



Improved Dissolution Behavior of Dipyridamole Formulation with Precipitation Inhibitor

Maryam Maghsoodi¹ , Omid Narimanpour¹

¹School of Pharmacy and Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Article Info

Article History:

Received: 13 August 2019
Accepted: 24 December 2019
ePublished: 20 September 2020

Keywords:

-Supersaturation
-Dipyridamole
-Eudragit L100
-Hydroxypropyl cellulose
-Precipitation inhibition
-Dissolution

Abstract

Background: Physiologically generated supersaturation and subsequent precipitation of a weakly basic drug in the small intestine leads to compromised bioavailability.

Methods: In this work, the pH -induced precipitation of dipyridamole (DPD) as a model weakly basic drug in the presence of Eudragit L100 (Eu) and hydroxypropyl cellulose (HPC) was investigated. Inhibitory effects of the polymers on precipitation of DPD at varying drug/polymer ratios were examined. The effects of the polymers on the DPD dissolution property were assessed using drug/polymer physical mixtures (PMs) and solid dispersions (SDs).

Results: Significant inhibitory effects on precipitation were found using Eu, while HPC as well inhibited precipitation, but to a lower level than found with Eu. The PMs resulted in higher area under the dissolution curve (AUDC) compared to SDs. For SDs, the AUDC was limited by the slow release of the drug from the polymers in acidic pH which in turn decreased supersaturation of DPD following acidic to neutral pH transition.

Conclusion: From these results, it may be supposed that both the ability to create and stabilize supersaturation separately of each other to be important for enhancing dissolution of DPD.

Introduction

Weakly basic drugs have gained much interest due to their physiologically generated supersaturation and subsequent precipitation in the small intestine; however, they also include the majority of drugs candidates. The oral bioavailability of weakly basic drug is a widespread challenge for scientists as a consequence of their pH-induced precipitation. At acidic pH of the stomach, the ionized form of drug which displays much higher solubility compared to the free base predominates. Therefore, partial or complete drug solubilization can be got in the stomach. Following a pH change from the stomach to the small intestinal the drug encounters neutral condition that favors the generation of the free base. Thus, in the small intestine, weakly basic compound may undergo supersaturation due to lower solubility of the free base.¹⁻⁴ It is worth nothing that the higher thermodynamic activity of a drug in the supersaturated state enhances its permeation across the biological membrane. It is well demonstrated that if drug supersaturation can be prolonged for a physiologically adequate time in the small intestine it can lead to improved drug transition across the intestinal epithelia and consequently increased drug absorption.⁵⁻¹⁰ However, in spite of the potential benefit of supersaturated state, due to excess free energy of the supersaturated solutions, which will eventually result in precipitation of the drug, erratic absorption and low

bioavailability for weakly basic drugs may be attained.⁵ In fact, precipitation of weakly basic drugs in the small intestine is behind poor oral bioavailability with large intra- and inter-individual variations. Therefore, the challenge is in inhibiting precipitation of weakly basic drug following the passage from the stomach into the small intestine. In order to benefit from high thermodynamic activity of a drug in supersaturated state and consequently high free drug concentration, a precipitation inhibitor is needed which preferably would not limit diffusion of drug in the solution, such as that attained by micelles, cyclodextrins, and emulsions. Polymer based drug precipitation inhibitors have been used to inhibit or retard such precipitation. The use of polymers is a progressively more widespread way for inhibiting precipitation from the supersaturated state used to improve the dissolution performance of poorly water soluble drugs. It has been shown that HPMC and PVP capable of forming hydrogen bonds with the drugs are two of the best polymers for stabilizing supersaturated solution of poorly water-soluble drugs through inhibiting their crystallization.¹¹⁻¹⁵ However, the capability of other polymers to maintain supersaturated solutions and inhibit crystallization is rarely known.¹⁶ Considering this fact, in this work, the inhibitory effect of Eudragit L100 (Eu) and HPC on pH- induced precipitation of DPD was quantified. Dipyridamole (DPD), as a model compound, was

*Corresponding Author: Maryam Maghsoodi, E-mail: maghsoodim@tbzmed.ac.ir

©2020 The Author(s). This is an open access article and applies the Creative Commons Attribution License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, as long as the original authors and source are cited.

examined in the present study. DPD is weakly basic drug with pK_a 6.4 which partially precipitates in small intestine following gastric emptying.^{2,17,18} Previous works evaluating the bioavailability of DPD have revealed that absorption is erratic and absolute bioavailability is between 18% and 43%.¹⁹⁻²¹

The main purpose of this work was to investigate DPD solid compositions with different polymeric additives regarding the ability to maintain supersaturation of DPD following an acidic to neutral pH transition.

Materials and Methods

Materials

Dipyridamole (DPD) was acquired from Osvah Pharmaceutical Co (Iran), hydroxypropyl cellulose (HPC) with MW of 370000 was purchased from Sigma Aldrich (Germany), and Eudragit L100 (Eu) from Degussa (Germany). Also were used monobasic potassium phosphate USP-standard (KH_2PO_4), dibasic potassium phosphate (K_2HPO_4), trisodium phosphate (Na_3PO_4), ethanol analytical grade, dichloromethane analytical grade from (Merck, Germany)

Supersaturation experiment

Stock solution of DPD was prepared by dissolving 30 mg of DPD in 10 ml HCl solution (0.1 N). 1 ml of this solution was then added to 50 ml buffer solution (pH=6.8) to induce an initial drug solution concentration of 60 μ g/ml DPD, corresponding to a supersaturation ratio of 10, into which accurate amount of polymer had been pre-dissolved. The total time of supersaturation experiment was 120 min, buffer solution was shaken using water bath, 100 rpm and 37 ± 0.5 °C. After adding HCl solution to the buffer solution, samples were taken at predetermined time points (10, 20, 30, 60 and 120 min) and filtrated. The obtained filtrate was directly diluted in buffer solution to avoid DPD precipitation and analyzed using UV-Vis spectrophotometer (UV-160A, Shimadzu, Kyoto, Japan) at 291 nm. The concentration of DPD (n = 3) was plotted as a function of time.

No interference from the polymers on the DPD assay was detected at 291 nm.

The same supersaturation tests were carried out in buffer solution in the absence of polymer.

Solubility

The equilibrium solubility of DPD was determined in phosphate buffer (pH 6.8) at 37 °C using an excess of DPD, in the presence of various concentrations of Eu and HPC. The solubility was achieved after 48 h by using UV-Vis spectrophotometer at 291 nm following filtration through a 0.45 μ m nylon membrane syringe filter.

Preparation of solid formulations

Physical mixtures (PM) of DPD and polymers at different weight ratios were prepared by weighting out the accurate amount of DPD and polymers and triturating for at least

10 min in the mortar and pestle. Preparation of DPD-polymer solid dispersions (SD) were carried out by a rotary evaporation method. First, DPD and the polymer were dissolved in a mixture of ethanol /dichloromethane (1:1 v/v) and then solvent removal was performed by rotary evaporation. After that, the solid dispersions were dried in a vacuum oven overnight at 40 °C to take away any remaining solvent. The solid dispersions were subsequently ground with a mortar and pestle and then sieved to separate a particle size fraction of 150-250 μ m.

In vitro dissolution studies

Dissolution experiment was conducted using the USP II paddle method. Firstly, samples were subjected to acid phase examination in 750 ml of 0.1 N HCl for 2 hours. After that, 250 ml of 0.2 M Na_3PO_4 was added to begin the neutral phase examination which was carried out for three further hours. Samples equivalent to 60 mg of DPD were calculated, weighted and added to each vessel. This amount of drug represented a theoretical 60 μ g/ml DPD concentration for the neutral stage of dissolution testing which corresponds to a 10-fold level of supersaturation supposing an equilibrium solubility of 6 μ g/ml in neutral phase (pH 6.8).²² The dissolution medium was stirred at 100 rpm and held at 37 ± 0.5 °C throughout the experiment. Samples were taken at determined time points by withdrawing 5 ml from vessels; then the aliquots were filtered using a nylon membrane syringe filter (0.45 μ m, Whatman\, Florham Park, NJ). Filtered samples were immediately diluted to avoid drug precipitation. DPD concentrations were assessed as mentioned above.

Fourier transform infrared (FT-IR) spectroscopy

Fourier-transform Infrared (FTIR) Spectroscopy was carried out using a Spectrometer (M-B-100, Bomem, Canada) (32 scans at 4 cm^{-1} resolution). The samples were mixed with KBr, compressed into a disc, and analyzed directly over a wavenumber range of 400–4000 cm^{-1} .

Differential scanning calorimetry (DSC)

DSC analyses of the samples were performed using an automatic thermal analyzer system (DSC-60, Shimadzu, Tokyo, Japan). Samples were weighted to 5 mg in aluminum crimped pans and heated with a heating rate of 10°C/min from 25 to 300°C. Indium as standard was used to calibrate temperature.

Statistical evaluation of data

The data were reported as the mean \pm standard deviation (SD). The SPSS software (version 18.0), ANOVA test, and Tukey post-test were used for data analysis. $P < 0.05$ was considered as the level of significance.

Results and Discussion

Supersaturation experiment

Eu and HPC were examined to assess their suitability to retard the precipitation of DPD from neutral solution.

Inhibitory effect of each polymer on drug precipitation was investigated by evaluating the maintenance ability of drug concentration after forming drug-supersaturated solution. In the supersaturation experiment, the polymers were pre-dissolved at various concentration (50, 100 and 200 µg/ml) in neutral solution. The polymer concentrations of 50, 100 and 200 µg/ml represent the concentration of the polymer that would be obtained in solution subsequent dissolution polymer- based formulations at drug/polymer ratios of 60:50, 60:100 and 60:200, respectively.

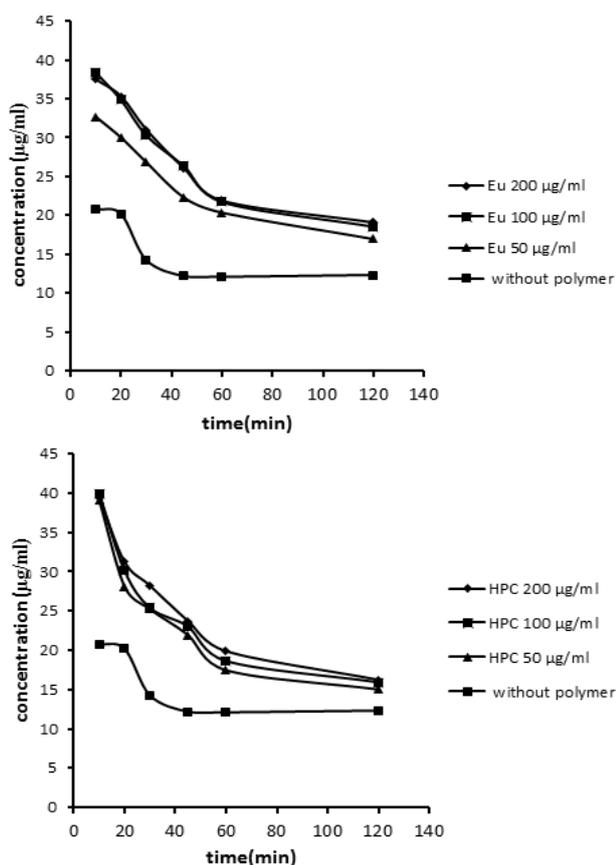


Figure 1. Inhibitory effects of polymers on precipitation of a supersaturated solution of DPD (60 µg/ml) at pH 6.8.

Then a concentrated solution of DPD in acidic (i.e., the “spring”) was added to polymer solution to provide an initial degree of supersaturation equal to 10 based on determined solubility and then the solution concentration was monitored as a function of time. Figure 1 illustrates the results of the anti-precipitant screening. As shown in Figure 1, the concentration of DPD in the non-polymer solution decreased rapidly. This fast decrease in DPD concentration demonstrates that DPD precipitated from the supersaturated solution immediately. Similar findings have been reported in other studies wherein celecoxib and felodipine quickly precipitated in the lack of polymers.^{23,24} According to Figure 1, the DPD concentration decreased more slowly in the presence of Eu and HPC, meaning that Eu and HPC acted as efficient anti-precipitant to prevent the precipitation of DPD. For example, the DPD concentration measured after 20 min was 35 µg/ml for 200

µg/ml Eu concentration, whereas it was 30 µg/ml for 200 µg/ml HPC concentration. In order to take into account possible solubilizing effect of Eu and HPC, the equilibrium solubility of DPD was determined in neutral solution containing various concentration of the polymers (50, 100 and 200 µg/ml) of the polymers. According to results, no significant difference was found between the equilibrium solubility of DPD in HPC solutions and non-polymer solution ($p > 0.05$).

This implies that HPC have no solubilization effect, and reveals that supersaturated state of drug in the presence of HPC are attributed to maintenance effect of the polymers on DPD supersaturation. The equilibrium solubility of DPD in Eu solution was slightly higher than in non-polymer solution. However, results indicated that at each Eu concentration the solubility was markedly lower than the DPD concentration determined in the supersaturation assay.

This confirmed that all solutions were supersaturated and demonstrates that Eu (i.e., the “parachutes”) inhibited precipitation.

After 120 min, DPD reached concentration of 19 µg/ml for 200 µg/ml Eu solution and 16 µg/ml for 200 µg/ml HPC solution. The DPD concentrations in the polymer solution after 120 min were still higher than in the non-polymer solution. The results demonstrated that Eu and HPC (i.e., the “parachutes”) efficiently suppressed the precipitation of DPD and Eu, compared to HPC, is more efficient in maintaining supersaturated level of DPD ($p < 0.05$). The area under the concentration–time (AUC) profile of the supersaturation curve was evaluated to give more quantitative data for supersaturation results. The AUC provides estimation of both degree and duration of supersaturation so evaluating of the extent of supersaturation. AUC values for different polymers are presented in Table 1. The AUC values also clearly confirmed the superiority of Eu in respect to stabilizing DPD supersaturation and inhibiting precipitation. The Eu solution (200 µg/ml) showed about 1.21-fold and 1.87-fold greater mean AUC values than HPC solution (200 µg/ml) and non-polymer solution, respectively.

The influence of polymer concentration on the precipitation of DPD is also shown in Figure 1 and Table 1. It is obvious that a direct correlation between the polymer amount and the drug concentration was not obtained. Concentration of DPD increased with increasing pre-dissolved polymer concentration from 50 to 100 µg/ml ($p < 0.05$).

However, DPD concentrations for polymers with 100 and 200 µg/ml concentrations were not significantly different. This proposed that the inhibitory effect of polymers on DPD precipitation was not proportional with their amounts, but rather there was an optimal amount where the increasing in the drug concentration was highest.

In vitro dissolution of PMs

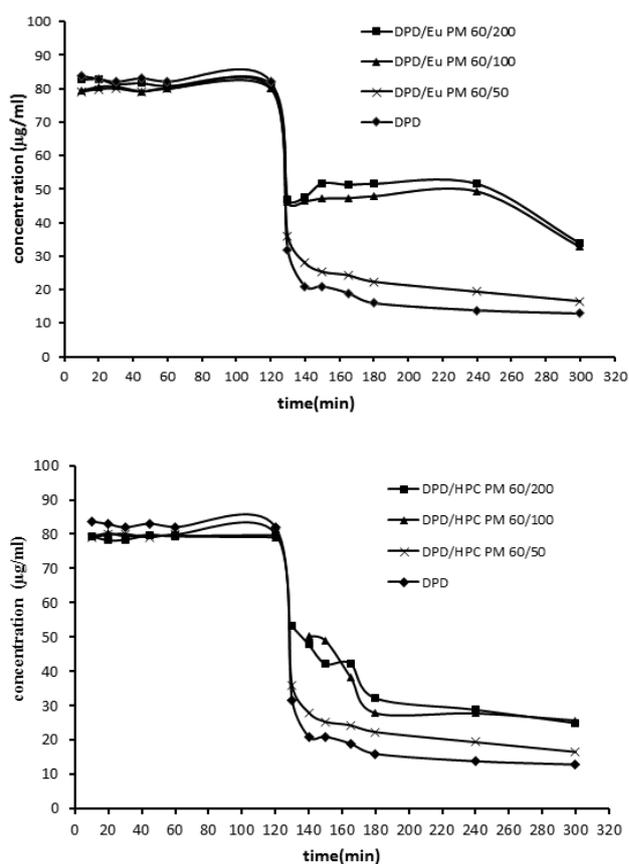
The adding of DPD “springs” to neutral solution containing polymers is a valuable method for initial screening to find

Table 1. The area under the concentration–time (AUC) profile of the supersaturation curve in presence and absence of polymers.

Polymers	Concentration ($\mu\text{g/ml}$)	Solubility of DPD ($\mu\text{g/ml}$)	AUC ($\mu\text{g}\cdot\text{min/ml}$)
Without polymer	-	6.0 ± 0.06	754.3 ± 25.1
Eu L100	50	7.16 ± 0.10	1202.1 ± 28.2
	100	7.76 ± 0.06	1341.6 ± 21.3
	200	7.87 ± 0.04	1411.0 ± 20.9
HPC	50	6.04 ± 0.10	995.9 ± 29.1
	100	6.04 ± 0.06	1112.7 ± 27.2
	200	6.04 ± 0.10	1169.9 ± 29.6

a polymer that would stabilize supersaturation of the drug. However, this method cannot guarantee that the efficient polymer dissolve quickly enough under gastrointestinal conditions to function appropriately when used in solid formulation. It is possible that the drug in solid formulation dissolves and subsequently precipitates before the polymers dissolve an adequate amount to be efficient. Consequently, to begin to concentrate on this matter, evaluation of dissolution of solid formulations consisting of DPD with polymers would be necessary. Taking into account the results of supersaturation experiments, dissolution tests were firstly carried out for the plain drug and its PMs with Eu and HPC at various Drug/polymer ratios. To study the dissolution performance of DPD from solid formulations, tests were performed by a pH switch dissolution method, starting with an acidic pH of 1.2 for two hours followed by a pH adjusting to 6.8 to start the neutral phase testing which was conducted for three additional hours. The pH switch in this dissolution model was preferred based on previous studies with the intention to simulate biorelevant pH conditions while keeping the method uncomplicated.^{25,26} Taking into account the high solubility of DPD in pH 1.2, it is supposed that the applied amount (60 mg) of DPD would be wholly soluble in acidic medium and produce supersaturated solution with starting neutral phase as a consequence of dramatic decrease in DPD solubility at pH 6.8 ($6\ \mu\text{g/ml}$).²² Thus, this pH switch in dissolution test clearly implies the effect of different formulations on stabilizing supersaturation of DPD in neutral solution.

The *in vitro* dissolution results of the PM samples and plain DPD are depicted in Figure 2. Complete dissolution of the plain drug was achieved within 10 min at acidic pH. These findings were consistent with previous observation of the rapid dissolution behavior of DPD in acidic condition.²⁷ Drug release characteristics for Eu and HPC PMs were almost identical to that of the plain drug in acidic medium. Therefore, at the beginning of neutral phase, the extent of supersaturations were similar for plain DPD and its PMs with Eu and HPC ($p>0.05$). Following the acid-to-neutral pH change, in the absence of any polymer, significant precipitation of DPD was seen as mean value of almost $21\ \mu\text{g/ml}$ DPD was determined 20 min after the pH transition and over 60% of the drug precipitated during this time. However, the Eu-based and HPC-based PMs showed the stabilization effect against DPD precipitation. These formulations kept on to provide obvious stabilization of supersaturated DPD up to 3 h after the pH transition.

**Figure 2.** In vitro release of PM formulations at different DPD/polymer ratios.

As mentioned before, DPD solubility was not markedly changed in the presence of these polymers. Therefore, the positive effect of the polymers on dissolution performance of DPD was not likely attributable to an increase in the equilibrium solubility.

To give a more quantitative evaluation of the dissolution profile, the area under the dissolution curve (AUC) for the neutral phase was considered because the main difference between dissolution performance of DPD and PMs was in this phase. Moreover, AUC neutral is the key metric by which to assess the different formulations as it is likely to correlate to *in vivo* absorption. AUC neutral for different samples are described in Table 2.

The AUC neutral values further show the superiority of the Eu based PMs with regard to the promotion of DPD supersaturation in neutral phase. For example, at 60/100 DPD/polymer ratio the Eu-based PM showed AUC

Table 2. The area under the dissolution curve (AUCD) for the neutral phase for different formulations.

Samples	AUCD ($\mu\text{g}\cdot\text{min}/\text{ml}$)
Plain DPD	1517.9 \pm 16.6
PM(DPD/Eu) 60:50	1820.9 \pm 30.1
PM(DPD/Eu) 60:100	3988.8 \pm 35.2
PM(DPD/Eu) 60:200	4010.1 \pm 32.2
PM(DPD/HPC) 60:50	1698.5 \pm 31.2
PM(DPD/HPC) 60:100	2430.5 \pm 29.5
PM(DPD/HPC) 60:200	2462.4 \pm 30.4
SD(DPD/Eu) 60:50	2159.6 \pm 27.9
SD(DPD/Eu) 60:100	3283.2 \pm 35.1
SD(DPD/Eu) 60:200	3569.4 \pm 28.9
SD(DPD/HPC) 60:50	2120.8 \pm 24.6
SD(DPD/HPC) 60:100	2177.7 \pm 31.2
SD(DPD/HPC) 60:200	2268.4 \pm 34.6

neutral values of 3988.8 $\mu\text{g}\cdot\text{min}/\text{ml}$, while HPC-based PM produced significantly lower AUCD neutral value of 2430.5 $\mu\text{g}\cdot\text{min}/\text{ml}$ ($p < 0.05$). HPC provided supersaturation to a lesser extent than observed with Eu, which could either be a consequence of the lower dissolution rate of HPC (as it tends to swell before it dissolves) compared to Eu or alternatively because Eu is a better precipitation inhibitor than HPC.

These findings were consistent with the results attained from supersaturation tests examining the inhibitory effects of the polymers against DPD precipitation in solutions containing pre-dissolved Eu and HPC. Dissolution results of PMs consistent with the results of supersaturation experiments demonstrated the superiority of Eu in respect to inhibiting precipitation of DPD. The influence of polymer amount in PMs on the dissolution profiles of DPD was evaluated using various DPD:polymer ratios (60:50, 60:100 and 60:200). The dissolution results signify that Eu/HPC-based PMs at all concentrations stabilized supersaturated levels of DPD maintaining drug concentration significantly higher than the equilibrium solubility of DPD (6 $\mu\text{g}/\text{ml}$) for the whole period of neutral phase (3h) ($p < 0.05$ in all cases) (Figure 2). However, as can be seen from this Fig, a direct correlation between the polymer content and the maximum DPD concentration was not observed. For example, in the case of Eu- based PMs, the maximum DPD concentration for PM (drug/polymer 60:200) and PM (drug/polymer 60:100) was relatively similar (around 47 $\mu\text{g}/\text{ml}$ after 20 min) ($p > 0.05$), while PM (drug/polymer 60:50) differed with a lesser concentration of DPD (almost 28 $\mu\text{g}/\text{ml}$ after 20 min) ($p < 0.05$).

Both Eu- based PM (drug/polymer 60:100) and PM (drug/polymer 60:200) provide AUCD neutral improvement > 2.6 fold of the plain drug, however, AUCD statistical analysis demonstrated no significant difference among these PMs ($p > 0.05$). Eu -based PM (drug/polymer 60:100) was chosen as the most promising PM for achieving the greatest DPD concentration, with the highest drug loading and lowest polymer proportion. According to previous studies, interaction of polymer with drug and viscosity of

fluid are possible factors which affect the precipitation of a drug from supersaturated solution.²⁸ Thus, viscosity should be regarded as a potential factor contributing to the effect of the polymers on stabilizing supersaturation.

It is evident that the solution viscosity was increased consistently with increasing polymer amount, whereas increasing the polymer amount in PMs resulted in higher AUCD values up to 60:100 (DPD:polymer) ratio. Since persistent benefit by increasing polymer amount above 60:100 (DPD:polymer) ratio was not observed, it appears that viscosity is an insignificant factor in the mediated stabilizing supersaturation.

This appears to reveal that intermolecular interaction between DPD and polymers (Eu and HPC) mainly governs the stabilizing of supersaturation in neutral phase. It has been demonstrated that stabilization of drug supersaturation by the polymers is mostly due to intermolecular interaction between drug and polymer. When there is attractive intermolecular interaction between drug and the polymer in solution, this will retard nucleation and following crystal growth of drug. Finally the result is inhibition of precipitation, and so maintenance of supersaturated state.²⁹ According to previously published findings, the ability of polymer to interact with drug is mainly dependent on its functional sites.³⁰ Eu and HPC have the numerous hydroxyl groups on the polymer backbone. Therefore, it is reasonable to assume that Eu and HPC with abundance of hydrogen bond donor sites provide the suitable condition for interaction with DPD molecules having hydrogen bond acceptor sites (C-N groups). Similarly, Hydrogen bonding has been accounted as a most important mechanism to stabilize supersaturation of other drugs in presence of the polymer.¹⁴

However, it is worth pointing out that the mechanism of drug supersaturation maintenance by polymer is still not comprehensively understood. In another work, carried out to realize the suitability of various polymers to inhibit precipitation of felodipine, hydroxypropyl methylcellulose acetate succinate (HPCAS) in comparison to PVP and hydroxypropyl methyl cellulose (HPC) was more efficient in maintaining supersaturation of the drug and the reasons for that remained unknown.²⁴

In vitro dissolution of SDs

In order to investigate the influence of mixing type of polymer with DPD on its efficiency the dissolution properties of SDs were also evaluated.

As shown in Figure 3, the dissolution plots for SDs were very different to that of their PM counterparts. The dissolution profiles for DPD revealed that the SD generated lower drug concentration in neutral phase than was obtained for a PM at the same drug/polymer ratio as in the SD ($p < 0.05$) which may be explained as follow. According to previous works both generation and maintenance of a supersaturation separately of each other are essential to enhance dissolution properties of weakly basic drug.³¹

Dissolution results revealed that supersaturation was not

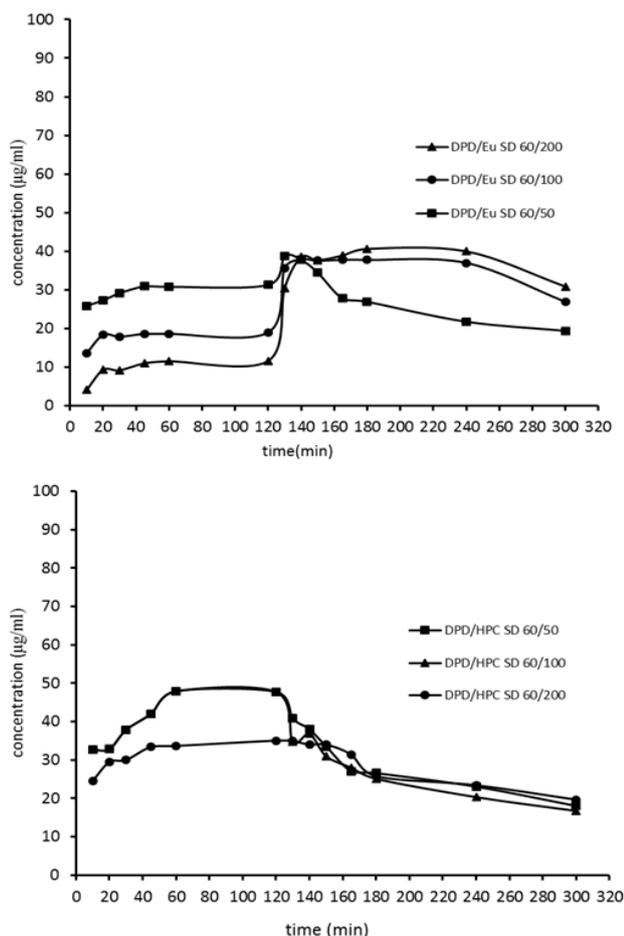


Figure 3. In vitro release of SD formulations at different DPD/polymer ratios.

generated in SDs as much as in PMs and consequently dissolution enhancement was not achieved to the extent that PMs in spite of presence of same amount of polymer with efficient supersaturation stabilizing effect.

In SDs, in acidic phase lower drug release was obtained than in PMs which may be related to incomplete dissolution of polymers in acidic phase and to the high molecular weight of DPD (455.96 Da).³² In fact, the SD inhibited the complete release of DPD under gastric pH while at neutral pH released the drug which precipitated out in the medium due to low solubility of DPD in neutral pH. However, in the case of PMs, complete dissolution of DPD in acidic phase resulting in substantial DPD supersaturation from these formulations following the pH change to 6.8.

This proposes the SD formulation of DPD would be less efficient in promoting dissolution of drug compared to PM, as SD formulation eliminates the acid-phase dissolution of DPD and subsequent supersaturation upon the acid to neutral pH change.

According to Figure 3, there was spring dissolution model of DPD from Eu-based amorphous SDs in neutral phase (pH6.8) which could be explained as follow. It is obvious from the DSC thermograms that Eu-based SDs do not show any signs of crystallinity (Figure 4). This demonstrated that DPD was dispersed in the SDs in an

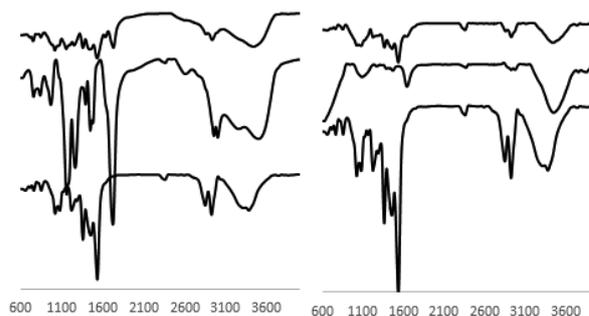


Figure 4. FT-IR of spectrum of samples (right) from up to down: Eu- based SD, Eu and plain DPD, (left) from up to down: HPC-based SD, HPC and plain DPD.

amorphous state. Amorphous SDs contain the drug in a high energy such that higher *apparent solubilities* than crystalline drugs are obtained. In many previous studies, it has been demonstrated that amorphous SDs containing pH dependent polymers may produce concentrations higher than equilibrium solubility of the drug as a supersaturation burst at pH in which the polymers dissolve.^{33,34} Therefore, it is reasonable to expect that Eu-based amorphous SD of DPD could trigger the high initial concentration to form supersaturated state at pH 6.8, considering the fact that Eu L100 is soluble at this pH.³⁵

FT-IR and DSC analysis

To investigate possible interaction between DPD and polymers, the FT-IR spectra of pure DPD and SDs were measured (Figure 5). The pure DPD has bands at 1535 cm^{-1} (C=N ring), 1360 cm^{-1} (C-N bands), 2930 cm^{-1} (asymmetrical stretch of CH₂ group), 2852 cm^{-1} (symmetrical stretch of CH₂ group), 3377 and 3303 cm^{-1} (OH stretching vibration).³⁶

The spectra of DPD:HPC (1:1) SD can be simply considered as the superposition of those of DPD and HPC. No difference was observed in the position of the peaks of DPD and HPC. However, in the case of DPD:Eu (1:1) SD formulation different result was obtained.

Eu has important functional peaks at 1700 and 1730 cm^{-1} for the C=O bonds in the case of the carboxylic acid group and the esterified carboxylic group, respectively.³⁷ The intermolecular interactions between two components could be represented by the appearance of new peaks, a shift in the present absorption bands, or a variation in the shape of bands in the spectra.³⁸ Formulation DPD:Eu SD showed a new distinct absorption band between 1730 and 1531 cm^{-1} . According to other researches, a usual carboxylate anion exhibits a strong carbonyl asymmetrical stretching band in the region of 1600 cm^{-1} .³⁹ The new band in the FT-IR spectra of formulation DPD:Eu SD was found at 1633 cm^{-1} that demonstrated generation of carboxylate anion of Eu. Moreover, a shift in the C=N stretching frequency in DPD:Eu SD from 1534 to 1531 cm^{-1} , representing the difference in DPD hydrogen bonding environment. This change could be as a result of the interaction between carboxylic acid group (donor) of Eu with C=N group (acceptor) of DPD. FT-IR results confirmed the expected

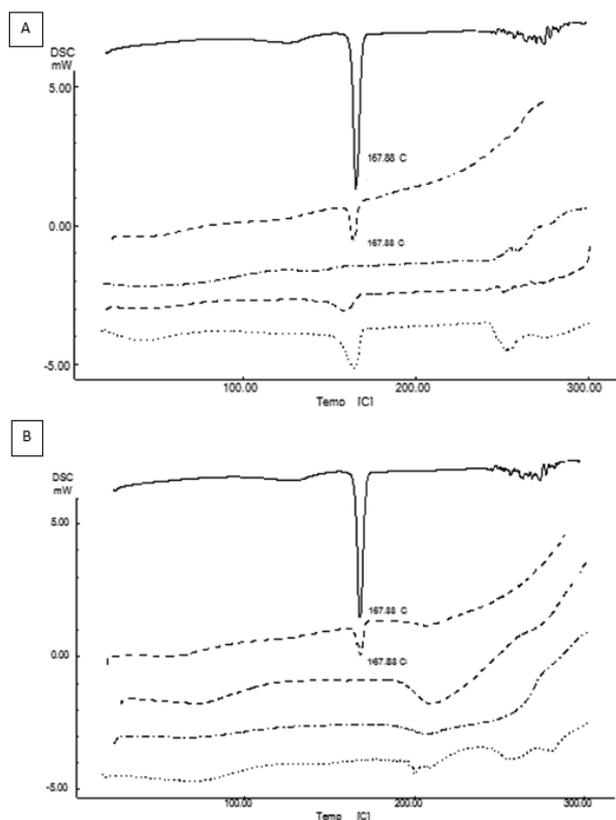


Figure 5. DSC scans of the samples (A) up to down: plain DPD, PM (DPD/HPC 60:100), SD (DPD/HPC 60:200), (DPD/HPC 60:100) and (DPD/HPC 60:50), (B) up to down: plain DPD, PM (DPD/Eu 60:100), SD (DPD/Eu 60:200), (DPD/Eu 60:100) and (DPD/Eu 60:50).

strong interaction between Eu and DPD which appears to be valuable for stabilizing DPD molecules in solution. The DSC thermograms of the samples are shown in Figure 5. In the case of Eu-based SD, contrary to plain DPD and its physical mixture with Eu, no melting peak of drug was seen suggesting that DPD was dispersed within Eu to generate dispersion at a molecular level. No melting peak in DPD:HPC SD at 60:200 ratio and the negative deviation in T_m at 60:100 and 60:50 ratios also imply that the drug-polymer interactions are stronger than drug-drug interactions.

Conclusion

The current study assessed DPD supersaturation and excipient-mediated precipitation inhibition in neutral pH. Following pH change from acidic to neutral, the effect on maintaining supersaturation of DPD was assessed using Eu and HPC. It was demonstrated that maximum maintaining DPD supersaturation was achieved by Eu. The stabilizing effect of polymers on DPD supersaturation in neutral phase may be related to drug-polymer interaction which was confirmed by FT-IR and DSC measurements results. The dissolution results demonstrated that the physical mixture of polymers with DPD markedly improved dissolution behavior of plain DPD, however, the polymers were less efficient in solid dispersions, because of their hindering

effect on generation of DPD supersaturation, revealing the importance of formulation type to efficiency of polymers. According to the results of this study, physical mixture of DPD with Eu is expected to provide a higher chance for DPD absorption in the small intestine and it may be valuable to investigate this formulation additional *in vivo*.

Conflict of Interest

The authors declare they have no conflict of interest.

Reference

1. Stahl HP, Nakano M. Pharmaceutical aspects of the drug salt form. In Stahl PH, Wermuth CG, editors. In: Handbook of pharmaceutical salts: Properties, selection, and use, 1st ed.. Zurich, Switzerland: VHCA, Verlag Helvetica Chimica Acta; Weinheim, Federal Republic of Germany; Wiley-VCH; 2002. p 83–116.
2. Zhou R, Moench P, Heran C, Lu X, Mathias N, Faria TN, et al. pH-dependent dissolution *in vitro* and absorption *in vivo* of weakly basic drugs: development of a canine model. *Pharm Res.* 2005;22(2):188-92. doi:10.1007/s11095-004-1185-3
3. Hsieh YL, Ilevbare GA, Van Eerdenbrugh B, Box KJ, Sanchez-Felix MV, Taylor LS. pH-Induced precipitation behavior of weakly basic compounds: determination of extent and duration of supersaturation using potentiometric titration and correlation to solid state properties. *Pharm Res.* 2012;29(10):2738-53. doi:10.1007/s11095-012-0759-8
4. Kostewicz ES, Wunderlich M, Brauns U, Becker R, Bock T, Dressman JB. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. *J Pharm Pharmacol.* 2004;56(1):43-51. doi:10.1211/0022357022511
5. Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? *J Pharm Sci.* 2009;98(8):2549-72. doi:10.1002/jps.21650
6. Stillhart C, Kuentz M. Trends in the assessment of drug supersaturation and precipitation *in vitro* using lipid-based delivery systems. *J Pharm Sci.* 2016;105(9):2468-76. doi:10.1016/j.xphs.2016.01.010
7. Brouwers J, Tack J, Augustijns P. *In vitro* behavior of a phosphate ester prodrug of amprenavir in human intestinal fluids and in the Caco-2 system: illustration of intraluminal supersaturation. *Int J Pharm.* 2007;336(2):302-9. doi:10.1016/j.ijpharm.2006.12.011
8. Mellaerts R, Mols R, Kayaert P, Annaert P, Van Humbeeck J, Van den Mooter G, et al. Ordered mesoporous silica induces pH-independent supersaturation of the basic low solubility compound itraconazole resulting in enhanced transepithelial transport. *Int J Pharm.* 2008;357(1-2):169-79. doi:10.1016/j.ijpharm.2008.01.049
9. Miller JM, Beig A, Carr RA, Spence JK, Dahan A. A win-win solution in oral delivery of lipophilic drugs: supersaturation via amorphous solid dispersions

- increases apparent solubility without sacrifice of intestinal membrane permeability. *Mol Pharm.* 2012;9(7):2009-16. doi:10.1021/mp300104s
10. Takano R, Takata N, Saito R, Furumoto K, Higo S, Hayashi Y, et al. Quantitative analysis of the effect of supersaturation on in vivo drug absorption. *Mol Pharm.* 2010;7(5):1431-40. doi:10.1021/mp100109a
 11. Vandecruys R, Peeters J, Verreck G, Brewster ME. Use of a screening method to determine excipients which optimize the extent and stability of supersaturated drug solutions and application of this system to solid formulation design. *Int J Pharm.* 2007;342(1-2):168-75. doi:10.1016/j.ijpharm.2007.05.006
 12. Raghavan SL, Kieper B, Davis AF, Kazarian SG, Hadgraft J. Membrane transport of hydrocortisone acetate from supersaturated solutions; the role of polymers. *Int J Pharm.* 2001;221(1-2):95-105. doi:10.1016/s0378-5173(01)00673-1
 13. Raghavan SL, Trividic A, Davis AF, Hadgraft J. Effect of cellulose polymers on supersaturation and in vitro membrane transport of hydrocortisone acetate. *Int J Pharm.* 2000;193(2):231-7. doi:10.1016/s0378-5173(99)00345-2
 14. Raghavan SL, Trividic A, Davis AF, Hadgraft J. Crystallization of hydrocortisone acetate: influence of polymers. *Int J Pharm.* 2001;212(2):213-221. doi:10.1016/s0378-5173(00)00610-4
 15. Gao P, Akrami A, Alvarez F, Hu J, Li L, Ma C, et al. Characterization and optimization of AMG 517 supersaturatable self-emulsifying drug delivery system (S-SEDDS) for improved oral absorption. *J Pharm Sci.* 2009;98(2):516-28. doi:10.1002/jps.21451
 16. Chauhan H, Hui-Gu C, Atef E. Correlating the behavior of polymers in solution as precipitation inhibitor to its amorphous stabilization ability in solid dispersions. *J Pharm Sci.* 2013;102(6):1924-35. doi:10.1002/jps.23539
 17. Xi Z, Sharma N, Paprikar A, Lin S. Development and evaluation of dipyridamole sustained release tablets containing micro-environmental pH modifiers. *J Drug Deliv Sci Tec.* 2019;54:101231. doi:10.1016/j.jddst.2019.101231
 18. Xu L, Luo Y, Feng J, Xu M, Tao X, He H, et al. Preparation and in vitro-in vivo evaluation of none gastric resident dipyridamole (DIP) sustained-release pellets with enhanced bioavailability. *Int J Pharm.* 2012;422(1-2):9-16. doi:10.1016/j.ijpharm.2011.10.014
 19. Russell TL, Berardi RR, Barnett JL, O'Sullivan TL, Wagner JG, Dressman JB. pH-related changes in the absorption of dipyridamole in the elderly. *Pharm Res.* 1994;11(1):136-43. doi:10.1023/a:1018918316253
 20. Terhaag B, Donath F, Le Petit G, Feller K. The absolute and relative bioavailability of dipyridamole from different preparations and the in vitro-in vivo comparison. *Int J Clin Pharmacol Ther Toxicol.* 1986;24(6):298-302.
 21. Kambayashi A, Yasuji T, Dressman JB. Prediction of the precipitation profiles of weak base drugs in the small intestine using a simplified transfer ("dumping") model coupled with in silico modeling and simulation approach. *Eur J Pharm Biopharm.* 2016;103:95-103. doi:10.1016/j.ejpb.2016.03.020
 22. Vora C, Patadia R, Mittal K, Mashru R. Preparation and characterization of dipyridamole solid dispersions for stabilization of supersaturation: effect of precipitation inhibitors type and molecular weight. *Pharm Dev Technol.* 2016;21(7):847-55. doi:10.3109/10837450.2015.1069330
 23. Abu-Diak OA, Jones DS, Andrews GP. An investigation into the dissolution properties of celecoxib melt extrudates: understanding the role of polymer type and concentration in stabilizing supersaturated drug concentrations. *Mol Pharm.* 2011;8(4):1362-71. doi:10.1021/mp200157b
 24. Konno H, Handa T, Alonzo DE, Taylor LS. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. *Eur J Pharm Biopharm.* 2008;70(2):493-9. doi:10.1016/j.ejpb.2008.05.023
 25. Heigoldt U, Sommer F, Daniels R, Wagner KG. Predicting in vivo absorption behavior of oral modified release dosage forms containing pH-dependent poorly soluble drugs using a novel pH-adjusted biphasic in vitro dissolution test. *Eur J Pharm Biopharm.* 2010;76(1):105-11. doi:10.1016/j.ejpb.2010.05.006
 26. Kalantzi L, Goumas K, Kalioras V, Abrahamsson B, Dressman JB, Reppas C. Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies. *Pharm Res.* 2006;23(1):165-76. doi:10.1007/s11095-005-8476-1
 27. Zecevic DE, Meier R, Daniels R, Wagner KG. Site specific solubility improvement using solid dispersions of HPMC-AS/HPC SSL-mixtures. *Eur J Pharm Biopharm.* 2014;87(2):264-70. doi:10.1016/j.ejpb.2014.03.018
 28. Usui F, Maeda K, Kusai A, Nishimura K, Yamamoto K. Inhibitory effect of water soluble polymers on precipitation of RS-8359. *Int J Pharm.* 1997;154(1):59-66. doi:10.1016/s0378-5173(97)00129-4
 29. Yokoi Y, Yonemochi E, Terada K. Effects of sugar ester and hydroxypropyl methylcellulose on the physicochemical stability of amorphous cefditoren pivoxil in aqueous suspension. *Int J Pharm.* 2005;290(1-2):91-99. doi:10.1016/j.ijpharm.2004.11.020
 30. Ilevbare GA, Liu H, Edgar KJ, Taylor LS. Understanding polymer properties important for crystal growth inhibition-impact of chemically diverse polymers on solution crystal growth of ritonavir. *Cryst Growth Des.* 2012;12(6):3133-43. doi:10.1021/cg300325p
 31. Guzmán HR, Tawa M, Zhang Z, Ratanabanangkoon P, Shaw P, Gardner CR, et al. Combined use of crystalline salt forms and precipitation inhibitors to improve oral absorption of celecoxib from solid oral formulations. *J Pharm Sci.* 2007;96(10):2686-702. doi:10.1002/jps.20906

32. Sieger P, Cui Y, Scheuerer S. pH-dependent solubility and permeability profiles: A useful tool for prediction of oral bioavailability. *Eur J Pharm Sci.* 2017;105:82-90. doi:[10.1016/j.ejps.2017.04.016](https://doi.org/10.1016/j.ejps.2017.04.016)
33. Albers J, Alles R, Matthée K, Knop K, Nahrup JS, Kleinebudde P. Mechanism of drug release from polymethacrylate-based extrudates and milled strands prepared by hot-melt extrusion. *Eur J Pharm Biopharm.* 2009;71(2):387-94. doi:[10.1016/j.ejpb.2008.10.002](https://doi.org/10.1016/j.ejpb.2008.10.002)
34. Overhoff KA, Moreno A, Miller DA, Johnston KP, Williams RO III. Solid dispersions of itraconazole and enteric polymers made by ultra-rapid freezing. *Int J Pharm.* 2007;336(1):122-132. doi:[10.1016/j.ijpharm.2006.11.043](https://doi.org/10.1016/j.ijpharm.2006.11.043)
35. Loftsson T, Fridriksdóttir F, sdóttir TK. The effect of water-soluble polymers on aqueous solubility of drugs. *Int J Pharm.* 1996;127(2):293-6. doi:[10.1016/0378-5173\(95\)04207-5](https://doi.org/10.1016/0378-5173(95)04207-5)
36. Vora C, Patadia R, Mittal K, Mashru R. Preparation and characterization of dipyridamole solid dispersions for stabilization of supersaturation: effect of precipitation inhibitors type and molecular weight. *Pharm Dev Technol.* 2016;21(7):847-55. doi:[10.3109/10837450.2015.1069330](https://doi.org/10.3109/10837450.2015.1069330)
37. Cilurzo F, Minghetti P, Selmin F, Casiraghi A, Montanari L. Polymethacrylate salts as new low-swelling mucoadhesive materials. *J Control Release.* 2003;88(1):43-53. doi:[10.1016/s0168-3659\(02\)00459-5](https://doi.org/10.1016/s0168-3659(02)00459-5)
38. Lin-Vien D, Colthup NB, Fateley WG, Grasselli JG. *The handbook of infrared and Raman characteristic frequencies of organic molecules.* Elsevier; 1991.
39. Parmar VK, Shah SA. Hydrochloride salt co-crystals: preparation, characterization and physicochemical studies. *Pharm Dev Technol.* 2013;18(2):443-453. doi:[10.3109/10837450.2012.696270](https://doi.org/10.3109/10837450.2012.696270)