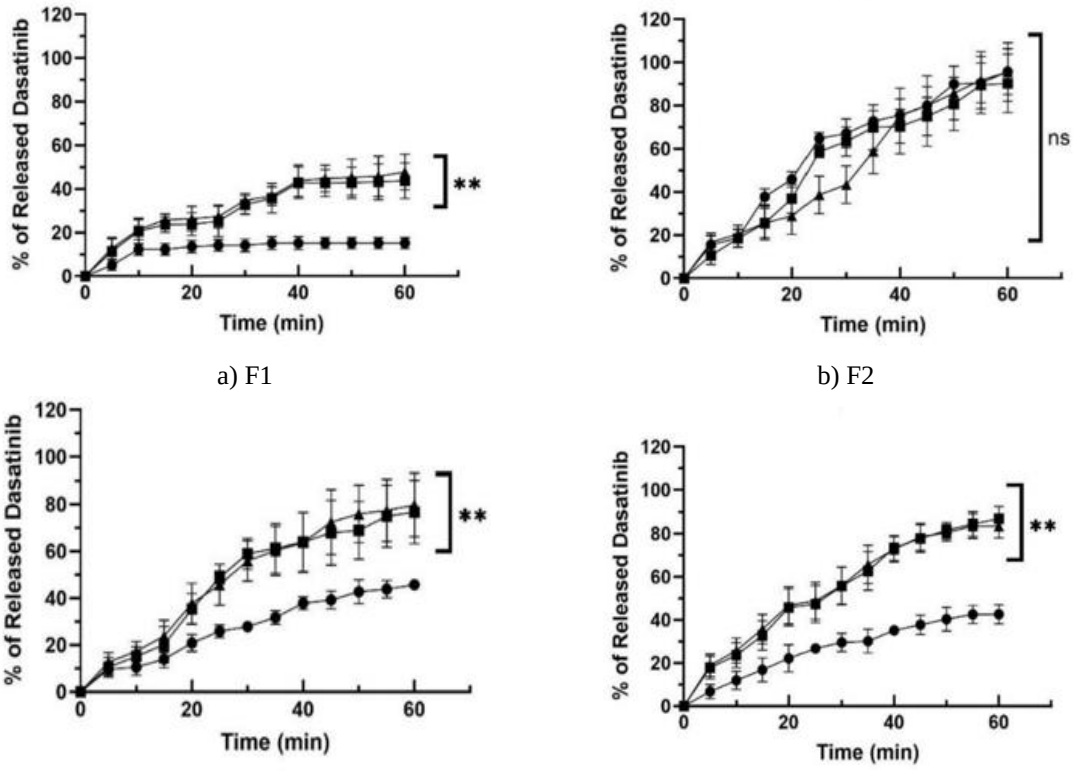


Figure 2. Dissolution profile of zein–HPMC SD tablets containing dasatinib. ns= no significant difference between the formulations. ** mean P-value < 0.05.

Solid dispersion is a well-known technique used to improve poor drug dissolution and bioavailability, particularly in drugs used for cancer treatment [10-16]. However, SD components play a major role in the treatment effect. Herein, natural hydrophobic prolamin zein, accompanied by hydrophilic HPMC, was utilized to prepare spray-dried SD powders. Different ratios of both components were used to determine the optimal ratio that would yield the most desirable characteristics. Zein is a promising natural pharmaceutical excipient because of its unique alcohol solubility and poor aqueous solubility, which consequently provides flexible deformation in polar solvents [28]. Furthermore, zein can reduce the photolytic degradation of the drug and lessen the harsh gastric pH [27, 28]. Conversely, HPMC is a well-known biodegradable hydrophilic polymer used to enhance the solubility of active pharmaceutical ingredients (APIs). Herein, it also contributed to further enhancing the compatibility of the co-processed excipients. Both zein and HPMC were added to achieve a high degree of controlled dasatinib release in the intestinal environment. Moreover, an excipient combination was added to the SD mixtures during the spray-drying process to produce more stable co-processed excipients with enhanced properties compared to the physical mixture. The excipients used herein were excellent directly compressible excipients [20, 22]. The excipients included a binder, filler, and lubricant, which facilitated the compaction process and enhanced the physical stability of the tablets.

The spray-drying technique is commonly used to produce typically small particles (10–100 μm), which allows them to rapidly disperse in a proper medium [10-16]. In all the preparations, the average sizes of the different zein

SDs prepared by spray-drying were less than half of those of the physical mixture, indicating a significant size reduction, compared to the physical mixture, of the SD blends. The smaller particle size of the spray-dried zein–HPMC SD powders compared to the physical mixtures agrees with the literature, which notes that the spray-drying technique reduces agglomerated particle size [11, 12]. Consequently, this increases the surface area of the SDs to be occupied by the co-processed excipients. Therefore, the small particle sizes of the various zein–HPMC SDs successfully facilitated the disintegration and dissolution of dasatinib.

The blends of zein–HPMC SDs and other excipients were evaluated for hardness, thickness, tensile strength, and friability. The various types of tablets were mostly within acceptable USP limits as reported in several studies [27, 28, 30, 34]. This indicated that the zein–HPMC SD tablets were mechanically stable **(Table 5)**. However, the tablets containing HPMC alone or excipients were not compliant with the permissible USP guidelines for tablet friability (less than 1%) [28, 30-32, 34]. Conversely, the F3 and F4 (containing different ratios of zein and HPMC) tablets were able to withstand the mechanical stress produced during the friability test. Collectively, the current data support the feasibility of zein as a suitable matrix for tablets [27, 28, 30, 34]. However, zein cannot be used as an excipient on its own and requires other functional excipients to improve tablet integrity. Therefore, other components or excipients must be included in zein formulations.

The results of all the developed formulations were within the acceptable ranges reported in the official compendia **(Tables 4 and 5)**. This indicated the consistency of tablet compression between the tablets, which may be due to the stability of the spray-dried SD powder blends used herein. Generally, the tablet weight had a direct influence on the drug content within the tablets, which was reflected in the similarly high content of dasatinib in all the formulations (except F5) **(Table 5)**. This result also indicated that the SD powder blend, dasatinib, and excipient distributions were homogenous [10, 11]. The disintegration times obtained for all the formulations were significantly different, depending on the medium used for the disintegration test. The disintegration time was shortest in the following order: FedSSGF medium > FaSSGF > DW. This order is compatible with the fact that zein is poorly soluble in water, but it seems that the zein–HPMC SDs and other excipient blends enhanced the disintegration of all the formulations. Contrastingly, the disintegration of all the formulations was significantly reduced in both states of the gastric simulated media (fasted and fed), but the formulations favored the fed state, where disintegration occurred in <40 min. This substantially shorter disintegration time of the tablets prepared using the zein and HPMC complex implied that the formation of a solid dispersion of zein and HPMC facilitated de-agglomeration and did not prevent acidic media ingress. It appears that this composition of tablets favors fasted-state disintegration more than fed-state disintegration.

The dissolution profiles of all the tablets were analyzed **(Figure 2)**. Owing to the low solubility of zein and dasatinib in aqueous media, it was expected that a low percentage of release would be achieved in the DW medium compared to that in the other gastric media. However, the combination of the zein–HPMC SD with suitable excipients significantly improved release across all the aqueous and gastric media used herein. A comparison of the F1 and F2 formulations indicated that the inclusion of water-soluble HPMC in the zein SD (F2) successfully enhanced the dissolution rate of dasatinib. This is because of the higher solubility of HPMC in water, along with some of the other excipients used herein. The presence of zein–HPMC SDs in the F3 and F4 formulations improved their dissolution profiles, which demonstrated a gradual increase within the first 45 min, regardless of the zein amount used. Generally, the trend for the dissolution rate was similar to that of disintegration in terms of favoring the fed-state gastric medium. However, increasing the amount of zein can adversely prolong the dissolution, which in turn limits the extensive use of zein as an excipient.

CONCLUSION

From the present study, it can be concluded that the solubility of the oral chemotherapeutic dasatinib can be successfully improved by formulating the drug into a solid dispersion that includes zein, HPMC, and other excipients. Hence, zein–HPMC SD may be considered a suitable alternative for formulating poorly soluble therapeutic agents into tablets that have improved gastric absorption, which is a requirement for enhanced bioavailability.

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