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Drug Release Pattern of Oral Dual-Release Pellets Through the Gastrointestinal Tract: Case Example of Diclofenac Sodium

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ABSTRACT

The purpose of this research was to evaluate the release pattern of the dual-release pellets of diclofenac sodium (DS), coated with enteric- and sustained-release layers, in dissolution media that resemble the physiological variables of the gastrointestinal (GI) fluid. Dissolution testing in three pH stages (acidic, intermediate, and basic) was conducted using USP apparatus I (basket) rotating at 100 rpm. The acidic pH stage resembles the gastric fluid during fasted and fed states, the intermediate pH stage resembles the fluid of the proximal small intestine (duodenal fluid), and the basic pH stage resembles the fluid of the small intestine during fasted and fed states and distal GI. DS pellets showed excellent gastric resistance in the acidic pH stage for 2 h. In the intermediate pH stage, DS pellets showed a gastric resistance for 2 h, followed by a low percent of DS release thereafter (15.2% after 10 h). DS release was accelerated in the basic pH stage, particularly in pH media 6.5–7.2. This is because the enteric-coated film starts to dissolve at pH > 5.5. In addition, DS release was influenced by the buffer capacity (β)/ionic strength (I) of the dissolution media, where DS release increased with increasing β/I of phosphate buffers (pH 6.8) up to a concentration of 50 mM and then decreased at 100 mM. These dissolution results corroborated with equilibrium solubility data and sink conditions (*S* values) of DS in the media of the three pH stages. This study provides an insight into the release pattern of the dual-release DS pellets throughout the GI tract to better correlate the in vitro release data of these pellets to those in vivo.

KEYWORDS: Dual-release pellets, diclofenac sodium, enteric-coated layer, sustained-release layer, dissolution

INTRODUCTION

Diclofenac sodium (DS) is a potent non-steroidal anti-inflammatory drug (NSAID) used in pain management (*1*). It exerts its action by inhibiting cyclooxygenase-1 and cyclooxygenase-2 (*2*). Due to the gastrointestinal (GI) adverse events of DS, ranging from dyspepsia to acute and chronic GI ulcer, DS is commonly administered in enteric-coated formulations (*3*). Furthermore, to maintain the analgesic effects of DS for longer periods of time, which is clinically important, DS is preferred to be administered in sustained-release formulations (*4*, *5*).

Recently, a combination of immediate-, enteric-, or sustained-release patterns of pain management drugs delivered in one pharmaceutical dosage form has been of interest (*1*, *6*, *7*). This is because these dosage forms can enhance patient compliance and manage the pain in a controlled manner. For instance, Elzayat et al. prepared multi-layered tablets of diclofenac potassium, which offer both immediate- and sustained-release patterns (*1*). In addition, once-a-day controlled release tablets of aceclofenac were developed using the bilayered dual-release strategy (*6*). Furthermore, ketoprofen pellets with a pH-responsive dual-pulse were designed to release the drug at pH > 5.5 after 2 h (first pulse) and at pH > 7.0 after 5 h (second pulse) (*7*).

A dual-release strategy of DS pellets, filled into capsules, has been introduced to the market. Each capsule contains 25 mg DS in enteric-coated pellets and 50 mg DS in sustained-release pellets (*1*). This dual-release strategy combines fast- and sustained-release patterns, where the mean plasma concentration is reached within 1 h after oral administration with a sustained analgesic effect thereafter (*8*). The enteric-coated pellets offer a safety profile by limiting the GI adverse events of DS. The DS sustained-release pellets provide better pain control with less dosing frequency, thus enhancing patient compliance.

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Two polymers of different release properties were used in the preparation of the dual-release DS pellets. The first polymer is Eudragit L 100, which is an anionic copolymer of methacrylic acid and methyl methacrylate of 1:1 ratio. Eudragit L 100 is a gastro-resistant polymer which is insoluble in the gastric fluid; however, it is soluble in the intestinal fluid, allowing release of the drug (*9*). The second polymer is Eudragit RL or Eudragit RS (acrylic and methacrylic esters), which is insoluble in water and GI fluid, pH-insensitive, and swells and controls the release of the drug by diffusion (*10*).

The compendial dissolution testing for enteric-coated formulations of DS involves two stages. In the first stage, dissolution testing is carried out in acidic medium which resembles the gastric fluid and composed of 0.1 N hydrochloric acid (HCl) for 2 h. In the second stage, dissolution testing is performed in basic medium that resembles the intestinal fluid (phosphate buffer [PB], pH 6.8) for another 45 min. In sustained-release formulations of DS, dissolution testing is performed in PB medium (pH 7.5) for up to 24 h.

The wide range of the physiological variables of the GI tract (specifically pH range of 1.2–7.2, buffer capacity (β) range of 0.003–0.030 M/ΔpH, and ionic strength (I) of 0.051-0.166) from the stomach to the small intestine can markedly alter the release pattern of drugs from the enteric- and sustained-coated pellets (*11–16*). This suggests that a single dissolution medium that represents either the gastric or intestinal condition of the GI fluid may not be physiologically sufficient to study the release pattern of drugs from dosage forms prepared with different coating-forming polymers. This results in a discrepancy between the in vitro and in vivo performances of the enteric- and sustained-coated pellets that are frequently reported in literature (*16*, *17*).

Therefore, the purpose of the present research was to investigate the enteric efficiency and sustained-release pattern of the dual-coated enteric- and sustained-release DS pellets in dissolution media that resembles the acidic pH condition in the stomach, the intermediate pH condition in the proximal GI, and the basic pH condition in the small intestine, with various physiological variables (pH, β, and I).

MATERIALS AND METHODS

Materials

DS (USP 40, 99.7% purity, 0.01% total impurity, lot no. DS/1804/0145A; Amoli Organics, Mumbai, India) was given as a gift from Tabuk Research Center (Amman, Jordan). DS pellets (75 mg DS) were purchased from the local market. No further confirmatory methods were done in our laboratory to substantiate the content uniformity of DS pellets, where the label claim of 75 mg DS was considered. All other chemical reagents were of analytical grade. Double-distilled water was used in preparing the dissolution media.

Media Used in Three-Stage Dissolution Testing of DS Pellets

Three-stage dissolution testing was carried out for DS pellets employing blank acidic, intermediate, and basic pH media, where pepsin, pancreatin, lecithin, and sodium taurocholate were not added to the media.

The acidic pH stage, which resembles dissolution of DS pellets in the stomach, includes dissolution media of 0.1 N HCl, simulated gastric fluid sine pepsin (SGFsp), fasted-state simulated gastric fluid (blank FaSSGF), and fed-state simulated gastric fluid (blank FeSSGF). The intermediate pH stage, which resembles dissolution of DS pellets in the duodenal fluid, includes acetate buffer (pH 4.5). The basic pH stage, which resembles dissolution of DS pellets in the small intestine, includes dissolution media of fasted-state simulated intestinal fluid (blank FaSSIF), fed-state simulated intestinal fluid (blank FeSSIF), simulated intestinal fluid sine pancreatin (SIFsp), PB 6.25–100 mM (pH 6.8), and PB 100 mM (pH 7.2). The composition of the dissolution media was previously described (*18*, *19*). Table 1 illustrates the physiological variables (pH, β, and I) of the media employed in the solubility/dissolution testing of the acidic, intermediate, and basic pH stages.

Equilibrium Solubility Study of DS

The equilibrium solubility study of DS was conducted in media employed in the acidic, intermediate, and basic pH dissolution stages for equilibration times of 6, 24, and 48 h to ensure that the equilibrium solubility had been reached (*20*). Briefly, excess amount of DS was added into 3 mL of each medium. Samples were incubated in a shaker water bath at 37 ± 1 °C. After each time interval, samples were centrifuged and the pH of the supernatant was reported for each sample. Supernatants were diluted appropriately using the tested medium. Samples were analyzed using UV/VIS spectrophotometer (Cary 50, Varian, Palo Alto, CA, USA) at a peak maximum (λ_{max}) of 275 nm as described (*21*). The concentration of DS in each sample was determined using standard calibration curves of DS prepared in the corresponding medium of concentrations ranging between 0.002 and 0.020 mg/mL. The calibration graphs were linear with absorption ranging between 0.050 and 0.750. The resulting concentration was then multiplied by the dilution factor. For each medium, the

Table 1. Physiological Variables (pH, β, and I) of Media Employed in Acidic, Intermediate, and Basic pH Dissolution Testing

Dissolution Media	pH	β (M/ΔpH)	I (M)
Acidic pH Stage			
0.1 N HCl	1.2 ± 0.1	-	0.084
SGFsp	1.2 ± 0.1	-	0.118
Blank FaSSGF	1.6 ± 0.1	-	0.070
Blank FeSSGF	5.0 ± 0.1	0.025	0.273
Intermediate pH Stage			
Acetate buffer	4.5 ± 0.1	0.034	0.037
Basic pH Stage			
Blank FaSSIF	6.5 ± 0.1	0.120	0.020
Blank FeSSIF	5.0 ± 0.1	0.130	0.304
SIFsp	6.8 ± 0.1	0.034	0.072
PB 6.25 mM	6.8 ± 0.1	0.003	0.013
PB 12.5 mM	6.8 ± 0.1	0.006	0.025
PB 25 mM	6.8 ± 0.1	0.012	0.050
PB 50 mM	6.8 ± 0.1	0.024	0.100
PB 100 mM	6.8 ± 0.1	0.047	0.200
PB 100 mM	7.2 ± 0.1	0.058	0.244

β: buffer capacity; I: ionic strength; M: molar; HCl: hydrochloric acid; SGFsp: simulated gastric fluid sine pepsin; blank FaSSGF: blank fasted-state simulated gastric fluid; Blank FeSSGF: blank fed-state simulated gastric fluid; Blank FaSSIF: blank fasted-state simulated intestinal fluid; Blank FeSSIF: blank fed-state simulated intestinal fluid; SIFsp: simulated intestinal fluid sine pancreatin; PB: phosphate buffer; mM: millimolar.

solubility measurements were performed in at least triplicate and the mean values of the equilibrium pH and equilibrium solubility were reported. The sink condition (S) of DS in each dissolution medium was calculated with the following equation: $S = C_S / C_D$; where C_S is the equilibrium solubility of DS in the acidic, intermediate, and basic pH media reached after 24 h, and C_D is the concentration of DS in 1000 mL of the acidic, intermediate, and basic pH media (0.075 mg/mL). The sink condition is considered maintained when the *S* value is > 3 (*22*).

Dissolution Studies

Dissolution studies were performed using a VK 7000 USP apparatus I fitted with an auto-sampling station consisting of a VK810 peristaltic pump, VK750 digitally controlled heater/circulator, and a UV/VIS spectrophotometer (Varian). Baskets were rotated at 100 rpm. DS pellets were subjected to two dissolution tests. In the first dissolution test, one capsule containing the DS pellets was placed in each dissolution vessel containing 1000 mL of the acidic and intermediate pH media, maintained at 37.0 ± 0.5 °C for 2 h. Samples were withdrawn at 0, 30, 60, 90, and 120 min and passed through a 45-µm polytetrafluoroethylene (PTFE) filter (SUN-Sri, Rockwood, TN, USA). In the second dissolution test, one capsule containing the DS pellets was placed in each dissolution vessel containing 1000 mL of the intermediate and basic pH media, maintained at 37.0 ± 0.5 °C for 10 h. Samples were withdrawn at predetermined time intervals (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 10 h). The volume of the withdrawn samples during the dissolution studies was not replaced. This is because the auto-sampling station pulls the sample into the flow cell and then returns it to the vessel after measuring the absorbance of the sample. The absorption of the samples was measured at λ_{max} 275 nm as described in (*21*, *23–25*). The cumulative percent release of DS in the three pH stage dissolution media was calculated against standard calibration curves of DS prepared in each corresponding medium. Dissolution profiles were constructed by plotting the cumulative percent release of DS versus time (min or h). The similarity or dissimilarity between the dissolution profiles was determined using the similarity factor (f_2) calculated with the simple model independent approach, where dissolution profiles are deemed similar when f_2 is in the range of 50–100 and dissimilar when $f_2 < 50$ (26).

Statistical Analysis

A *t* test was used to compare the means of DS solubility after 24 and 48 h using GraphPad. A $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Equilibrium Solubility of DS

DS is a weakly acidic BCS class II drug that is characterized by its low solubility in the acidic pH and high solubility in the basic pH (*27*). The solubility study of DS was performed in the three pH-stage dissolution media for equilibration times 6, 24, and 48 h.

The solubility of DS in acidic and intermediate pH media was negligible. It is expected that no release of DS should take place in these media due to the enteric-coated layer of pellets. The negligible solubility of DS in these low pH media is in accordance with Kincl et al. who showed that the solubility of DS depends on the pH and that DS is practically insoluble in acidic media and acetate buffer pH 4.5 (*21*).

In basic pH media, the solubility of DS increases due to the high pH (Table 2), aligning with Chuasuwan et al. who found that the solubility of DS increases gradually from pH 1.2 to 8.0 (*27*). Due to the low pH of blank FeSSIF (pH 5.0), the solubility of DS was negligible after 6 h, attaining less than 0.1 mg/mL after 24 and 48 h. Furthermore, although the solubility of DS was high in PB 6.25–50 mM (pH 6.8),

Table 2. Equilibrium Solubility of DS and Equilibrium pH of Basic pH Media at 6, 24, and 48 h

Media	Initial pH	Equilibration Time (h)	Equilibrium Solubility (mg/mL)	*p*-value of DS Solubility (24 h vs 48 h)	Equilibrium pH	S value (24 h)
Blank FaSSIF	6.5 ± 0.1	6	3.6 ± 0.3	0.207	7.2 ± 0.1	78.7
		24	5.9 ± 0.2		7.1 ± 0.0	
		48	6.2 ± 0.4		7.1 ± 0.1	
Blank FeSSIF	5.0 ± 0.1	6	-	N/A	-	< 1.3
		24	< 0.1		5.4 ± 0.0	
		48	< 0.1		5.4 ± 0.0	
SIFsp	6.8 ± 0.1	6	3.1 ± 0.1	0.379	7.5 ± 0.1	61.3
		24	4.6 ± 0.3		7.4 ± 0.0	
		48	4.9 ± 0.5		7.4 ± 0.0	
PB 6.25 mM	6.8 ± 0.1	6	18.6 ± 0.1	0.069	7.7 ± 0.1	293.3
		24	22.0 ± 0.4		7.9 ± 0.0	
		48	21.5 ± 0.4		7.7 ± 0.0	
PB 12.5 mM	6.8 ± 0.1	6	14.4 ± 0.9	0.694	7.8 ± 0.0	316.0
		24	23.7 ± 0.5		7.8 ± 0.0	
		48	23.6 ± 0.2		7.8 ± 0.1	
PB 25 mM	6.8 ± 0.1	6	7.0 ± 0.5	0.350	7.4 ± 0.0	109.3
		24	8.2 ± 0.3		7.5 ± 0.0	
		48	8.5 ± 0.4		7.5 ± 0.0	
PB 50 mM	6.8 ± 0.1	6	3.4 ± 0.2	1.000	7.5 ± 0.0	100.00
		24	7.5 ± 0.6		7.4 ± 0.0	
		48	7.5 ± 0.4		7.4 ± 0.1	
PB 100 mM	6.8 ± 0.1	6	1.3 ± 0.1	0.065	7.2 ± 0.0	52.0
		24	3.9 ± 0.2		7.3 ± 0.1	
		48	3.5 ± 0.2		7.2 ± 0.0	
PB 100 mM	7.2 ± 0.1	6	4.8 ± 0.2	0.630	8.4 ± 0.0	133.3
		24	10.0 ± 0.4		8.4 ± 0.0	
		48	9.9 ± 0.2		8.3 ± 0.0	

DS: diclofenac sodium; S value: sink condition; Blank FaSSIF: blank fasted-state simulated intestinal fluid; Blank FeSSIF: blank fed-state simulated intestinal fluid; SIFsp: simulated intestinal fluid sine pancreatin; PB: phosphate buffer; mM: millimolar.

it decreased in PB 100 mM (pH 6.8) due to high buffer concentration. This can be explained by the common ion effect, where the presence of high concentration of the common ion (Na^+) reduces the dissociation and hence the solubility of the sodium salt of acidic drugs (*28*). This is also in agreement with Kincl et al. who found that the solubility of DS in buffer solutions of higher ionic strengths and same pH was lower than in that at lower ionic strengths (*21*).

Data showed that the solubility of DS after 6 h was lower compared to that after 24 and 48 h, where more DS is being solubilized after 6 h. This indicates that the 6 h-time period was not adequate for the equilibrium to be reached. Moreover, no significant difference was found between the solubility of DS at 24 and 48 h ($p > 0.05$, Table 2), indicating that equilibrium has been reached after 24 h. This is in agreement with Kincl at el., who determined the solubility of DS in aqueous media that mimic the GI fluid for an equilibration time of 24 h (*21*).

The equilibrium pH, which is the pH of the supernatant of the solubility samples at the three equilibration times (6, 24, and 48 h) in basic pH media, are summarized in Table 2. There was an increase in the equilibrium pH for all basic pH media after 6, 24, and 48 h. This is in agreement with Plöger et al. who found that using excessive amounts of drug to determine the equilibrium solubility can lead to a change in the pH of the buffer solutions, particularly if the drug has a weak acidic or basic property (*29*). This is because the resultant high concentration of dissolved drug would likely exceed the buffer capacity of the small-volume media (*29*). DS is a weakly acidic drug; the sodium salt would increase the pH as it is the conjugate base of the weak acid. The equilibrium pH can be used as an indicator to determine the equilibration time. The equilibrium pH for the basic pH media was the same for the supernatants after 24 and 48 h, indicating that the equilibrium has been achieved after 24 h (*30*).

Sink condition was calculated for the solubility measurements after 24 h. Sink condition was maintained in all basic pH media ($S > 3$). However, in acidic and intermediate pH media, sink condition was not met ($S < 3$), due to negligible solubility of DS in these media (Table 2).

Dissolution Studies

Dissolution testing in the acidic pH stage

Figure 1 illustrates the enteric efficiency of DS pellets in various acidic media that resemble the gastric fluid for 2 h. Pellets showed an excellent acid resistance (0% release of DS for 2 h) in 0.1 N HCl, SGFsp, and blank FaSSGF. This is due to the resistance efficiency of the enteric-coated polymer Eudragit L 100 at low pH (1.2–1.6). In blank FeSSGF (pH 5.0), the acid resistance decreases slightly, where 6.5% of DS was released after 2 h. The low percent of DS release in blank FeSSGF (6.5% after 2h) complies with the USP requirements for enteric-coated dosage forms, where < 10% of the drug should be released after 2 h in the acid medium, 0.1 N HCl (*15*). The relatively higher DS release in blank FeSSGF, compared to that in 0.1 N HCl, SGFsp and blank FaSSGF (6.5% vs. 0%), can be related to its higher pH value (5.0 vs. 1.2–1.6). The fed state of the simulated gastric fluid has been proposed by Jantratid et al, where the presence of food elevates the pH and β (5.0 and 0.025 M/ΔpH, respectively) of the gastric fluid, which might dissolve the enteric-coated layers, resulting in premature drug release in some cases (*31*, *32*). Therefore, it is always better for patients to take their enteric-coated medications on an empty stomach (*15*).

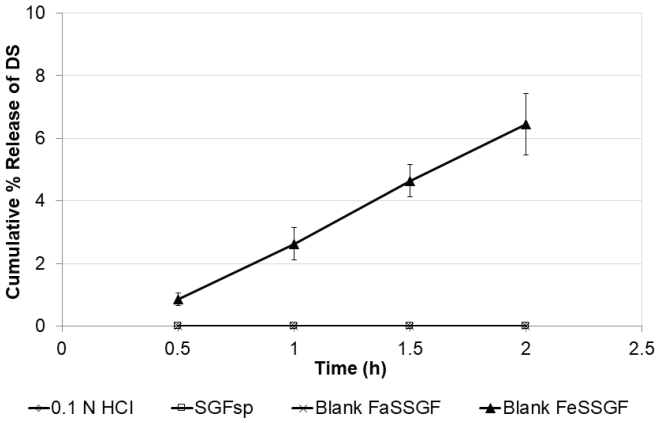

Figure 1. Enteric efficiency of DS pellets in media employed in acidic pH dissolution media: 0.1 N HCl, SGFsp, blank FaSSGF, and blank FeSSGF. Data are presented as mean ± SD (n = 6). DS: diclofenac sodium; HCl: hydrochloric acid; SGFsp: simulated gastric fluid sine pepsin; blank FaSSGF: blank fasted-state simulated gastric fluid; Blank FeSSGF: blank fed-state simulated gastric fluid; SD: standard deviation. Note: Data lines of 0.1 N HCl, SGFsp, and blank FaSSGF are overlaying on top of each other with 0% release of DS for 2 h.

Dissolution testing in the intermediate pH stage

Figure 2 illustrates the dissolution profile of DS in acetate buffer (pH 4.5), which represents the fluid of the upper small intestine (duodenal fluid) (*33*, *34*). DS release achieved an average of 7.5% after 2 h, complying with USP requirements for enteric-coated dosage forms. After 2 h, DS attained an average release of only 15.2% over the next 10 h. This low percent of DS release is aligned with the negligible solubility of DS in acetate buffer due to the low pH medium, resulting in the absence of sink condition.

Although the gastric-resistant polymer Eudragit L 100 targets drug release at pH > 5.5, a slight release was found

in acetate buffer. Nevertheless, this percent of release was within the acceptable criteria of the enteric-coated dosage forms (i.e. < 10%). Missaghi et al. have shown that lansoprazole enteric-coated pellets exhibited excellent enteric protection in the intermediate pH acetate buffer (pH 4.5), with complete release thereafter in phosphate buffer pH 6.8 (*35*).

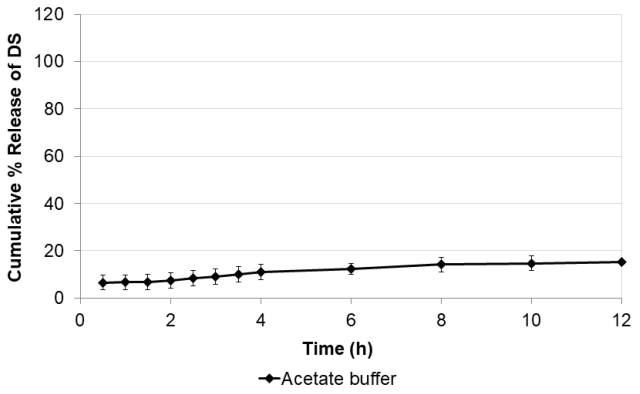

Figure 2. Dissolution profiles of DS pellets in medium employed in intermediate pH dissolution media: acetate buffer (pH 4.5). Data are presented as mean ± SD (n = 6). DS: diclofenac sodium; SD: standard deviation.

Dissolution testing in the basic pH stage

Figure 3 shows the dissolution profiles of DS in media that resemble the intestinal fluid during fasted and fed states within a pH range 5.0-7.2. In these media, and due to their high pH (> 5.5), it is expected that the enteric polymer dissolves and drug dissolution occurs.

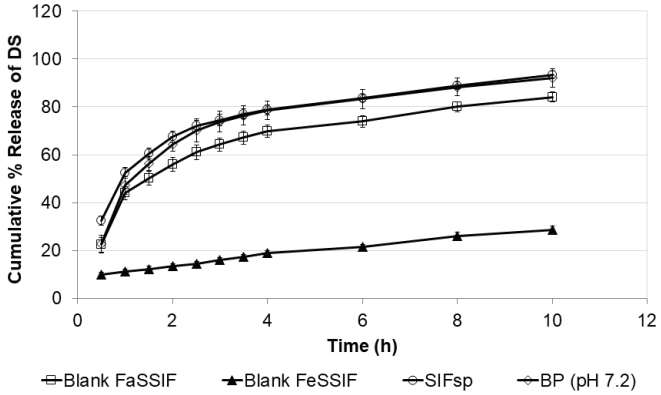

Figure 3. Dissolution profiles of DS pellets in media employed in basic pH dissolution media: blank FaSSIF, blank FeSSIF, SIFsp, and PB 100 mM (pH 7.2). Data are presented as mean ± SD (n = 6). DS: diclofenac sodium; Blank FaSSIF: blank fasted-state simulated intestinal fluid; Blank FeSSIF: blank fed-state simulated intestinal fluid; SIFsp: simulated intestinal fluid sine pancreatin; PB: phosphate buffer; SD: standard deviation.

The dissolution rate of DS in blank FaSSIF was extremely higher compared to that in blank FeSSIF (44.0 vs. 11.3% after 1 h and 84.1 vs. 28.6% after 10 h, respectively), resulting in dissimilar dissolution profiles (f_2 = 17.1, Table 3). These results are aligned with the equilibrium solubility data, where the solubility of DS in blank FaSSIF was higher than that in blank FeSSIF (5.9 vs. < 0.1 mg/mL, Table 2). This results in higher concentration gradient and sufficient sink condition in blank FaSSIF, with S value of 78.8 (Table 2), which accelerates the release of DS. A previous study by Kambayashi et al. has found that the dissolution rate of the enteric-coated diclofenac tablets in FaSSIF was more rapid than that in FeSSIF due to the higher solubility of diclofenac in FaSSIF (*36*).

Table 3. Similarity Factor (f2) of Dissolution Profiles of DS Dual-Release Pellets in Basic pH Dissolution Media

Dissolution Media	f_2 value	Similarity/Dissimilarity of Dissolution Profiles
Blank FaSSIF vs. Blank FeSSIF	17.1	Dissimilar
Blank FaSSIF vs. SIFsp	50.1	Similar
Blank FaSSIF vs. PB (pH 7.2)	55.2	Similar
Blank FeSSIF vs. SIFsp	13.0	Dissimilar
Blank FeSSIF vs. PB (pH 7.2)	13.7	Dissimilar
SIFsp vs. PB (pH 7.2)	69.7	Similar
PB 6.25 mM vs. PB 12.5 mM	74.8	Similar
PB 6.25 mM vs. PB 25 mM	68.0	Similar
PB 6.25 mM vs. PB 50 mM	55.5	Similar
PB 6.25 mM vs. PB 100 mM	62.4	Similar
PB 12.5 mM vs. PB 25 mM	57.7	Similar
PB 12.5 mM vs. PB 50 mM	48.8	Dissimilar
PB 12.5 mM vs. PB 100 mM	63.3	Similar
PB 25 mM vs. PB 50 mM	70.6	Similar
PB 25 mM vs. PB100 mM	52.0	Similar
PB 50 mM vs. PB 100 mM	46.9	Dissimilar

f_2: similarity factor; DS: diclofenac sodium; Blank FaSSIF: blank fasted-state simulated intestinal fluid; Blank FeSSIF: blank fed-state simulated intestinal fluid; SIFsp: simulated intestinal fluid sine pancreatin; PB: phosphate buffer; mM: millimolar.

The rate of DS release increases in SIFsp (pH 6.8) and BP 100 mM (pH 7.2), which resemble the physiological conditions of the mid-jejunum and distal GI, respectively (*15*). This is because these media exhibited high pH, resulting in high solubility of DS that provided sink conditions with S values of 61.3 and 133.3 for SIFsp and PB 100 mM (pH 7.2), respectively (Table 2). Thus, these media act as a driving force for dissolution. For SIFsp, DS attained averages of 52.3% and 93.5% after 1 and 10 h, respectively. Whereas in PB 100 mM (pH 7.2), DS attained averages of 47.2% and 92.1% after 1 and 10 h, respectively. The efficient drug release from the enterically-coated DS pellets in SIF (pH 6.8) was reported by Alotaibi et al., where at this pH, pellets swell and Eudragit L 100 dissolves, resulting in water penetration

and drug dissolution (*23*). Whereas, in PB 100 mM (pH 7.2), the high buffering capacity of 0.058 M/ΔpH enhances drug release, particularly for acidic drugs like DS (*15*). The dissolution profiles of blank FaSSIF, SIFsp, and PB 100 mM (pH 7.2) were similar with each other (f_2 > 50) (Table 3). Moreover, these dissolution profiles were dissimilar to that of blank FeSSIF (f_2 < 50) (Table 3).

The rate of DS release in PBs (pH 6.8) varied with varying the concentration of buffer attaining an average of 90.8, 90.4, 100.1, 99.9, and 84.9% in PB 6.25, 12.5, 25, 50, and 100 mM, respectively, after 10 h (Fig. 4). When comparing the dissolution profiles of DS in PB 6.25–100 mM (pH 6.8), the dissolution profiles were similar, except for PB 12.5 and 50 mM (f_2 = 48.8) (Table 3). It is apparent that the DS release was increased concomitant to an increase in the β and I of PB 6.25–50 mM from 0.003–0.024 M/ΔpH and 0.013–0.1 M, respectively. Whereas, low percent of DS release was found in PB 100 mM, aligning with the low solubility of DS in this medium (3.9 ± 0.2 mg/mL, Table 2). The increase in DS release in PB 6.25–50 mM is in agreement with Karkossa and Klein, who showed that the release of the enteric-coated aspirin formulations was influenced by β and I of the dissolution media, where drug release was accelerated with increasing the β and I of the media (*37*).

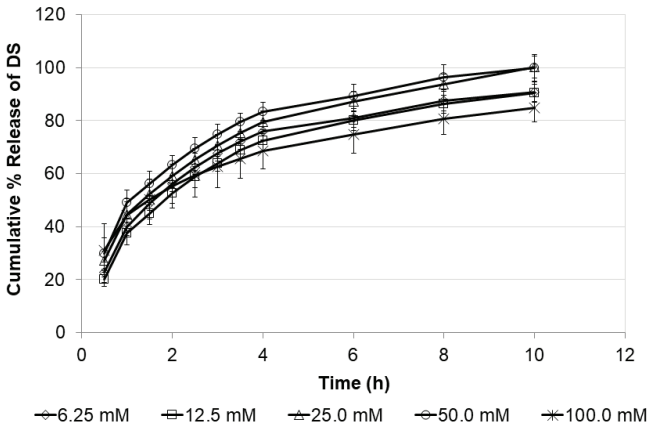

Figure 4. Dissolution profiles of DS pellets in media employed in basic pH dissolution media: PB 6.25-100 mM (pH 6.8). Data are presented as mean ± SD (n = 6). DS: diclofenac sodium; PB: phosphate buffer; SD: standard deviation.

CONCLUSION

The DS release pattern from the dual-release (enteric and sustained) pellets was evaluated in three pH-stage dissolution media that resemble the physiological variables of the GI fluid (pH, β, and I). The equilibrium solubility of DS was negligible in the acidic and intermediate pH media; however, it was high in the basic pH media (range, < 0.1–23.7 mg/mL). The dual-release DS pellets showed excellent gastric resistance in acidic and intermediate pH media, which resemble gastric fluid and proximal small intestine, respectively. DS release was substantially accelerated in the physiological conditions that resemble the small intestine (basic pH) during fasted and fed states and distal GI fluid. The buffer capacity and ionic strength of PBs markedly influence the release of DS, where DS release increases with increasing β/I of the dissolution media in PB 6.25–50 mM (pH 6.8) and then decreased at PB 100 mM (pH 6.8). Future studies will focus on correlating the in vitro and in vivo data to serve as a surrogate for the in vivo bioavailability studies.

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CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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