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Development of Delayed-Release Matrix Tablets Comprising Solid Dispersion of Mefenamic Acid

Namfa Sermkeaw[1,2] and Thipapun Plyduang[1,2,*]

[1]School of Pharmacy, Walailak University, Nakhon Si Thammarat 80160, Thailand
[2]Drug and Cosmetics Excellence Center, Walailak University, Nakhon Si Thammarat 80160, Thailand

([*]Corresponding author's e-mail: thipapun.pl@wu.ac.th, thipapun.pl@mail.wu.ac.th)

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Abstract

Mefenamic acid (MA), a member of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), has been widely use to relief pain and inflammation. Its medical uses are limited by poor aqueous solubility resulting in low bioavailability and gastric irritation. The aim of this study was to develop a mefenamic acid delayed-release matrix tablet formulation using solid dispersion (SD). Delayed-release drug delivery systems were designed to retard drug release in upper gastrointestinal tract avoiding gastrointestinal (GI) adverse reactions. SDs of MA were successfully prepared by solvent evaporation method employing methanol as a solvent. SDs incorporated surfactant and super disintegrant gave much higher rates of dissolution than SDs with combined carriers (PEG and surfactant), SD containing PEG and pure drug, respectively. The optimal SD containing MA:PEG4000:poloxamer188:crospovidone in the ratio 1:8:1:3 exhibited higher amount of drug release up to 8-fold compared with pure MA. FTIR and DSC were performed to identify the physicochemical interaction between drug and polymers. The resulting data justified that no change in the chemical structure of MA and the crystalline MA transformed into the amorphous state after preparation. The formulation F4 delayed-release tablet comprising SD of MA dissolved less than 4 % in artificial gastric fluid in the initial 2 h and released more than 95 % at 3 h in the artificial intestinal fluid. Accordingly, formulation F4 containing polyethylene oxide as a time-controlled matrix-forming polymer was a promising delayed-release solid dispersion system of MA.

Keywords: Mefenamic acid, Solid dispersion, Delayed-release, Matrix tablet, Dissolution

Introduction

Mefenamic acid (MA) is an anthranilic acid derivative which has been widely used to relieve mild to moderate pain. MA is licensed in clinical therapy to relieve primary dysmenorrhea and menorrhagia and to treat postoperative pain, soft tissue injuries, and other musculoskeletal painful conditions [1-3]. Its medical uses are limited by 2 drawbacks, 1, as a poorly water-soluble drug with solubility in water of approximately 0.004 mg mL^{-1} at 37 °C [4]. The other, concerns the increasing incidence of gastrointestinal (GI) adverse reactions, such as gastritis, peptic ulcers, etc [5,6].

Pharmaceutical efforts have recently focused on overcoming the solubility limitation of MA through several approaches such as complexation [7,8], self-emulsifying drug delivery system (SEDDS) [9], SMEDDS [10], Nanocrystals [11], freeze drying techniques [12], liposome encapsulation [13], and also solid dispersion (SD) [14,15]. SD technology is now firmly established as improving the solubility, dissolution rate, and oral absorption of poorly aqueous-soluble drugs. SD generally provides the molecular dispersion of a drug within a polymer carrier and hence, provides a large drug surface area for dissolution [16]. Although SDs of MA have been previously formulated [14-23], there is an inherent lack of studies involving the combination of surfactants and super disintegrants in SDs of MA.

In this study, polyethylene glycol (PEG) was used as a carrier, alone and in combination with surfactants and super disintegrants to enhance the dissolution of MA. PEG was selected owing to its hydrophilicity, wide drug compatibility, and low toxicity [21,24]. Non-ionic surfactants (Tween 20 and poloxamer 188) and super disintegrants (sodium starch glycolate and crospovidone) were incorporated into the systems to increase the wettability [25], and reduce the drug aggregation [26], respectively.

The delayed-release dosage form is designed to postpone the onset of drug release until the dosage form has reached the small intestine [27]. SD of MA was prepared on delayed-release matrix tablets to

avoid gastric irritation by MA. In the matrix system, the drug substance is homogeneously distributed throughout a polymer matrix. The advantages of matrix-type preparations are short developing time and an easy-to-apply technique for formulating the drug using conventional manufacturing equipment [28]. Among various polymers, Kollidon® SR, Eudragit® RS PO, and polyethylene oxide (PEO) were selected for use in this study because they have been reported to formulate appropriate sustained release matrix formulations [28-32].

The aims of the present study were to; (1) prepare SDs of MA using PEG as a carrier and study the effect of surfactants and super disintegrants incorporated in the SDs on the dissolution profile, and (2) develop delayed-release matrix tablets containing SD of MA using different time-controlled release polymers.

Materials and methods

Materials

Mefenamic acid (98.5 % purity), PEO (MV CA. 1,000,000), and PEG 4000 were purchased from Sigma-Aldrich (Missouri, USA). Crospovidone (Polyplasdone XL-10) was a gift sample from Ashland (Calvert City, Kentucky). Tween 20 was supplied by NOF Corporation (Tokyo, Japan). Sodium starch glycolate was procured from P.C. Drug Center Co., Ltd. (Bangkok, Thailand). Poloxamer 188 was obtained from Croda (Fogars de la Selva, Spain). Eudragit® RS PO was a donation from Evonik Nutrition & Care GmbH (Essen, Germany). Kollidon® SR was a gift sample from BASF (Ludwigshafen, Germany). Avicel PH 102 was purchased from Mingtai Chemical Co., Ltd. (Cosco, Hong Kong). Methanol (HPLC grade) was obtained from RCI Labscan (Bangkok, Thailand). All other chemicals were of analytical grade.

Preparation of SDs

The required quantities of MA, PEG 4000, and surfactant (Tween 20 or Poloxamer 188) were dissolved in methanol to obtain a clear solution. The super disintegrant (sodium starch glycolate or crospovidone) was then dispersed to the drug solution. The solvent was removed by evaporation and the obtained product was dried at 50 °C for 24 h in a vacuum oven. The product was crushed, pulverized, and screened through a 100-mesh sieve. Several SDs were prepared with their ratios of composition as shown in **Table 1**.

Table 1 Formulations of solid dispersions containing MA.

SD. No.	SD code	MA	PEG 4000	Surfactant		Super disintegrant	
				Tween 20	PL	SSG	CP
1	MA-PEG 18	1	8	-	-	-	-
2	MA-PEG-TW 181	1	8	1	-	-	-
3	MA-PEG-TW-SSG 1813	1	8	1	-	3	-
4	MA-PEG-TW-CP 1813	1	8	1	-	-	3
5	MA-PEG-PL 181	1	8	-	1	-	-
6	MA-PEG-PL-SSG 1813	1	8	-	1	3	-
7	MA-PEG-PL-CP 1813	1	8	-	1	-	3

SD: Solid dispersion, MA: Mefenamic acid, PEG: Polyethylene glycol 4000, TW: Tween 20, PL: Poloxamer 188, SSG: Sodium starch glycolate, CP: Crospovidone

Preparation of physical mixtures

Physical mixtures were first prepared by weighing and physically mixing all compounds in a sealed plastic bag. The compositions of the physical mixtures were similar to those of the SDs No. 4 and 7 as shown in **Table 1**.

Physical characterization of solid dispersions

Estimation of SDs of MA

The absorbance of MA solutions in phosphate buffer (pH 6.8) was measured using a UV-Vis spectrophotometer (Jasco V-630, Japan) at 284 nm to determine the amount of MA. The mean peak areas for each concentration were calculated from 3 determinations. The standard curve was constructed by plotting concentrations against the peak areas. The concentration ranges of 4 - 20 µg mL^{-1} showed good linearity with a correlation coefficient of 0.9998. The intraday precision of the method was obtained with 3 replicates for each concentration of sample showing a percentage relative standard deviation (%RSD) of 0.24 - 0.70, and the %RSD of the interday precision was obtained in the range of 0.53 - 0.80. The recovery percentage of the method was between 98.89 ± 0.05 and 99.85 ± 0.04.

Drug content determination

Three samples of 50 mg of SDs from each batch were selected and the amount of MA was evaluated. Weighed samples were transferred into a 100 mL volumetric flask. Methanol was added to dissolve the drug from the dispersion. The solution was filtered through a 0.45 µm membrane filter and then carefully collected in another 100 mL volumetric flask. The solution was made up to volume with phosphate buffer (pH 6.8). The solution was suitably diluted with appropriate dissolution fluid and the assay was conducted at 284 nm for MA. All determinations are shown as mean ± SD of 3 determinations.

Dissolution studies

Dissolution of MA was performed in an USP paddle apparatus (Varian VK-7010, Canada) using 900 mL phosphate buffer solution at pH 6.8. The paddle stirrer speed of 50 rpm and temperature of 37 ± 0.5 °C were used in each test. Pure drug, physical mixture, or SD of drug equivalent to 100 mg of MA was used in each dissolution test. At different time intervals (5, 15, 25, 35, 45, 60 and 120 min), a 5 mL sample of dissolution medium was passed through a filter (0.45 µm), suitably diluted, and assayed for MA using a UV spectrophotometer (Jasco V-630, Japan) at 284 nm. In addition, 5 mL fresh medium was replaced after each withdrawal. The dissolution experiments were conducted in triplicate. The cumulative percentages of the drug dissolved from the physical mixture or SD were calculated (n = 3, mean ± SD).

Fourier-transform infrared (FTIR) spectroscopy

Infrared studies were performed to examine the interaction between the drug and carrier used in the formulation of SD using the potassium bromide disc method with an FTIR spectrophotometer (Vertex 80, USA). The samples were scanned over a wavenumber ranging between 4,000 and 400 cm^{-1} for 20 scans.

Differential scanning calorimetry (DSC)

Thermal analysis was performed on the pure drug, carriers (PEG 4000, poloxamer 188, and crospovidone), physical mixture, and SD to evaluate any change in melting point of the formulations which ensures the stability of the drug when heat is applied. The DSC thermograms were recorded using a differential scanning calorimeter (PerkinElmer Sciex ELAN 6000, USA). Approximately 5 mg of each sample was heated in an aluminum pan from 25 to 260 °C at a heating rate of 10 °C min^{-1} under a stream of nitrogen.

Preparation of delayed-release tablets comprising SDs of MA

Tablet preparation

The SD, MA-PEG-PL-CP 1813 was selected to prepare delayed-release tablets based on the dissolution results. Tablets containing SD of MA were prepared by dry granulation. The powder particles of SD were compressed into large flat tablets (diameter 25 mm) using a single punch tablet press machine (Charatchai machinery CMT-12, Thailand). These slugs are broken, and the milled slugs are passed through a 14-mesh screen to obtain granules. The excipients (Avicel PH-102, Kollidon® SR, Eudragit® RS PO, or PEO) were passed through sieve no. 18. The formulations (F1 - F4) are shown in **Table 2**. The granules of SD and excipients were added in geometric proportions and thoroughly mixed for 15 min. The blend was mixed slightly with lubricant (magnesium stearate) for 2 min. A single punch tablet press machine (Charatchai machinery CMT-12, Thailand) equipped with a 17×6.5 mm^2 caplet-shape punch and die set was used in the process of compressing tablets.

Table 2 Compositions and physical characteristics of delayed-release tablets containing MA solid dispersion.

Formulation	F1	F2	F3	F4
Composition (mg)				
SD equivalent to MA 60 mg	780	780	780	780
Avicel PH-102	88	-	-	-
Kollidon® SR	-	88	-	-
Eudragit® RS PO	-	-	88	-
Polyethylene oxide (PEO)	-	-	-	88
Magnesium stearate	8.7	8.7	8.7	8.7
Total weight	876.7	876.7	876.7	876.7
Physical characteristics				
Width (mm)	7.07 ± 0.01	7.07 ± 0.01	7.06 ± 0.01	7.07 ± 0.01
Thickness (mm)	7.55 ± 0.32	7.40 ± 0.30	7.50 ± 0.20	7.70 ± 0.15
Length (mm)	17.38 ± 0.02	17.45 ± 0.02	17.40 ± 0.02	17.30 ± 0.02
Hardness (kg/cm^2)	7.48 ± 0.40	7.93 ± 0.52	7.76 ± 0.66	7.97 ± 0.46
Friability (%)	0.33	0.25	0.36	0.27
Drug content (%)	98.30 ± 2.11	100.18 ± 2.45	97.90 ± 2.15	99.25 ± 3.10

Data are expressed as mean ± SD, SD: Standard deviation

Tablet characterization

The compressed tablets were evaluated for thickness, length, and hardness using a 3-in-1 hardness, diameter, and thickness tester (Pharma test PTB 311E, Germany). Vernier caliper (Mitutoyo Series 530, Japan) was used to measure their width. The friability of the tablets was tested using a tablet friability tester (Erweka TA 220, Germany). Ten tablets of known weight were de-dusted in a drum for a fixed time (25 rpm for 4 min), and weighed again. Tablet friability was calculated as the percentage of weight loss, which should not be more than 1 %.

Drug content

From each formulation, 5 tablets were weighed and powdered; then, 112.4 mg tablet powder (equivalent to 100 mg of SD) was collected and transferred into a 100 mL volumetric flask. MA was extracted with methanol. The methanolic extracts were mixed, the volume adjusted with phosphate buffer (pH 6.8), and then filtered through a 0.45 µm membrane filter. The solution was subsequently diluted with appropriate dissolution fluid and analyzed for MA content by measuring absorbance at 284 nm.

Dissolution studies on delayed released tablets

Drug release behaviors of pure drug, SD of MA, and tablets comprising SDs of MA were analyzed using the USP dissolution apparatus II equipped with a paddle which was operated at 37.0 ± 0.5 °C and a speed of 50 rpm. The dissolution media were 0.1 N hydrochloric acid (pH 1.2) for the first 2 h, followed by phosphate buffer (pH 6.8) for a further 3 h. Samples of 5 mL were withdrawn at 15, 30, 45, 60 and 120 min from the HCl solution and at 15, 30, 45, 60, 120 and 180 min from the phosphate buffer solution. Fresh medium (5 mL) was also added after each sampling. The content of MA was analyzed spectrophotometrically at 284 nm. The release studies were performed in triplicate and the mean values of the cumulative percent drug release were plotted versus time.

Results and discussion

Preparation of SDs

SDs of MA were successfully prepared using the solvent evaporation method employing methanol as the solvent. The obtained SDs were a white powder. The drug content in all SDs was evaluated using UV-Vis spectrophotometry. All products exhibited the presence of high drug loading within the acceptance criterion of 95 - 105 % and the coefficient of variation of the triplicate drug content measurement was within 5 % as shown in **Table 3**. These results indicate that the drug was uniformly dispersed in the polymer. Thus, the method and the carriers used in this study were found to be reproducible for the preparation of SDs of MA.

Table 3 Drug content of solid dispersion formulations.

SD Code	MA content		Drug loading (%)
	Percentage	CV	
MA-PEG 18	10.88 ± 0.24	2.21	97.92
MA-PEG-TW 181	9.68 ± 0.37	3.82	96.82
MA-PEG-TW-SSG 1813	7.58 ± 0.30	3.96	98.56
MA-PEG-TW-CP 1813	7.82 ± 0.27	3.45	101.7
MA-PEG-PL 181	9.84 ± 0.35	3.56	98.39
MA-PEG-PL-SSG 1813	7.52 ± 0.27	3.59	97.81
MA-PEG-PL-CP 1813	7.64 ± 0.31	4.06	99.28

Values are expressed as mean ± SD of triplicate measurements, CV: Coefficient of variation = (SD/mean)×100.

Dissolution studies of SDs of MA

In vitro dissolution profiles of pure drug, SDs, and physical mixtures in phosphate buffer (pH 6.8) are presented in **Figures 1** and **2**. Pure MA exhibited a very poor dissolution rate in which only 11.87 and 26.78 % of the drug was released after 45 and 120 min, respectively. All the SDs exhibited a markedly higher drug release than MA alone at all-time points. Approximately 5-fold increase in the amount of MA released was obtained for MA-PEG 18 after 45 min when compared with that of pure MA. PEG is known to increase aqueous solubility and improve dissolution rate of drugs in SD through weak complexation resulting in the decrease of drug crystallinity.

Incorporation of surfactants, such as Tween 20 or poloxamer 188 resulted in enhancing the dissolution rate over that of MA-PEG 18, especially the initial dissolution rate. The SD comprising poloxamer 188 provided more drug release than that of Tween 20. Within the initial dissolution time of 5 min, 30.68 and 40.68 % of MA was released from MA-PEG-TW 181 and MA-PEG-PL 181, respectively, whereas a small amount of MA (1.45 %) was detected from the pure drug. At the same time period of 45 min, 62.35 and 64.58 % of drug release was found from MA-PEG-TW 181 and MA-PEG-PL 181, respectively (**Figures 1** and **2**). The probable reason for the enhancement of dissolution in these formulations is the locally imposed surfactants of Tween 20 or poloxamer 188 as the dissolution enhancers. High wettability of the drug in the presence of a dissolution enhancer could also be considered as the mechanism for improvement in the solubility of MA.

Incorporation of water dispersible super disintegrants, including sodium starch glycolate and crospovidone, in SDs resulted in rapid and higher dissolution of MA than that with the pure drug, the SD in PEG, as well as the SDs in combined carriers (PEG and surfactant). SDs containing crospovidone showed higher drug release than that of sodium starch glycolate both in the case of Tween 20 and poloxamer 188. This might be because crospovidone in SD markedly decreased the interfacial tension between the hydrophobic drug and dissolution medium [19]. At 45 min, 70.89 and 64.64 % of MA was measured from MA-PEG-TW-CP 1813 and MA-PEG-TW-SSG 1813, respectively. Similarly, 98.81 and 73.94 % of MA was detected from MA-PEG-PL-CP 1813 and MA-PEG-PL-SSG 1813, respectively (**Figures 1** and **2**). The super disintegrant surrounding the drug particles may decrease aggregation and agglomeration of these

particles, resulting in their rapid contact with the dissolution medium with wetting of their surfaces, and thus, enhancing its dissolution rate. Among all SDs, MA-PEG-PL-CP 1813 showed the highest drug release of 8.32 times in comparison to that of the pure drug after 45 min; furthermore, it enhanced MA release up to 100 % within 120 min (**Figures 2**). Thus, MA-PEG-PL-CP 1813 was selected for further study in the preparation of delayed-release tablets of MA.

The dissolution behavior of physical mixtures (MA-PEG-PL-SSG 1813 PM and MA-PEG-PL-CP 1813 PM) was a little better than that of the pure drug. Less than 29 % of total MA was released from the physical mixtures within 45 min (**Figures 1** and **2**). Physical mixtures were prepared by physical mixing and thus, the MA could be in crystalline form, whereas the drug in SD was converted into the amorphous status, consistent with the DSC observations. These results also demonstrated that the SD approach was necessary in enhancing the dissolution rate and extent of MA.

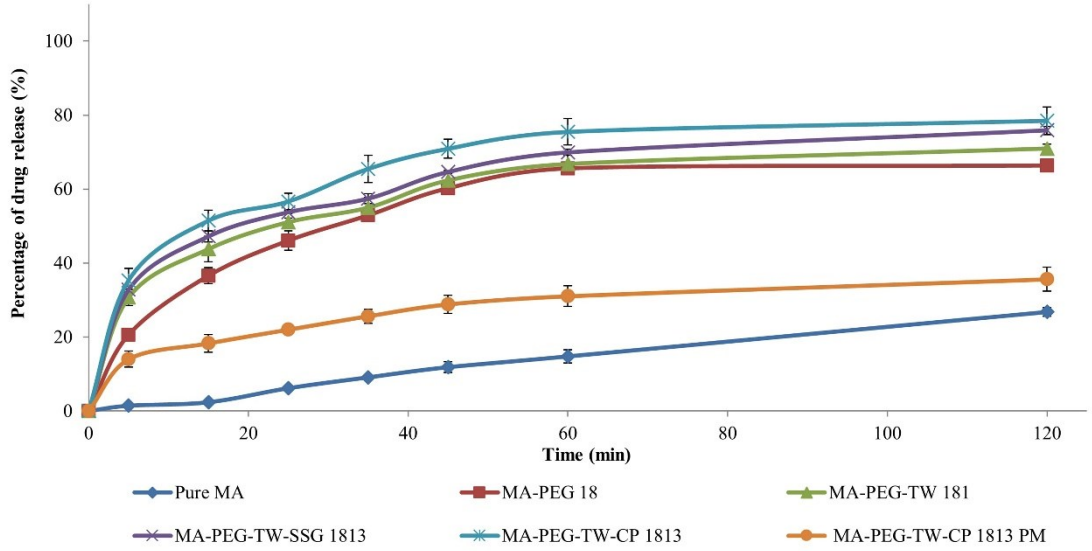

Figure 1 Dissolution profiles of pure MA, solid dispersions (MA-PEG 18, MA-PEG-TW 181, MA-PEG-TW-SSG 1813, MA-PEG-TW-CP 1813) and physical mixture (MA-PEG-TW-CP 1813 PM) in pH 6.8 phosphate buffer solution. The data shown are mean ± SD of 3 replicates.

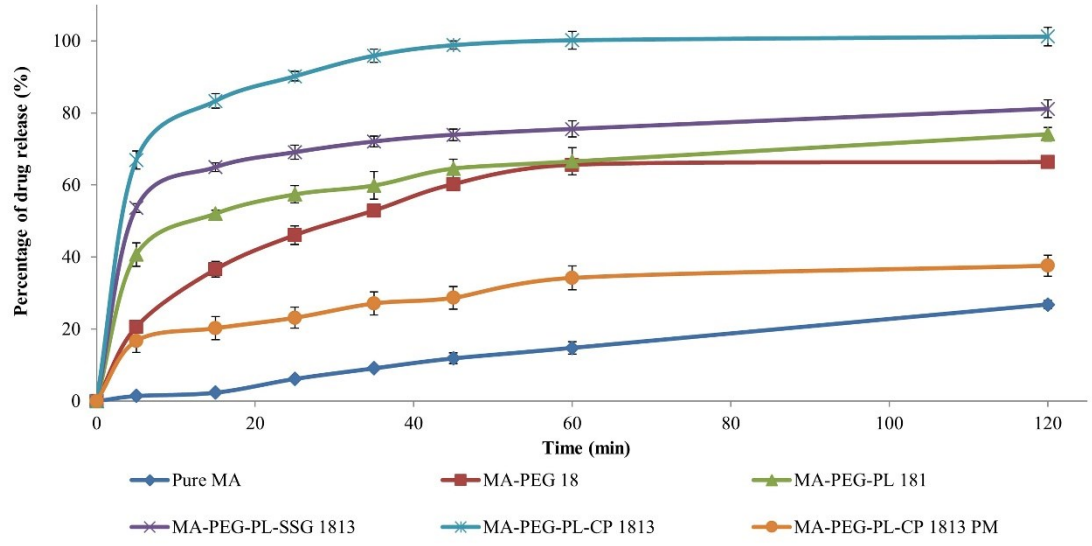

Figure 2 Dissolution profiles of pure MA, solid dispersions (MA-PEG 18, MA-PEG-PL 181, MA-PEG-PL-SSG 1813, MA-PEG-PL-CP 1813) and physical mixture (MA-PEG-PL-CP 1813 PM) in pH 6.8 phosphate buffer solution. The data shown are mean ± SD of 3 replicates.

FTIR spectroscopy

The FTIR spectra of pure MA, PEG 4000, poloxamer 188, crospovidone, SD (MA-PEG-PL-CP 1813), and physical mixture (MA-PEG-PL-CP 1813 PM) are presented in **Figure 3**. The spectra of the pure drug exhibited peaks at 3,300 cm^{-1} (N-H stretch), 1,650 cm^{-1} (C=O stretch), 1,575 cm^{-1} (N-H bending), 1,505 - 07 cm^{-1} (C=C stretch), and 750 cm^{-1} (aromatic stretch). PEG 4000 showed characteristic peaks at 3,500 cm^{-1} (O-H stretch), 2,900 cm^{-1} (C-H stretch), and 1,100 cm^{-1} (C-O-C stretch). The spectra of poloxamer 188 showed peaks at 2,900 cm^{-1} (C-H stretch) and 1,100 cm^{-1} (C-O-C stretch). Crospovidone had vibrational peaks at 2,900 cm^{-1} (C-H stretch), 1,650 cm^{-1} (C=O stretch), and 1,300 cm^{-1} (C-N stretch). FTIR spectra of SD and physical mixture of MA showed almost all bands of MA and carriers, without affecting the peak position and trends, which indicated the absence of well-defined chemical interactions between MA, PEG 4000, poloxamer 188, and crospovidone.

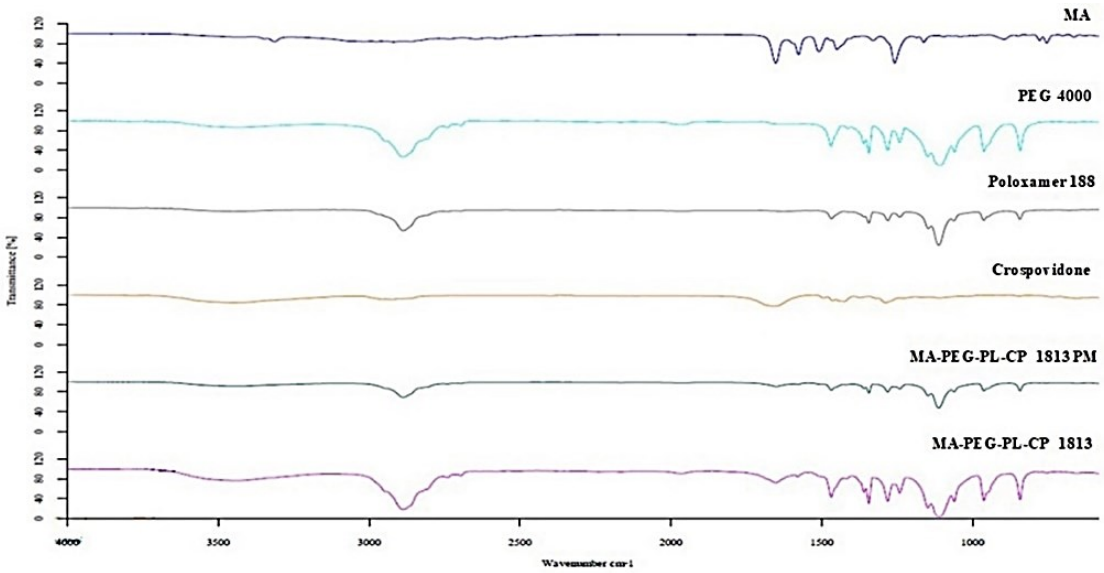

Figure 3 FTIR spectra of MA, PEG 4000, poloxamer 188, crospovidone, SD (MA-PEG-PL-CP 1813), and physical mixture (MA-PEG-PL-CP 1813 PM).

DSC

DSC was performed to investigate the physical state and degree of crystallinity of pure drug, PEG 4000, poloxamer 188, crospovidone, SD (MA-PEG-PL-CP 1813), and physical mixture (MA-PEG-PL-CP 1813 PM). It is known that MA has 2 polymorphic forms including polymorph I and II with melting points at 170 and 231 °C, respectively [20]. As shown in the thermograms (**Figure 4**), the pure MA exhibited a small endothermic peak at 170.7 °C and a sharp endothermic peak at 233.9 °C which were close to the values reported in literature. The DSC thermograms of SD and physical mixture demonstrated the board endothermic peaks of the carriers, PEG 4000 and poloxamer 188 at 55 - 60 °C. The endothermic peak of crospovidone was not detected from both SD and physical mixture owing to a weak broad peak characteristic of crospovidone. The physical mixture presented a relatively weak endothermic peak of MA at 170.5 and 222.9 °C, whereas the melting endotherm was not observed in the SD, suggesting absence of crystallinity and presence of the amorphous state of the drug. MA was amorphously dispersed in the SD resulting in enhanced dissolution of MA.

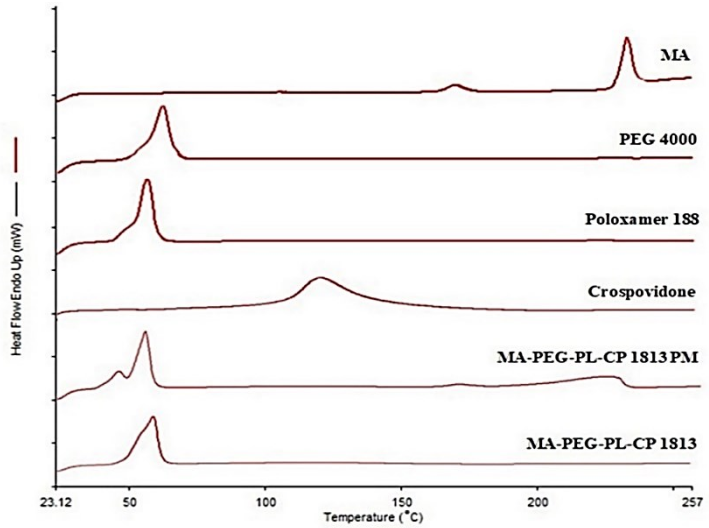

Figure 4 DSC thermograms of MA, PEG 4000, poloxamer 188, crospovidone, SD (MA-PEG-PL-CP 1813), and physical mixture (MA-PEG-PL-CP 1813 PM).

Preparation of delayed-release tablets comprising SD of MA

As the results from the dissolution studies of the SD of MA (MA-PEG-PL-CP 1813) showed an 8-fold increase in drug release compared to that with pure drug and conventional tablets containing 500 mg of MA, the SD equivalent to MA 60 mg was used to prepare the tablets. Matrix tablets can be investigated employing different controlled-release polymers (Kollidon® SR, Eudragit® RS PO, and PEO) using the dry granulation process. The prepared tablets had a width of approximately 7.05 - 7.08 mm, thickness approximately 7.10 - 7.87 mm, and length approximately 17.28 - 17.47 mm. The hardness of the tablets was in the range of 7.08 - 8.45 kg cm^{-2}. Weight loss in the friability test was less than 0.36 % in all formulations. The tablets contained MA within 95.75 - 102.63 % of the labeled claim (**Table 2**). As such, all physical parameters of the produced matrix tablets were found to be practically within the official limits. Therefore, polymer and other additives had no effect on the physical properties of the tablets.

Dissolution studies of tablets comprising SD of MA

The *in vitro* drug release studies for pure MA, SD of MA, and all the matrix tablet formulations were conducted in pH 1.2 dissolution media for the first 2 h followed by pH 6.8 phosphate buffer solution for a further 3 h, and the results are presented in **Figure 5**. We expected that the tablets released less than 10 % MA in the artificial gastric fluid in 120 min, and released more than 80 % in the artificial intestinal fluid within 165 min (after 45 min in pH 6.8 phosphate buffer solution).

For pure MA, the drug was not found in pH 1.2 media and detected at less than 30 % in pH 6.8 buffer solution at 300 min owing to its characteristic of poorly water-soluble drug with pK_a 4.54 at 37 °C [33]. Its solubility in pH 1.2, 4.5 and 7.4 buffer solution were 0.002, 0.016 and 1.360 mg mL^{-1}, respectively, at 37 °C [34].

The release profile of F1 containing Avicel PH 102 without the controlled-release polymer was similar to that of the SD of MA which released nearly 20 % MA in the acid condition within 2 h and released MA too quickly in the next 30 min in pH 6.8 PBS. F2 - F4, tablets comprising the delayed-release polymers, released very low amounts of MA (lower than 4 %) in the artificial gastric fluid in the first 2 h; after that the drug release started in pH 6.8 buffer medium, exhibiting a typical delayed-release profile. F4 released 3.73 % of MA in the first 2 h in the artificial gastric fluid and quickly released 87.28 and 95.38 % at 165 and 180 min, respectively, in the artificial intestinal fluid. According to the requirement, F4 was the most superior among the 4 formulations as seen in **Table 2**.

In this study, matrix polymers including Kollidon® SR, Eudragit® RS PO, and PEO were pH-independent delayed release polymers with a time-controlled mechanism. Kollidon® SR and Eudragit® RS PO are hydrophobic polymers which provide drug release with diffusion type through the matrixes [28,35]. Release of the drug from a matrix tablet containing a hydrophilic polymer such as PEO involves mechanisms of diffusion and matrix erosion. In the initial stage of dissolution, PEO started to uptake water and swell, resulting in an expansion of the tablets volume and formation of a viscous gel [27]. Hence, the system released faster in pH 6.8 buffer solution.

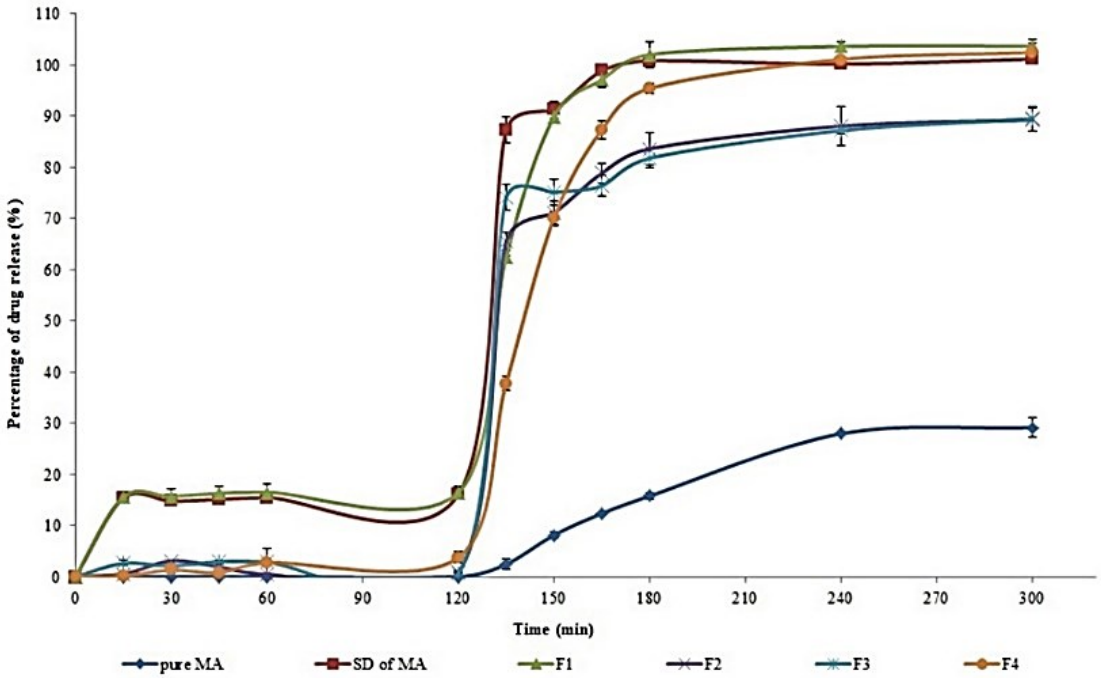

Figure 5 Release profiles of delayed-release tablets comprising solid dispersion of mefenamic acid in pH 1.2 media for the first 2 h followed by pH 6.8 PBS for the following 3 h. The data shown are mean ± SD of 3 replicates.

Conclusions

The present study demonstrated the development of MA delayed-release matrix tablet formulations using SDs. SDs of MA were successfully prepared to overcome its low aqueous solubility. Incorporation of surfactant and super disintegrant in SDs gave rapid and higher dissolution of MA when compared to that of SDs with combined carriers (PEG and surfactant), SD containing PEG and pure drug, respectively. Among the prepared SDs, MA-PEG-PL-CP 1813 exhibited the higher amount of drug release (8-fold) compared with that of the pure drug after 45 min. FTIR and DSC were adopted to study the physical state of MA in SD and demonstrated that the crystalline MA transformed into the amorphous state after preparation. SD of MA was then prepared in the form of delayed-release tablets to omit gastric irritation. The formulation F4 tablet released less than 4 % in pH 1.2 media in the first 2 h and released more than 95 % at 3 h in pH 6.8 PBS. Thus, this investigation indicates that F4 is capable of releasing MA in a typical delayed-release profile.

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