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Research Article

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Enhancing and Sustaining AMG 009 Dissolution from a Bilayer Oral Solid Dosage Form via Microenvironmental pH Modulation and Supersaturation

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Abstract. Enhancing and sustaining AMG 009 dissolution from a matrix tablet via microenvironmental pH modulation and supersaturation, where poorly soluble acidic AMG 009 molecule was intimately mixed and compressed together with a basic pH modifier (*e.g.*, sodium carbonate) and nucleation inhibitor hydroxypropyl methylcellulose K100 LV (HPMC K100 LV), was demonstrated previously. However, not all acidic or basic drugs are compatible with basic or acidic pH modifiers either chemically or physically. The objective of this study is to investigate whether similar dissolution enhancement of AMG 009 can be achieved from a bilayer dosage form, where AMG 009 and sodium carbonate are placed in a separate layer with or without the addition of HPMC K100 LV in each layer. Study results indicate that HPMC K100 LV-containing bilayer dosage forms gained similar dissolution enhancement as matrix dosage forms did. Bilayer dosage forms without HPMC K100 LV benefitted the least from dissolution enhancement.

KEY WORDS: bilayer dosage form; enhancing; matrix dosage form; microenvironmental pH; nucleation inhibitor; pH modifier; precipitation; supersaturation; sustaining; tablet dissolution.

INTRODUCTION

The oral bioavailability of a drug is mainly a function of its dissolution, stability in gastrointestinal fluids, permeation into the systemic circulation, and metabolic stability. For a low soluble compound, its dissolution is often more rate-limiting than its ability to cross the intestinal mucosa (1); therefore, it is important to enhance drug dissolution in order to increase its bioavailability. The dissolution of a drug is a function of the drug's solubility in the diffusion layer (2,3). This has been established by the relationship between the dissolution rate and the solubility of the compound according to the Noyes–Whitney (4). For weak acidic/basic drugs, this solubility can be a function of the pH of the diffusion layer.

A number of studies (5–9) have been performed in the past, especially in the area of control release, in which organic or inorganic acids or bases, used as pH modifiers, were added to formulations to control the pH of the environment immediately surrounding the solid. Through this control of the microenvironment of the dosage form, pH-independent release has been achieved for basic or acidic drugs in the gastrointestinal (GI) tract where the pH can vary from 1.0 to 7.4. These studies demonstrated that the pH of the microenvironment (*i.e.*, pH of diffusion layer) and therefore, the dissolution of weak acidic and basic drugs can be modulated. Because of this finding, dissolution of poorly soluble weak acidic and basic drugs in both immediate release (10,11) and control release (12–18) dosage forms has been successfully enhanced or retarded by the application of the concept of microenvironmental pH modulation.

In the previous studies (19), it was found that pH modifiers, through the control of microenvironmental pH of the dosage form, are critical for increasing the transient solubility of poorly soluble weak acidic and basic drugs in the diffusion layer and, therefore, their dissolution. It was also found in the previous studies (19) that nucleation inhibitors are important as well for enhancing the dissolution by preventing the crystallization of dissolved AMG 009 (a proprietary medicinal compound of Amgen) in the diffusion layer and bulk dissolution medium. Although pH modifiers and nucleation inhibitors are important in enhancing the dissolution of poorly soluble acidic and basic drugs in the solid dosage forms, in some cases, they might be physically or chemically incompatible with the acidic or basic drugs in the matrix tablets thus preventing the application of the concept of microenvironmental pH modulation and the demonstrated benefit of dissolution enhancement.

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It is hypothesized that dissolution enhancement can be still achieved even without obtaining intimate contact between acidic/basic drugs and pH modifiers in the dosage form. This can be done by manufacturing a bilayer capsule or bilayer tablet in which the pH modifier layer is physically separated from the drug layer to minimize physicochemical interaction between the drug and the pH modifier. In addition, HPMC K100 LV (hydroxypropyl methylcellulose K100 LV) can be added to each layer to function as both a nucleation inhibitor to prevent the precipitation of dissolved drugs and a gel matrix former to prevent the premature loss of the pH modifiers into the dissolution medium. It is believed that such a technique would have the combined effect of modulating the microenvironmental pH of the bilayer dosage forms and, in turn, increasing the drug solubility, preventing the crystallization of the dissolved drugs, and thus enhancing the overall dissolution. It is further hypothesized that adding gel matrix former, HPMC K100 LV, in each layer is critical for the successful enhancement of the dissolution of bilayer dosage forms.

AMG 009 is indicated for the treatment of inflammatory diseases. It is a BCS class II compound with an intrinsic solubility of 0.6 μg/ml. Its chemical structure is shown in Fig. 1. AMG 009, a poorly soluble weak acidic drug, will be used as the model compound to investigate whether a bilayer dosage form, where pH modifiers and AMG 009 are in separate layers, can enhance AMG 009 dissolution to the same extent as a matrix dosage form does, where pH modifiers and AMG 009 are in intimate contact.

MATERIALS

Micronized AMG 009 was discovered and manufactured at Amgen, Inc, CA, USA. Size 2, white opaque hard gelatin capsules were purchased from Capsugel (Peapack, NJ, USA). Excipients used include lactose monohydrate FF 316 (Foremost Farms USA, Baraboo, WI, USA) and microcrystalline cellulose, Avicel PH 102, as fillers (FMC, Philadelphia, PA, USA), HPMC E5 LV (hypromellose 2,910) and HPMC K100 LV (hypromellose 2,208) as polymeric nucleation inhibitors and matrix formers (Dow Chemical, Michigan, USA), sodium carbonate, Na_2CO_3, as pH modifier (EMD Chemicals Inc, NJ, USA), and magnesium stearate as lubricant (Mallinckrodt Baker, Inc, NJ, USA). All other chemicals were of analytical grade and used as received.

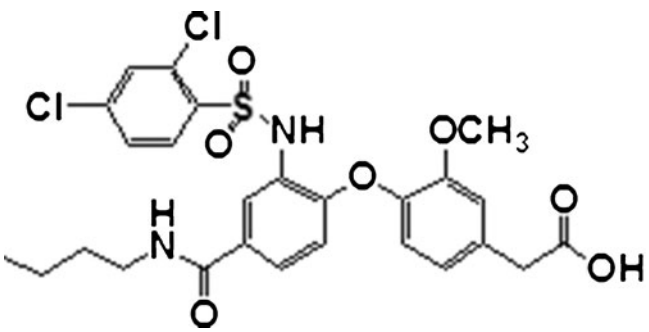

Fig. 1. Chemical structure of AMG 009

METHODS

Solubility Studies

An excess amount of AMG 009 was added to water, 0.01 N HCl and 50 mM buffers (*i.e.*, sodium citrate, sodium phosphate, or sodium carbonate) with desired target pH to give a suspension in 4-ml glass vials. These vials were rotated on a specimen tube rotator (Glas-Col, LLC, In, USA) for 48 h to achieve equilibration at room temperature. After 48 h, all samples were filtered using a 0.45-μm PTFE filter, which has been tested to provide >99% recovery of AMG 009 after filtration. An aliquot was taken from each filtrate for HPLC analysis. The remaining filtrate was used to measure the final pH. Chromatographic analysis was carried out on an Agilent HP 1100 equipped with a multi-wavelength detector (G1365A) and Chromeleon™ software for data analysis. The mobile phase consisted of (a) 0.1% trifluoroacetic acid/2% acetonitrile/97.9% water (% *v*/*v*) and (b) 0.1% trifluoroacetic acid/98% acetonitrile/1.9% water (% *v*/*v*). A gradient program (mobile phase **A** from 90% to 10% for the first 5 min followed by 10% mobile phase **A** for 4 min and then 90% mobile phase **A** in 1 min) was used to elute AMG 009. The separation was achieved using a Zorbax SB-C18 column (5 μm, 4.6×150 mm, Agilent Technologies, CA, USA). A flow rate of 1 ml/min, an injection volume of 20 μl, ambient column temperature, and run time of 10 min were employed. Detection was by UV at 225 nm.

Dissolution Studies

Unless otherwise specified, all dissolution studies were conducted in 900 ml of 0.01 N HCl containing 0.033% HPMC E5 LV at 37°C using USP Apparatus II at an agitation rate of 50 rpm. The samples were analyzed using the Opt-Diss Fiber Optic UV system (Distek Inc, NJ, USA). This UV fiber optic system was equipped with a multichannel CCD spectrometer (210–400 nm). Fiberoptic arch probes, which connect individually to the CCD spectrometer, were calibrated and inserted directly into the dissolution vessels to measure real-time dissolution at 225 nm. Cumulative percentage of drug release was calculated in real time with the Opt-Diss software. The mean of two determinations was used in the data analysis. The dissolution data of placebo tablets and capsules were also collected and subtracted from those of the active ones. The placebo capsule and tablet formulations are the same as the active ones except that they do not have AMG 009 in the formulations.

Manufacturing of Matrix Capsule and Tablet

As shown in Table I, matrix capsules and tablets were manufactured at 20 g per batch. AMG 009 was mixed with all ingredients in a 100-ml glass bottle using a Turbula mixer (GlenMills Inc, NJ, USA) for 3 min, and then the mixture was screened through a #40 mesh screen. The screened mixture was then put back into the bottle with a magnetic stir bar. The blend was then further mixed on a magnetic stir plate for approximately 5 min at 400 rpm. The resulting blends were either manually filled into capsules or compressed into tablets

Table I. Formulation Compositions of Matrix Capsules and Tablets

Ingredients	% *w/w* Composition	mg/unit
AMG 009 Micronized	20.00	25.00
Lactose Monohydrate FF316	28.57	35.71
Avicel PH102	25.00	31.25
HPMC K100 LV	15.00	18.75
Na_2CO_3	10.93	13.66
Magnesium stearate	0.50	0.63
Total	100.00	125.00

using a semiautomatic Carver Press (Carver Inc, IN, USA) at 4.89 kN using 7 mm round concave tooling.

Manufacturing of Bilayer Capsule and Tablet

Table II shows the formulation compositions of bilayer capsules and tablets. They were manufactured at 40 g per batch. Four powder blends were prepared as indicated in Table II. Blend A contains AMG 009, Avicel pH102, lactose monohydrate FF 316, HPMC K100 LV, and magnesium stearate; blend B contains sodium carbonate, Avicel pH 102, lactose monohydrate FF 316, HPMC K100 LV, and magnesium stearate. Blends C and D contain the same ingredients as blends A and B, respectively, but without HMPC K100 LV in the formulation. Each blend was manufactured by mixing all the ingredients in a 150-ml glass bottle using a Turbula mixer for 3 min followed by screening through a #40 mesh screen. The screened blend was once again put back into the bottle with a magnetic stir bar. The blend was then further mixed on a magnetic stir plate for approximately 5 min at 400 rpm. For the manufacturing of bilayer capsules, 82.5 mg of blend A or C was weighed and dispensed into a size 2 hard gelatin capsule and gently tapped using a size 2 tooling. About 42.5 mg of blend B or D was then weighed, layered, and tapped on the top of blend A or C, respectively. The capsule cap and body were then locked manually. For the manufacture of the bilayer tablet, the same amount of blends A, B and C, D was weighed and layered into the die in the same manner as described for the capsule and compressed using 7 mm round concave tooling at 4.89 kN on a Carver Press. As a result of the aforementioned process, bilayer capsules and tablets manufactured using blends A and B contained HPMC K100 LV, while those manufactured using blends C and D did not.

RESULTS AND DISCUSSION

The pH solubility profile of AMG 009 is shown in Fig. 2. Intrinsic solubility of the unionized drug is very low (0.6 μg/ml). Solubility increases with pH, reaching 4.7 mg/ml at pH 8.3. These facts indicate that a strong basic pH modifier, such as sodium carbonate with a pk_a value of 10.3, is needed in the dosage form to increase the pH of the microenvironment and thus the solubility, resulting in increased dissolution of AMG 009. The detailed study and selection of basic pH modifiers were described in a previous publication (20).

Figure 3 shows the dissolution profiles of matrix and bilayer capsules. The results shown in Fig. 3 indicate that bilayer capsules containing HPMC K100 LV achieved similar dissolution enhancement as matrix capsules did. Bilayer capsules without HPMC K100 LV, on the other hand, show much lower dissolution profile than that obtained with matrix capsules. These results indicate that similar pH modulation, resulting in similar microenvironmental pH, to that of matrix capsules occurred in the HPMC K100 LV-containing bilayer capsules. It can be expected that HPMC K100 LV in the bilayer matrix would quickly hydrate to form a gel mass after contacting the dissolution medium. The formation of gel mass in the bilayer capsules would delay its disintegration. This is supported by the observation that there was no gel mass disintegration during the dissolution experiments. Instead, the gel mass was slowly eroded and completely dissolved in about 50 min after dissolution was started. The slow erosion process might have prevented the premature loss of the pH modifier, sodium carbonate, into the dissolution medium, and therefore, it had an opportunity to dissolve and diffuse into the drug layer to modulate the microenvironmental pH and increase the drug's solubility in the diffusion layer resulting in enhanced AMG 009 dissolution.

In comparison to the HPMC K100 LV-containing bilayer capsules, it was observed that bilayer capsules without HPMC

Table II. Formulation Compositions of Bilayer Capsules and Tablets

Ingredients of drug layer	% *w/w* Composition	mg/unit	% *w/w* Composition	mg/unit
	Blend A		Blend C	
AMG 009 Micronized	30.30	25.00	30.30	25.00
Avicel pH 102	25.26	20.84	25.26	20.84
Lactose FF 316	28.86	23.81	43.98	54.98
HPMC K100 LV	15.15	12.50	–	–
Magnesium stearate	0.5	0.41	0.5	0.41
Subtotal	100.00	82.50	100.00	82.50
	Blend B		Blend D	
Na_2CO_3	32.19	13.68	32.19	13.68
Avicel pH 102	24.53	10.42	24.53	10.42
Lactose FF 316	28.05	11.92	42.77	53.46
HPMC K100 LV	14.73	6.26	–	–
Magnesium stearate	0.50	0.21	0.50	0.21
Subtotal	100.00	42.50	100.00	42.50
Total	–	125.00	–	125.00

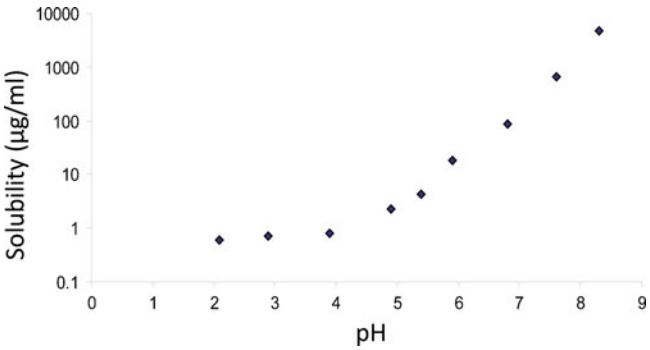

Fig. 2. pH solubility profile of AMG 009

K100 LV quickly disintegrated at the beginning of dissolution experiments, and this might have led to the loss of sodium carbonate to the dissolution medium and neutralized by 0.01 N HCl. As a result, microenvironmental pH modulation of the AMG 009 might have been partially or completely lost resulting in little or no increase of AMG 009 solubility, which, in turn, leads to lower dissolution enhancement of AMG 009.

The dissolution results shown in Fig. 3 were obtained using 0.01 N HCl dissolution medium which does not contain any nucleation inhibitor. Because neither the dissolution medium nor the bilayer capsules, *i.e.*, those manufactured from blends C and D, has any nucleation inhibitors (*i.e.*, HPMC K100 LV or HPMC E5 LV), it might be concluded that the lower dissolution enhancement of these dosage forms may be due to the precipitation of dissolved AMG 009 as a result of its supersaturation in 0.01 N HCl medium. However, the results presented in Fig. 4 indicate that these capsules still had lower dissolution enhancement than HPMC K100 LV-containing bilayer capsules even though 0.033% HPMC E5 LV was already added into the dissolution medium as a nucleation inhibitor.

Adding HPMC E5 LV into the dissolution medium instead of placing it in the tablets is to maintain its nucleation inhibition effect and to eliminate its gel matrix formation effect. It is believed that two events helped to enhance AMG 009 dissolution, one is HPMC gel matrix formation to prevent the premature loss of Na_2CO_3 into the dissolution medium,

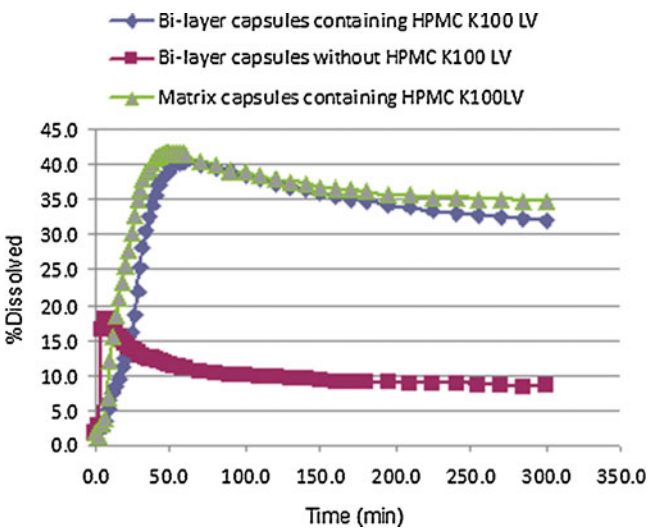

Fig. 3. Dissolution profiles of capsules in 900 ml of 0.01 N HCl using USP Apparatus II

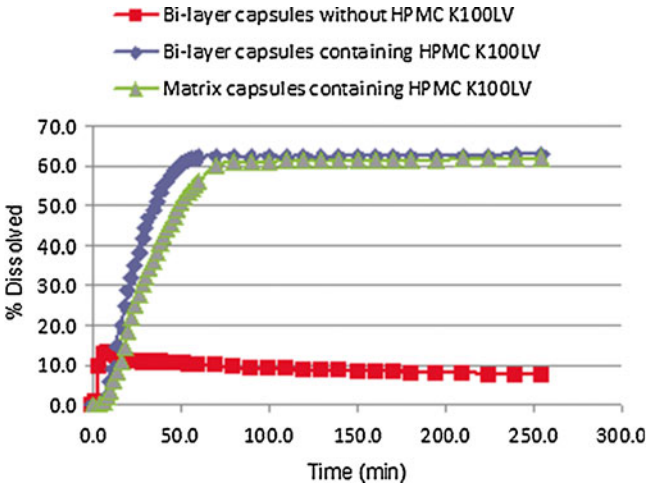

Fig. 4. Dissolution profiles of capsules in 900 ml of 0.01 N HCl containing 0.033% HPMC E5 using USP Apparatus II

resulting in effective microenvironmental pH modulation and AMG 009 solubility increases in the diffusion layer. The other is to prevent the precipitation of dissolved AMG 009 by the nucleation inhibitors. As a result of these two events, the dissolution enhancement of AMG 009 was achieved. In order to elucidate the root cause of lower dissolution enhancement of bilayer capsules without HPMC K100 LV as the gel matrix former, HPMC E5 LV was added in the dissolution medium instead of in the tablets to deconvolute the two events to prove the hypothesis that gel matrix formation is critical for the successful enhancement of AMG 009 dissolution.

Although the exact molecular mechanism is unknown, previous studies (19) have shown that HPMC E5 LV was a very effective nucleation inhibitor, and it was more effective than HPMC K100 LV, which is in fact collaborated by the comparison of the data presented in Figs. 3 and 4. Analysis of the results obtained in Figs. 3 and 4 indicates that the addition of HPMC E5 LV resulted in more than 20% increase in the dissolution of AMG 009. Therefore, the differences in dissolution enhancement between the two types of bilayer capsules, *i.e.*, those with and without HPMC K100LV, cannot be attributed to the prevention of AMG 009 precipitation. Rather, the primary cause is probably due to the premature loss of sodium carbonate to the dissolution medium resulting in the loss of pH modulation in the bilayer capsules.

Both HPMC K100 LV and HPMC E5 LV are hydroxypropyl methylcellulose. However, they have different degree of hydroxypropoxyl and methoxyl substitution. HPMC E5 has more methoxyl and less hydroxypropoxyl substitution. HPMC K100 is opposite to HPMC E5, and it has less methoxyl and more hydroxypropoxyl substitution, and thus, HPMC K100 LV is more hydrophilic and hydrates faster, resulting in less loss of Na_2CO_3 into the dissolution medium due to the initial burst release. HPMC K100 LV is more viscous than HPMC E5 LV (about 100 cP *vs.* 5 cP in a 2% aqueous solution at 20°C), and it forms a better gel matrix with a very high efficiency than HPMC E5 LV does. However, HPMC K100 LV, being the least viscous in control release (CR) grade of HPMC polymers, does not accommodate a lot of water and erodes fast during hydration. As a result, the swelling phenomenon is visually minimal.

The concentration of HPMC K100 LV, when used alone in the CR dosage forms, is usually higher than that used in current bilayer capsules and tablets. Higher HPMC K100 LV concentration in the formulation will help to form a strong gel mass that will not be disintegrated upon contacting with fluid. On the other hand, a very low concentration of HPMC K100 LV, *i.e.*, <5%, in the formulation will form a very weak gel mass, which may be easily broken by internal (superdisintegrant) or external (hydrodynamic) forces. In this study, it was found that 10% to 15% HPMC K100 LV in the bilayer capsules and tablets forms acceptable gel mass, and its integrity was maintained during the dissolution studies. Since this concentration is not as high as those used in CR dosage forms, the gel mass was eroded very fast, resulting in complete drug release within 1 h. Although HPMC K100 LV has a relatively large molecular weight and high viscosity, its dissolution rate is faster enough to qualify it to be an efficient nucleation inhibitor (19). Consequently, HPMC K100 LV can be used as both a gel matrix former and a nucleation inhibitor. Of course, there are many other HPMC polymers that are available commercially and can be evaluated to be a gel matrix former and nucleation inhibitor, which is beyond the scope of this work. In the future, specific attention should focus on gel strength investigation because GI motility force may break the weak gel mass and split the bilayer dosage forms into drug layer and pH modifier layer and lead to the loss of microenvironmental pH modulation, resulting in lower dissolution, lower bioavailability, possible large intra- and inter-subject variability, or increased food effect. Thus, it is strongly recommended to optimize the gel strength before conducting any *in vivo* studies.

In the previous studies (20), it was found that, when Na_2CO_3 was removed from the formulation and dissolved in the dissolution medium prior to tablet dissolution study, only 4% AMG 009 was released from the matrix tablets. This indicates that the dissolution enhancement in aforementioned study is a result of microenvironmental pH modulation by Na_2CO_3 because the pH of bulk dissolution medium is the same before and after dissolution and is not impacted by such a small amount of Na_2CO_3. Therefore, it is critical to use a gel matrix former to prevent the premature loss of Na_2CO_3 into the dissolution medium, and then, microenvironmental pH modulation can be maintained to enhance AMG 009 dissolution.

The dissolution profiles of bilayer and matrix tablets are shown in Fig. 5. The results presented in Fig. 5 show that HPMC K100 LV-containing bilayer tablets achieved much higher dissolution than bilayer tablets manufactured using blends C and D. The results also show that HPMC K100 LV-containing bilayer tablets had a relatively lower rate and extent of dissolution than the matrix tablets did, which is different from what was observed with the capsule dosage forms. The reason for the difference might be that Na_2CO_3 is more difficult to diffuse in the tablets than in the capsules due to the inherent density differences between the two dosage forms. It can thus be surmised that the tablets lost more Na_2CO_3 to the dissolution medium than the capsules during the dissolution experiments, and this adversely affected the pH modulation of the tablets, resulting in lower AMG 009 dissolution enhancement. The results presented in Fig. 5 also indicate that the extent of cumulative dissolution decreases with time. This phenomenon has been observed from the data

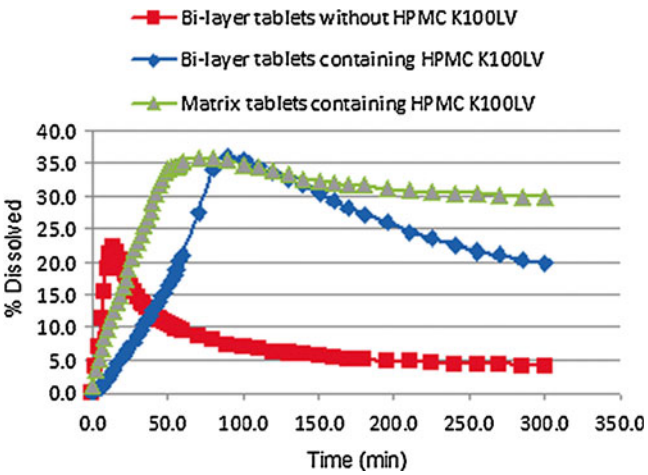

Fig. 5. Dissolution profiles of tablets in 900 ml of 0.01 N HCl using USP Apparatus II

presented in Fig. 3 too. The exact cause has not been investigated. However, it is most likely that dissolved AMG 009 gradually precipitated in the dissolution medium as a result of its supersaturation and lack of enough nucleation inhibition in the dissolution medium. This may be supported from the analysis of data presented in Fig. 4, which indicates less precipitation occurs when extra amount of nucleation inhibitor HPMC E5 LV was added into dissolution medium to prevent the precipitation of dissolved AMG 009.

Finally, all dissolution experiments in this study were conducted using 0.01 N HCl as dissolution medium. If dissolution medium is replaced with 0.1 N HCl, it is expected that dissolution may be slowed down as a result of higher buffer capacity of 0.1 N HCl. It is believed that some of Na_2CO_3 in the dosage form is consumed by the infiltrated hydrogen ions and others were used to modulate the micro-environmental pH. When more hydrogen ions infiltrate into the dosage form as a result of its high buffer capacity, more Na_2CO_3 will be consumed by buffer ions and less will be available for microenvironmental pH modulation, leading to lower dissolution enhancement. In order to increase the dissolution, more Na_2CO_3 has to be added in the dosage form to compensate the buffer capacity increases in the dissolution medium.

Although none of above formulations released 100% AMG 009 in all dissolution studies, the assay of each formulation was between 98.0% and 99.8% of claim value. This indicates that formulation can be further optimized to enhance AMG 009 release to 100% by adding more sodium carbonate in the formulation. However, this is beyond the scope of this study.

In summary, the aforementioned studies support the hypothesis that dissolution enhancement can be achieved even in the absence of intimate contact between pH modifiers and active ingredients in the dosage form. This is consistent with the previous study (21), which showed that dissolution enhancement was achieved even though the pH modifier and active ingredients were placed in a separate layer in the dosage form. However, it was found from this study that *in situ* microenvironmental pH modulation during *in vitro* and *in vivo* dissolution process is definitely needed in order to enhance the solubility and therefore the dissolution of poorly

soluble compound AMG 009, and this has been done by adding HPMC K100 LV as the gel matrix former throughout the bilayer dosage form to prevent the premature loss of Na_2CO_3 layer to the dissolution medium, and therefore, Na_2CO_3 can dissolve and diffuse into drug layer and increase AMG 009 solubility and dissolution.

CONCLUSIONS

Similar dissolution enhancement has been achieved between matrix and bilayer dosage forms. The results obtained in this study indicate that a bilayer dosage form can be used to enhance the dissolution of low soluble drugs. Bilayer dosage forms also have the added advantage of minimizing any potential incompatibilities that may exist between the drugs and pH modifiers. It was also found from this study that having a gel matrix former in the bilayer dosage form is critical for enhancing the dissolution of both tablet and capsule dosage forms. The gel matrix former prevented the disintegration of the bilayer dosage form during the dissolution experiments, and this might have prevented the premature loss of sodium carbonate to the dissolution medium. Prevention of the premature loss of the sodium carbonate ensured that similar pH modulation and microenvironmental pH were maintained in the bilayer dosage forms to achieve dissolution enhancements that were similar to those obtained with the matrix dosage forms. Bilayer dosage forms without a gel matrix former, on the other hand, showed minimal dissolution enhancement.

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