Sodium Mefenamate as a Solution for the Formulation and Dissolution Problems of Mefenamic Acid

Ahmad Bani-Jaber,* Imad Hamdan, and Bashar Al-Khalidi

College of Pharmacy, Jordan University; Amman, Jordan. Received January 14, 2007; accepted May 24, 2007

Sodium salt formation of mefenamic acid (MA) was studied as a way to solve the formulation and dissolution problems of MA. For this purpose, sodium salt of mefenamic acid (Na-MA) was prepared by reacting MA powder with equimolar sodium hydroxide in an aqueous phase, and consequently, Na-MA solution was obtained. The resultant solution was lyophilized and Na-MA powder was collected. The salt formation was confirmed by the results of fourier transformation–infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) studies on Na-MA powder in comparison to MA powder. Na-MA powder was assessed for direct compressibility, in comparison to MA powder, when formulated as a mixture with minimum amount of Avicel® pH 101 and then compressed into tablets using a hydraulic tablet press. Na-MA tablets exhibited satisfactory hardness and friability, and did not show capping or lamination. On the other hand, some MA tablets showed capping or lamination upon compression and all the tested MA tablets for friability capped. Na-MA tablets were also studied for drug dissolution, in comparison to MA tablets, in water, a pH 7.4 phosphate buffer, and a pH 7.4 phosphate buffer after soaking in 0.1 M HCl. Under these different dissolution conditions, Na-MA tablets showed much higher dissolution rate and extent than MA tablets. The results of the study suggested that Na-MA can be considered as a solution form for the formulation and dissolution problems of MA.

Key words mefenamic acid; sodium mefenamate; direct compression; dissolution

Mefenamic acid (MA) is a high-dose nonsteroidal anti-inflammatory agent prepared as immediate-release capsule and tablet formulation.[1)] It is a hydrophobic and poorly soluble drug in aqueous medium.[1)] As is the case for many poorly water-soluble drugs, dissolution of MA is a problem.[1,2)] The effect of wetting agents was evaluated to enhance the dissolution rate of MA.[1,2)] Considerable enhancement of the dissolution rates were obtained in these studies, however, it is imperative to mention that the used dissolution media, such as Tris buffer (pH 9), were of high pH indicating that ionization is a critical step for drug dissolution. Polymorphism was also studied for its effect on MA dissolution.[3)] The metastable polymorph II was found to have higher saturation solubility than polymorph I, however, polymorph II was unstable and was completely converted into polymorph I.

Poor drug dissolution is not the only problem of MA, capping and lamination, sticking to any type of surface and not easy handling in granulation and tableting processes are other encountered problems.[4)] The tendency of capping and lamination of MA tablets made by wet granulation was previously evaluated in relation to the amount of binder, the influence of the granulation technique, and relative humidity of the granules.[4)] Tablets made from fluidized bed granules using methylcellulose in the granulating liquid showed significantly lower capping and lamination than tablets made from conventional granules prepared by wet granulation using methylcellulose as a dry binder. The best results regarding capping and lamination were obtained tablets containing fluidized bed granules at a binder content of 4.1%. With this high concentration, lamination was completely eliminated, however, capping was not completely eliminated. In addition, the tablet with the best surface properties showed longer disintegration times and delayed dissolution rates due to the higher binder content. Storing the granules prior to tableting at various relative humidity values was found to significantly affect the capping tendency. An increase in relative humidity resulted in fewer cracked tablets, however, storage at higher humidity values did not lead to lower capping tendencies.

The previous problems of MA direct towards changing its chemical form for possible better dissolution and tableting properties. Salt formation is the best approach to be studied for its effect on MA dissolution and tableting without changing the pharmacological action of the drug. A salt form of MA would enhance drug dissolution due to the enhancement of wetability and aqueous solubility and could improve tableting of the drug if better compaction properties, such as more fragmentation upon compression, were achieved. This possible improvement in compaction could lead to a directly compressible drug powder, which would eliminate the lengthy and costly wet granulation process used for tablet production of MA. Accordingly, the objective of this study was to study the effect of sodium salt formation on direct compressibility and dissolution properties of MA. For this purpose, sodium mefenamate (Na-MA) was prepared by reacting MA powder with equimolar NaOH in an aqueous medium to give Na-MA solution with subsequent lyophilization into Na-MA powder. Na-MA and MA powders were separately formulated as simple direct compression mixtures having equivalent amounts of MA and the same types and amounts of inactive ingredients. The two mixtures were directly compressed into tablets using a manual hydraulic press. The tablets were observed for capping and lamination upon compression, characterized for hardness, friability, and disintegration, and tested for drug dissolution in aqueous media of various pH values.

Experimental

Materials MA was a gift from Dar Al-Dawa investment and development, Naur Jordan. Avicel® pH 101 was obtained from FMC Corporation, Switzerland. All other chemicals were of pure laboratory grade.

Preparation of Na-MA Powder MA powder was added to sodium hydroxide solution at an equimolar ratio of the base to the acid. The mixture was stirred on a magnetic stirrer until a clear solution was obtained, and then the solution was filtered on a Whatman filter paper under vacuum to remove any undissolved impurities. The filtered solution (pH around 7) was freeze

* To whom correspondence should be addressed. e-mail: abjaber@ju.edu.jo

dried for one week using Telstar® freezdryer (Spain). The water content of the lyophilized powder was measured using Karl-Fischer titration and was found to be of 4%. The powder was further oven dried overnight at 50 °C, and then placed in a well-closed container for further characterization and tablet formulation.

Characterization of the Prepared Na-MA Powder The prepared Na-MA powder was characterized in comparison to MA powder used to prepare the salt for the following:

Assay of MA Content: Exact weight (about 50 mg) of Na-MA powder was transferred into 200 ml volumetric flask and the volume was made up with 0.05 M NaOH. The mixture was stirred on a magnetic stirrer until a clear solution was obtained. The UV absorbance of the solution was measured after appropriate dilution with distilled water at 287 nm using a UV spectrophotometer (Ultrospec® II spectrophotometer). MA contents were calculated using a linear UV calibration curve of MA solutions prepared in 0.05 M NaOH. The assay procedure was performed for six samples and the assay values were expressed as % actual MA content of the theoretical MA content assuming 1 : 1 salt formation between NaOH and MA.

Angle of Repose Measurement: Angle of repose for the powders was measured in triplicate using the fixed-funnel method. A funnel was secured with its tip 10 cm (H) above a flat horizontal surface. Powder was carefully poured through the funnel until the apex of the formed conical pile just touches the tip of the funnel. The diameter of the formed conical pile (R) was measured and then the angle of repose (α) was calculated as $\tan\alpha = H/R$.

Differential Scanning Calorimetry (DSC): DSC curves were recorded using a differential scanning calorimeter (Mettler, Toledo DSC823e, Switzerland) configured to a Mettler® Star software system (Mettler, Toledo, Switzerland). The equipment was calibrated with indium. Powder samples were weighed into sealed aluminum pans with pierced cover. Thermograms were recorded under dry nitrogen atmosphere (80 ml/min) from ambient temperature to 300 °C at heating rate of 10 °C/min.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectra were recorded using an FTIR spectrometer (Shimadzu® 8400S IR spectrophotometer, Japan) for samples prepared according to the KBr disk method.

Formulation and Preparation of Tablets Direct compression mixtures for MA and Na-MA were prepared according to the formulations listed in Table 1. Avicel® pH 101 in the formulations was used as dry binder and disintegrant and magnesium stearate served as lubricant. Each drug form was mixed with the inactive ingredients for 15 min by a spatula in a plastic container followed by hand tumbling of the container after closing for another 15 min. Each mixture was compressed into tablets having MA equivalent amount of 250 mg *i.e.* tablet weight of 300 mg for MA and 323 mg for Na-MA. Compression was performed in 1 cm die at 50 kN using a manual hydraulic press. One hundred tablets were made for each formulation and the number of the tablets that showed capping or lamination upon compression was recorded.

Characterization of Tablets Crushing Strength: The crushing strength was determined using Erweka® hardness (Germany) tester for 10 tablets.

Friability: Twenty tablets of each formulation were subjected to 100 rotation at 25 rpm in Erweka® friability tester (Germany). Friability was calculated when none of the tested tablets showed capping. In the case of having capped tablets, friability was not calculated and the number of the tested tablets that showed capping was recorded.

Disintegration Studies: The disintegration times of the tablets were determined according to USP 23 in distilled water, 0.1 M HCl, and a pH 7.4 phosphate buffer solution (PBS) using a disintegration apparatus (Pharma test, Germany). Five tablets from each formulation were used for the determinations.

Dissolution Studies The dissolution studies were performed in triplicate using type II (paddle method) dissolution apparatus (Erweka® dissolution tester, Germany) in 900 ml of distilled water, 0.1 M HCl, and PBS (pH 7.4) for 2 h. Studying the drug dissolution in each of these media, although is useful to compare the dissolution behavior of the two drug forms, does not simulate what happens *in vivo*. Accordingly, to simulate the *in vivo* performance of the formulations as oral tablet, tablets were soaked in 600 ml of 0.1 M HCl for 2 h, and then the pH was adjusted to 7.4 using appropriate amounts of NaOH and monobasic potassium phosphate dissolved in 300 ml distlled water. The drug dissolution was then followed for another 2 h. Samples (5 ml) were taken at suitable time intervals with replacing the volume and then assayed for equivalent % of MA released using a UV spectrophotometer (Ultrospec® II spectrophotometer) at wavelength of 287 nm.

Table 1. Direct Compression Formulations of MA and Na-MA

Ingredient (mg)	Amount (mg) per tablet	
	MA formulation	Na-MA formulation
MA	250	—
Na-MA	—	272.8[a)]
Avicel® pH 101	47	47
Magnesium stearate	3	3.2
Total weight	300	323

a) Equivalent to 250 mg MA.

Results and Discussion

Characterization of Na-MA Powder The average MA content of the prepared Na-MA salt powder for six determinations was found to be 100.1±1.8% of the theoretical MA content of a salt formed at equimolar MA: NaOH, which indicated that the reaction was complete between sodium hydroxide and MA. The FTIR spectra of MA and Na-MA powders reported between 1200 to 1500 cm^{-1} are given in Fig. 1. MA showed a strong band at 1651 cm^{-1}. In the spectrum of Na-MA, this band disappeared and two new bands appeared at 1612 and 1373 cm^{-1}. Similar results of infrared spectra for MA and a prepared Na complex of MA were previously reported in a study by Topacli and Ide.[5)] In this previous study, the infrared spectrum of MA had a band at 1650 cm^{-1}, which was absent in that of the complex, and the corresponding spectrum of the complex had two new bands at 1583 and 1390 cm^{-1}. The band at 1650 cm^{-1} was assigned to ν(CO) stretching of COOH group of MA, while the new bands (at 1583 and 1390 cm^{-1}) were assigned to the $\nu_{as}(COO)^-$ and $\nu_s(COO)^-$ vibrations of the complex. These assigned bands for the stretching modes of COO^- allowed the authors to hypothesize that the hydrogen atom in the COOH of MA group was substituted by Na in the complex. According to this evident hypothesis, the FTIR spectra in our study strongly suggested that the obtained lyophilized powder was Na-MA. According to the DSC curves (Fig. 2), each powder of MA and Na-MA showed single sharp endothermic peak, which was assigned as melting peak. Consequently, MA had sharp melting with peak temperature of 235.6 °C, which is in accordance with a previously reported onset melting temperature of 230 °C for polymorph II of MA.[1)] On the other hand, Na-MA powder had sharp melting with peak temperature of 254.7 °C indicating a crystalline Na-MA powder was obtained. The difference in the peak temperature of melting be-

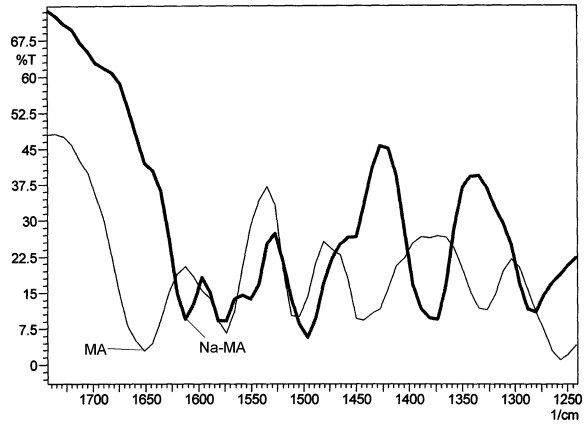

Fig. 1. FTIR Spectra of MA and Na-MA

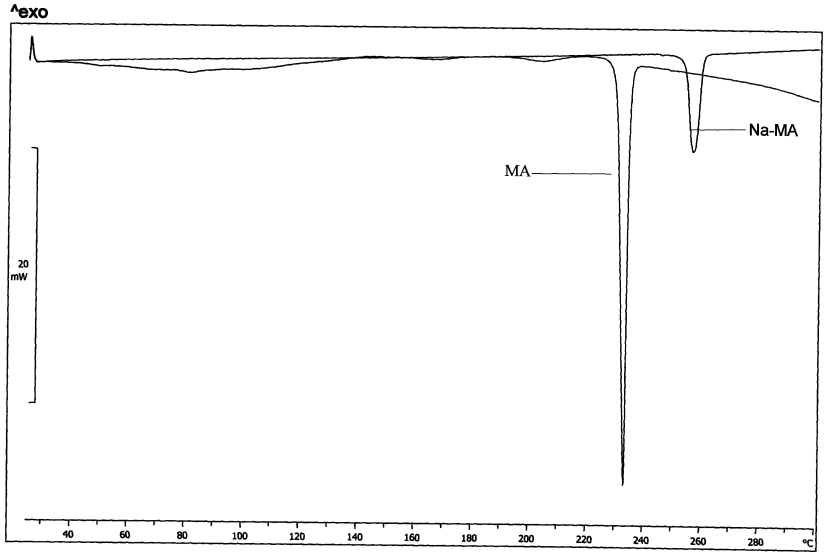

Fig. 2. DSC Thermograms of MA and Na-MA

tween the two forms of the drug are consistent with FTIR results by considering that having $COO^{-}Na^{+}$ in Na-MA molecules rather than COOH in MA molecules would have led to a different molecular arrangement and cohesive forces among the molecules in the solid state of Na-MA from those among the molecules of MA powder. Na-MA powder exhibited an angle of repose of $31.6° \pm 0.7$ for three determinations corresponding to $48.2° \pm 1.3$ for MA powder. As a general guide, powders with angle of repose grater than 50° have unsatisfactory flow properties whereas minimum angle close to 25° corresponds to very good flow properties.[6] Accordingly, the salt formation led to significant improvement of the unsatisfactory flow properties of MA and Na-MA powder was considered to have good flow properties. Accordingly, the unsatisfactory flow of MA powder is an obstacle for adopting a direct compression method for the drug and this obstacle is very likely to be overcome by having the prepared Na-MA powder instead of MA powder.

Characterization of Tablets The results of the characterization of MA and Na-MA tablets prepared by direct compression are summarized in Table 2. The hardness study showed that Na-MA tablets had greater mechanical strength than MA tablets; almost five folds increase in hardness was obtained with the use of Na-MA rather than MA. When a force is applied to a material, deformation occurs, and under higher pressure, the deformed particles may fragment, with an increase in new, clean surfaces that are potential bonding areas.[7] Accordingly, the greater mechanical strength of Na-MA tablets could be due to better compaction behavior of Na-MA powder during compression, such as higher fragmentation leading to formation of new clear surface for bonding. Upon compression, none of the 100 made Na-MA tablets showed capping or lamination upon compression, while the same number of MA made tablets showed four tablets with capping or lamination. Moreover, the friability test showed that all the tested MA tablets capped upon exposure to the test. On the other hand, none of the tested Na-MA tablets showed capping upon testing with % friability less than 0.5%. Conventional compressed tablets that lose less than 0.5 to 0.8% of their weight are considered acceptable.[8]

Table 2. Comparison of Tablet Properties of Direct Compression Formulations of MA and Na-MA

Parameter	Formulation	
	MA	Na-MA
Capped tablets upon compression	2	0
Laminated tablets upon compression	2	0
Hardness	2.7±(0.56)	15.2±1.45
Friability (20 tested tablets)		
Capped tablets	20	0
Friability (%)	—[a]	0.436
Disintegration time (min)		
Water	41.4±8.8	5.4±0.8
0.1 M HCl	18.0±4.8	11.2±0.4
PBS (pH 7.4)	24.2±5.4	5.2±0.4

a) Tablets showed capping.

The disintegration times of MA tablets were 8, 5 and 1.5 folds higher than those of Na-MA tablets in water, PBS, and 0.1 M HCl, respectively. The faster tablet disintegration for Na-MA tablets could be attributed of the higher hydrophilicity of the salt leading to higher wetability of the tablets. According to the previous observations and values for powder flow and tablet properties, Na-MA powder when mixed with minimal amount of Avicel® pH 101 is directly compressible, while direct compression MA tablets cannot be made using the same amount of Avicel® pH 101. Subsequently, salt formation of MA is not considered a costly and time-consuming step by considering that the flow and compaction properties of Na-MA powder allows for switching the costly and lengthy wet granulation method used for MA tablet production to a simple direct compression. In addition, enhancement of drug dissolution with the use of Na-MA instead of MA as will be seen below adds one more very important advantage.

Dissolution Studies Na-MA tablets showed rapid drug dissolution in water (Fig. 3) with % drug dissolved more than 90% at 15 min, which can be attributed to the rapid tablet disintegration and high aqueous solubility of the ionizable Na-MA. On the other hand, less than 5% drug dissolution in

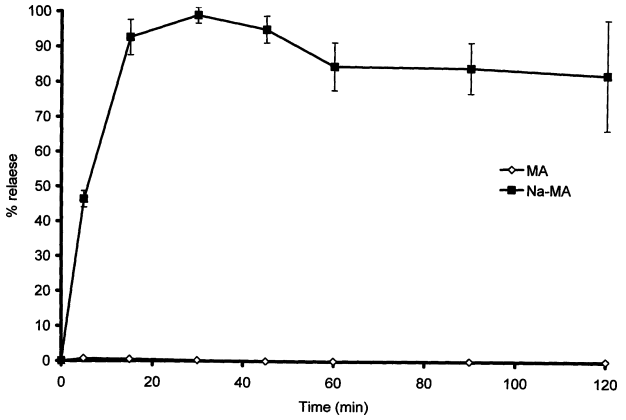

Fig. 3. Dissolution Profiles of Direct Compression Tablets of MA and Na-MA in Water

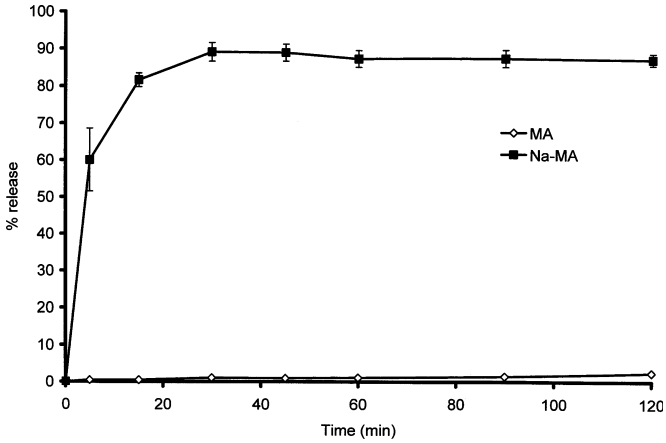

Fig. 4. Dissolution Profiles of Direct Compression Tablets of MA and Na-MA in PBS (pH 7.4)

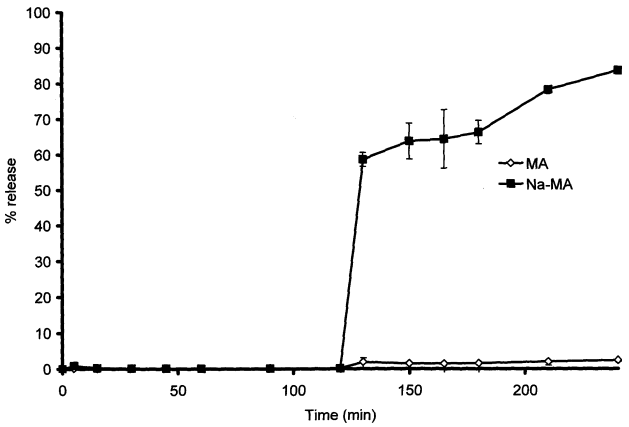

Fig. 5. Dissolution Profiles of Direct Compression Tablets of MA and Na-MA in PBS (pH 7.4) after Soaking in 0.1 M HCl (pH 1.2)

water (Fig. 1) was obtained from MA tablets at all time points, which can be attributed to the poor aqueous solubility of MA estimated as 0.5 μg/ml by TenHoor *et al.*[9] The dissolution profiles in 0.1 M HCl are not shown, since insignificant UV absorbance values (less than 0.05) were obtained for both MA and Na-MA tablets. For MA tablets, this non-detectable dissolution can be attributed to the poor aqueous solubility and lack of ionization of MA (pK_a=4.2) at a low pH of 1.2, while for Na-MA tablets it can be attributed to the protonation of Na-MA to form the poorly soluble MA. The drug dissolution profiles in PBS (pH 7.4) without and with acidic presoaking are shown in Figs. 4 and 5, respectively. Without acidic presoaking, the average % drug release from MA tablets was low of less than 5%, which is consistent with a previously reported low drug dissolution (less than 10% in 2 h) for MA tablets in pH 6.8 PBS.[1] Using Na-MA tablets instead led to 42 fold increase in drug release in the same medium. This huge difference in dissolution could be partly attributed to the faster tablet disintegration and better wetability of Na-MA tablets. Nevertheless, these dissolution results would contradict the fact that in a buffered medium an acid and its salt should ultimately exist in acid-base equilibrium with the same relative concentration of the hydrophilic ionized species. This could be clarified as that the pH of microclimate of the disintegrated Na-MA particles is higher than that of the disintegrated MA particles. In addition, any MA solid particles formed as a result of Na-MA protonation could have different physical properties, such as crystalinity and size, from those of the disintegrated MA particles from MA tablet. In the case of acidic presoaking, Na-MA tablets still achieved much higher dissolution rate and extent than MA tablets; 83.7% were released in PBS from Na-MA tablets in 120 min after the acidic soaking corresponding to only 2.4% from MA tablets. At a low pH of 1.2 during the acidic soaking, Na-MA (pK_a=4.2) is to be mostly protonated into MA, which again explains the non-detectable dissolution from Na-MA tablets during the acidic soaking. Accordingly, the two formulations will be almost chemically equivalent with respect to the drug form at the end of the acidic soaking, which will rule out the effect of ionizability on drug dissolution in PBS afterward. As it was explained for any formed MA particles upon the direct exposure of Na-MA tablets to PBS, the physical properties of the formed MA particles from Na-MA tablets in 0.1 M HCl, namely, crystalinity, particle size and surface area, could be different from those of the MA particles disintegrated from MA tablets. Consequently, if these differences were real they would affect the difference in drug dissolution performance between the two formulations when exposed PBS with or without acidic presoaking. In order to test for such differences, the following experiments were performed. Powders (10 mg) of MA or Na-MA were added into 10 ml 0.1 M HCl and 10 ml PBS (pH 7.4) and the mixtures were shaken for 2 h. Suspensions were obtained at the end of shaking for MA and Na-MA in the two media. The liquid suspensions were analyzed for particle size and surface area of the solid particles using laser diffraction particle size analyzer (Malvern®, U.K.). Another set of suspensions prepared according to the previous procedure were filtered, and the filtered solid particles were rinsed twice with distilled water and then allowed to dry for 24 h in an oven at 50 °C. The dried powders were thermally run according to the procedure of the DSC method. The results of these particle size analysis and DSC experiments are shown in Table 3. All the dried powders showed single sharp melting peak in the range of 234—237 °C, which matched the melting range of polymorph II of MA. Accordingly, Na-MA powder upon exposure to pH 1.2 and pH 7.4 forms MA solid particles as a result of protonation. These formed MA particles had less heat of fusion of

Table 3. Peak Melting Temperature (T_m), Heat of Fusion (ΔH), Mean Particle Size ($d_{0.5}$) and Specific Surface Area (A) of MA Solid Particles after Soaking of MA or Na-MA Powders in PBS (pH 7.4) and 0.1 M HCl (pH 1.2)

Medium	Soaked MA				Formed MA from soaked Na-MA			
	T_m (°C)	ΔH (mJ)	$d_{0.5}$ [a] (μm)	A [a] (m^2/g)	T_m (°C)	ΔH (mJ)	$d_{0.5}$ [a] (μm)	A [a] (m^2/g)
PBS (pH 7.4)	235.5	−651	39.0±3.5	0.220±0.033	235.7	−612	5.5±2.4	1.2±0.2
0.1 M HCl	237.0	−714	38.5±1.3	0.221±0.007	234.7	−632	19.4±3.4	0.5±0.1

a) Average of $n=3\pm$standard deviation.

63 and 20 mJ for 0.1 M HCl and PBS, respectively, than the corresponding values of the soaked MA particles. Subsequently, less crystalline MA particles were obtained from Na-MA upon soaking in the two media, particularly in PBS, than the soaked MA particles. In addition, soaking of Na-MA led to the formation of MA particles with significantly reduced particle size than the soaked MA powders in the two media. This reduction in size was almost of 7 and 2 folds in PBS and 0.1 M HCl, respectively. Similar comparisons can be exetended to the surface area. The results of the previous experiments indicated that any formed MA particles upon the exposure of Na-MA tablets to pH 7.4 or pH 1.2 during dissolution would be less crystalline and with much higher exposed surface area than the disintegrated MA particles from MA tablets. Accordingly, the high drug dissolution obtained for Na-MA tablets in PBS with or without acidic presoaking can be considered partly as due to the formation of MA particles with reduced size and crystalinity, in comparison to MA powder used to prepare Na-MA.

Conclusions

Na-MA powder prepared in this study was of good flow and a directly compressible form when formulated with a minimum amount of Avicel® pH 101 and compressed in a hydraulic press, as the resulting tablets were of acceptable hardness and friability and with no capping or lamination. On the other hand, using the same direct compression formulation with MA powder resulted in poor compactability, which was evident from the capping and lamination upon compression, and particularly during the friability testing. In addition, the salt formulation showed faster rate and higher extent of drug dissolution in water and in PBS (pH 7.4) with or without presoaking in 0.1 M HCl. Accordingly, Na-MA can be considered a solution for the tabletting and dissolution problems of MA.

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