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Original Research Article

Preparation and assessment of poly(methacrylic acid-co-ethylene glycol dimethacrylate) as a novel disintegrant

Siraprapa Chansatidkosol, Praneet Opanasopit, Tanasait Ngawhirunpat, Sontaya Limmatvapirat, Prasert Akkaramongkolporn*
Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand

For correspondence:* ***Email:* *akkaramongkol_p@su.ac.th*

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Abstract

Purpose: *To prepare and evaluate poly(methacrylic acid (MAA)-co-ethylene glycol dimethacrylate (EGD)) as a tablet disintegrant.*
Methods: *Poly(MAA-co-EGD) in acid (H) and sodium (Na) forms at cross-linker (EGD) levels of 0.25 - 16 % were synthesized and subjected to Fourier transform infrared spectroscopy. Swelling capacity, disintegration efficiency and cytotoxicity to Caco-2 cells were determined using standard procedures.*
Results: *Poly(MAA-co-EGD) in acid (H) and sodium (Na) forms were successfully prepared. In contact with water, the polymers in Na form swelled more than those in H form. The swelling capacities of polymers in H and Na forms decreased with increasing amounts of cross-linker. Incorporation of the polymers accelerated the disintegration of microcrystalline cellulose tablets (placebo), and the disintegration efficiency depended on the salt form and amount of cross-linker. The Na salt form of the polymer crosslinked at 16 % EGD was the best candidate disintegrant. When used at 2.5 and 10 %, the selected polymer effectively promoted the disintegration and drug release of propranolol hydrochloride tablets. Moreover, cytotoxicity tests showed that it was non-toxic to Caco-2 cells.*
Conclusion: *The developed poly(MAA-co-EGD) possesses good disintegration and dissolution functionalities. Thus, it may be adopted as a new super-disintegrant for fast-release tablets.*

Keywords: *Tablet disintegrant, Methacrylic acid, Ethylene glycol dimethacrylate, Propranolol hydrochloride*

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INTRODUCTION

The rapid disintegration of tablets and dissolution of drugs are generally assisted by disintegrants, which are categorized into traditional disintegrants and super-disintegrants. Generally, the traditional disintegrants are hydrophilic, linear or branch polymeric substances such as starch, gum and un-crosslinked cellulose, while the super-disintegrants, some of which are modified from the traditional disintegrants, are hydrophilic crosslinked polymeric substances such as croscarmellose sodium, sodium starch glycolate, crospovidone, and polacrilin potassium. The super-disintegrants have superior disintegrating efficiency, and accordingly require lower amounts (2 - 10 %) for tablet disintegration than the traditional disintegrants. Owing to their

hydrophilic nature, most disintegrants function through wicking and swelling. Other mechanisms that are occasionally involved in disintegrating action of disintegrants include deformation recovery and electric particle repulsion [1]. Despite the number of disintegrants present in the market, several efforts have been made to develop new and more efficient disintegrants. For instance, previous works showed that acid-hydrolyzed yam and breadfruit starches enhanced the disintegration of paracetamol tablets [2,3]. Alcohol-alkaline treated rice starch has been reported to be a very effective disintegrant for propranolol hydrochloride tablets [4]. Hydrochlorothiazide tablets containing the mucilage obtained from *Mimosa pudica* showed rapid disintegration capacity [5]. The disintegration property of crosslinked polyalkylammonium polymers was evaluated using hydrochlorothaizide and aspirin tablets as the model formulations. The results showed that the crosslinked polyalkylammonium polymer was a powerful disintegrant for both drug tablets [6]. Other developed novel disintegrants with improved efficiency were reported in recent publications [7,8].

The present study was aimed at developing a new efficient disintegrant poly(MAA-co-EGD) by copolymerization of methacrylic acid (MAA) and ethylene glycol dimethycrylate (EGD). The two monomers have been used for fabricating various biocompatible polymeric materials (hydrogels) intended for biomedical and pharmaceutical applications [9-11]. Since the poly(MAA-co-EGD) has hydrophilic structure it was anticipated that it should exhibit swelling property and hence disintegrating action.

EXPERIMENTAL

Materials

Methacrylic acid, ethylene glycol dimethacrylate, benzoyl peroxide were products of Sigma-Aldrich, Germany; propranolol hydrochloride was purchased from Beijing ShuangLu Pharmaceutical Ltd., China, while microcrystalline cellulose (Avicel® PH101) was obtained from FMC Corporation, USA. Sodium starch glycolate (Explotab®) was purchased from JRS Pharma, Germany, while magnesium stearate was obtained from Mallinckrodt Inc., USA.

Synthesis of poly(MAA-co-EGD) in H and Na form

Differently-crosslinked poly(MAA-co-EGD) in H form were synthesized by a modified method [9,10], as depicted in Figure 1. Benzoyl peroxide (1 g) and MAA (10 g) were reacted with EGD (crosslinking agent) at 0.25, 2, 8 and 16 % EGD mole of in an Erlenmeyer flask containing 10 ml of deionized water was added to the mixture. The mixture was continuously agitated at 80 ^{o}C in a silicone oil bath. Under this condition, the reacting mixture gradually transformed into a white polymeric paste. The polymer was washed with ethanol and deionized water and dehydrated in a hot air oven at 60 ^{o}C for 24 h. Each dried polymer was ground, screened through an 80 mesh sieve, and stored in a sealed bottle.

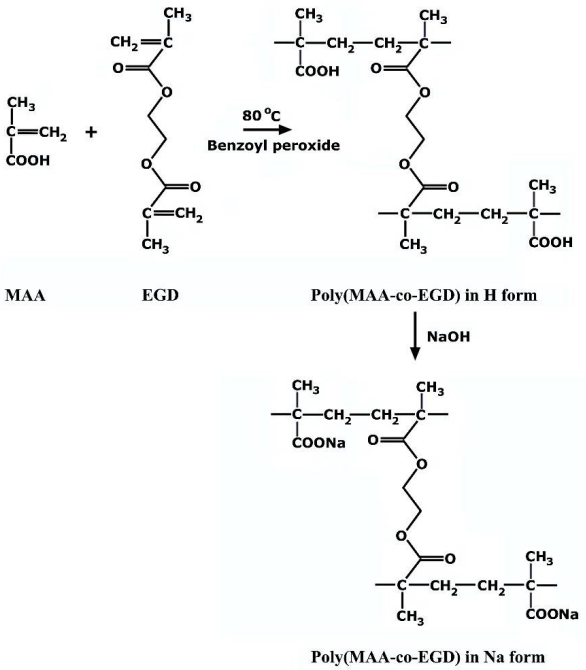

Figure 1: Synthesis and structure of poly(MAA-co-EGD)

The Na salt of poly(MAA-co-EGD) was prepared by dispersing a portion of the dried polymers in H form in 1 N NaOH at a volume ratio of 1 : 50 for 24 h. Thereafter, the treated polymer was collected by filtration and washed with deionized water until the pH was neutral. The washed polymer was dehydrated dried in a hot air oven at 60 ^{o}C for 24 h, screened through an 80 mesh sieve, and stored in a sealed bottle.

Fourier transform infrared (FTIR) spectroscopy

All samples were measured with KBr disc process using Fourier transform infrared spectrophotometer (Magna 4700, Nicolet, USA) in the wavenumber range of 400-4000 cm^{-1}.

Determination of swelling capacity

Each polymer was carefully poured into a

graduated cylinder and tapped to obtain a constant volume (V_1). Then, excess volume of deionized water was carefully poured into the cylinder. After soaking for 2 h, the volume of swollen polymer (V_2) was read and the % swelling capacity was computed as described in [12] using the relation:

$$Swelling\ capacity\ (\%) = 100 \times (V_2-V_1)/V_1$$

Assessment of disintegrating efficiency in placebo microcrystalline cellulose (MCC) tablet

Each polymer (10 %) was mixed with MCC for 15 min and then an accurately weighed portion of the mixture (100 mg) was compressed using a hydraulic press (P/N 15011/25011, Specac, UK) equipped with 6.5 mm flat-faced punches at a constant force (1 ton) of compression. The compressed tablets were then examined for disintegration time and hardness. From this study, the best candidate disintegrant was selected for use in further investigations.

Assessment of disintegrating efficiency in tablet formulation

The tablet formulations contained 20 mg of propranolol hydrochloride, 2.5 or 10 % of the selected polymer, 0.5 % of magnesium stearate, 1 % of fumed silica, and sufficient amounts of MCC to attain 100 mg final weight. The blends for the tablet formulations were prepared by mixing the drug, selected polymer and MCC for 15 min. Thereafter, fumed silica and magnesium stearate were added to the mixture and blended for a further 10 min. The mixed powder was accurately weighed and compressed (1 ton force) using the press machine described earlier. The resultant tablets were assessed for hardness, friability, drug content, disintegration time and drug release. In addition, for comparison, drug tablets with sodium starch glycolate (SSG), but without disintegrant were prepared and evaluated.

Tablet evaluation

Hardness

The hardness of ten tablets randomly taken from each batch was measured in a hardness tester (THB 225TD, Erweka, Germany) and the mean hardness was recorded.

Friability

Twenty tablets were weighed and put in a friabilator (TA120, Erweka, Germany) operated at 100 revolutions for 4 min [4]. After brushing off dust particles, the tablets were weighed again and the friability (%) was calculated in terms of percent weight loss.

Drug content

The drug content was determined in triplicate by dissolving each tested tablet in alcoholic solution. The mixture was properly diluted with phosphate buffer, pH 6.8, filtered and analyzed for propranolol hydrochloride content at the wavelength of 290 nm [13] using UV/Vis spectrophotometer (PG Instrument, United Kingdom). The drug content was expressed as % of the label claim.

Disintegration time

Disintegration times for six tablets were evaluated using a USP disintegration apparatus (ZT323, Erweka, Germany) in deionized water at 37 ± 0.5 ^{o}C. The disintegration time was recorded at the moment when all tablet fragments passed through the assembly screen.

Drug release

Drug release study was carried out using a paddle dissolution apparatus (Prolabo, United Kingdom) rotating at 100 rpm in 900 ml of 0.1 N HCl (pH 1.2) at 37 ± 0.5 ºC. Samples of supernatant (5 ml) were withdrawn at predetermined times and replaced with equivalent volume of fresh dissolution medium. The amount of drug released was determined spectrophotometrically at 290 nm [13]. Six tablets from each batch were examined in each test.

Cytotoxicity test

The cytotoxicity of polymers against Caco-2 cells was evaluated *in vitro* with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay [14,15]. The Caco-2 cells were seeded in Dulbecco's modified Eagle's medium (DMEM) in a humidified atmosphere containing 95 % relative humidity and 5 % CO_2 at 37 °C. At confluence, the cell was treated with the selected polymer and SSG at concentrations up to 10 mg/ml for 24 h. After treatment, the incubation medium was replaced with 200 ml of MTT solution (0.5 mg/ml in DMEM) and then incubated in a CO_2 atmosphere for 1 h. The supernatant was removed and the resultant formazan crystals were dissolved in dimethylsulfoxide (DMSO) (the number of viable cells is usually proportional to the amount of purple formazan crystals formed). Cell viability (%) was computed based on the absorbance of the purple formazan solution at

550 nm in a microplate reader (AOPUS01, Packard BioScience, USA). The viability of non-treated cells (100 %) was set as control.

Statistical analysis

The data are presented as mean ± standard deviation (SD). Statistical analysis of data was carried out with SPSS using one-way analysis of variance (ANOVA). Values of $p < 0.05$ were considered significantly different.

RESULTS

The polymerization of MAA and 0.25 - 16 % EGD formed stable crosslinked poly(MAA-co-EGD) in H form (Figure 2). The amount of cross-linker (EGD), i.e. the degree of crosslinking, had a profound effect on the texture of the resultant polymers. The polymer crosslinked at 0.25 % cross-linker appeared as a hard plastic-like mass (Figure 2a), and was difficult to grind. However, with increase in the amount of cross-linker from 2 to 16 %, the resultant polymers were softer (Figure 2b-d), which facilitated comminution. Polymers in Na salt form were prepared by placing the ground polymers in H form in aqueous NaOH. In this alkaline solution, H^+ of the polymers in acid form was displaced by Na^+ so that the polymers were converted to their Na salts.

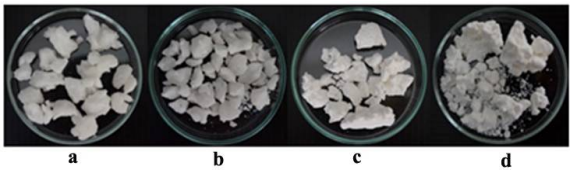

Figure 2: Appearance of poly(MAA-co-EGD) in H form at (a) 0.25, (b) 2, (c) 8 and (d) 16 % of EGD

Figure 3 presents the FTIR spectra of the synthesized polymers together with those of MAA, polymethacrylic acid (poly(MAA)) and EGD, for comparison. In the MAA spectrum (Figure 3a), the O-H and C=O stretching of carboxyl group (COOH) appeared as a broad peak at 3000 cm^{-1} and an intense peak at 1697 cm^{-1}, respectively. The presence of the carboxyl group was supported by the C-O stretching peaks at 1298 and 1204 cm^{-1}. The C=C stretching peak of MAA was observed at 1636 cm^{-1}. The EGD spectrum showed a peak at 1718 cm^{-1} assigned to the C=O stretching of the ester group, a peak at 1630 cm^{-1} assigned to the C=C stretching, and peaks at 1299 and 1173 cm^{-1} assigned to the C-O stretching of the ester group (Figure 3b). Poly(MAA) provided a different FTIR spectrum from its starting monomer (MAA), as shown in Figure 3c. The peak due to the O-H stretching of the carboxyl group was broader and shifted to 3455 cm^{-1}. In addition, the C=O stretching peak was shifted to 1755 cm^{-1}, while the C=C stretching peak disappeared.

The FTIR spectra of differently crosslinked polymers in H form are shown in Figures 3d - 3g. The FTIR spectrum of the 0.25 % crosslinked polymer (Figure 3d) was a superimposition between that of poly(MAA) and EGD, rather than MAA. As the amount of cross-linker (Figure 3e-g) was increased from 0.25 to 16 %, the intensity of the O-H stretching peak was decreased, while the C=O stretching peak disappeared because of the prevailing peak at 1718 cm^{-1} of the C=O stretching from EGD (Figure 3b). The peaks at 1271 and 1173 cm^{-1} were related to the superimposed C-O stretching of the carboxyl and ester groups, which were also more evident from the increased amounts of cross-linker.

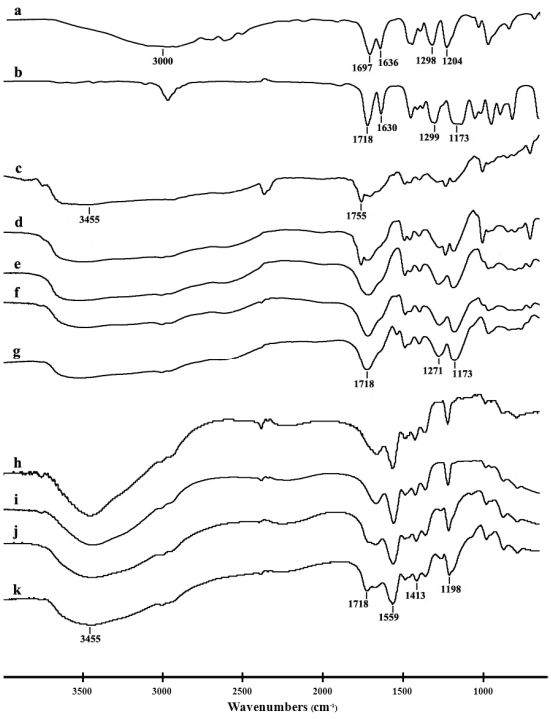

Figure 3: FTIR spectra of (a) MAA, (b) EGD, (c) poly(MAA) and poly(MAA-co-EGD) in H form at (d) 0.25, (e) 2, (f) 8, (g) 16 % EGD; and in Na form at (h) 0.25, (i) 2, (j) 8 and (k) 16 % EGD

Figure 3 (h-k) shows that the FTIR spectra of polymers in Na form clearly differed from those of the polymers in H form. After conversion to the salt forms, the peaks of O-H and C=O stretching from the carboxyl group significantly diminished and new peaks relating to the asymmetric and symmetric stretching of carboxylate anion (COO^-) occurred at 1559 and 1413 cm^{-1}, respectively [16]. In addition, the C-O stretching peaks originally found at 1271 and 1173 cm^{-1} changed to a single peak at 1198 cm^{-1}, which was presumably due to the superimposed C-O

stretching of the carboxylate and ester groups. In Figure 3k, the peak at 1718 cm^{-1} was assigned to the C=O stretching of the ester group: it became gradually evident with increase in the amount of cross-linker.

The swelling capacities of the synthesized polymers are shown in Figure 4. The polymers in Na form swelled significantly more than those in H form ($p < 0.05$). The swelling capacity of polymers in H and Na forms decreased with increase in the amount of cross-linker ($p < 0.05$).

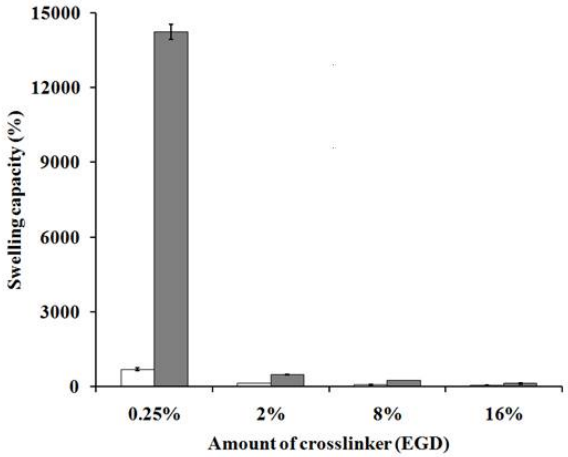

Figure 4: Swelling capacity of poly(MAA-co-EGD) in H form (clear bar) and N form (dark bar)

The disintegrating properties of polymers in H and Na forms were evaluated in placebo MCC tablets. The compression filler MCC was selected due to its excellent compactibility which results in hard tablets [1]. Thus the ability to break up a tablet made of MCC would suggest that the polymers would also be efficient disintegrants for tablets made from other compression fillers. As shown in Figure 5, MCC tablets containing the polymers provided high hardness and could disintegrate at different times. The disintegrating property of polymers was significantly influenced by the salt form and amount of cross-linker ($p < 0.05$).

These findings demonstrated that the polymers in H form were less effective as disintegrants

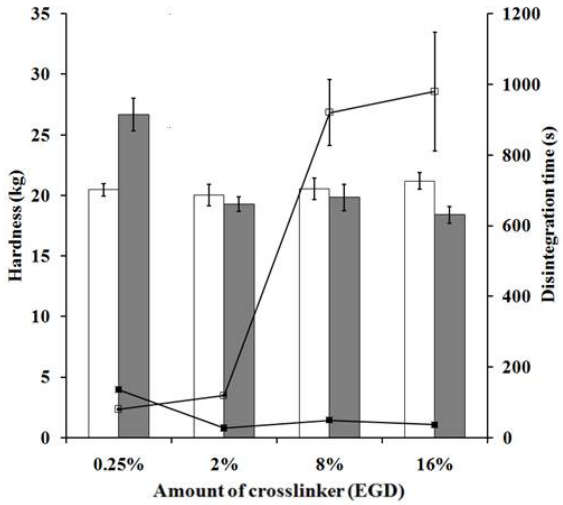

Figure 5: Hardness (bar graph) and disintegration time (line graph) of MCC tablets containing poly(MAA-co-EGD) in H form (clear bar/symbol) and N form (dark bar/symbol)

than those in Na form. The disintegrating efficiencies of the polymers in Na form were comparable, regardless of the amount of cross-linker. As mentioned in the earlier section, the comminution of a highly crosslinked polymer is more successful and more conveniently than that of a lowly crosslinked one. Therefore, the polymer in Na form at 16 % cross-linker was selected as the most suitable sample for further investigations.

The selected polymer was employed at 2.5 and 10 % to formulate propranolol hydrochloride tablets using MCC as the tablet filler. Tablet formulations with SSG and without disintegrant were also prepared and compared. The properties and dissolution profiles of the formulated drug tablets are summarized in Table 1 and depicted in Figure 6, respectively.

The *in vitro* cytotoxicities of the selected polymer and SSG against Caco-2 cells were determined using MTT assay. The results from the test are shown in Figure 7.

Table 1: Properties of formulated propranolol hydrochloride tablets

Disintegrant	Drug content (% label claim)	Hardness (kg)	Disintegration time (s)	Friability (%)
None	99.8±1.2	16.9±0.4	5304.3±90.6	0.199
SSG 2.5 %	95.1±1.1	16.3±0.4	740.3±8.0	0.250
Polymer* 2.5 %	96.6±2.1	16.3±0.4	474.7±3.6	0.151
SSG 10 %	101.5±0.7	15.6±0.3	91.0±1.6	0.329
Polymer* 10 %	99.2±3.2	11.6±0.5	18.3±0.5	0.020

Poly(MAA-co-EGD) in Na form at 16 % cross-linker

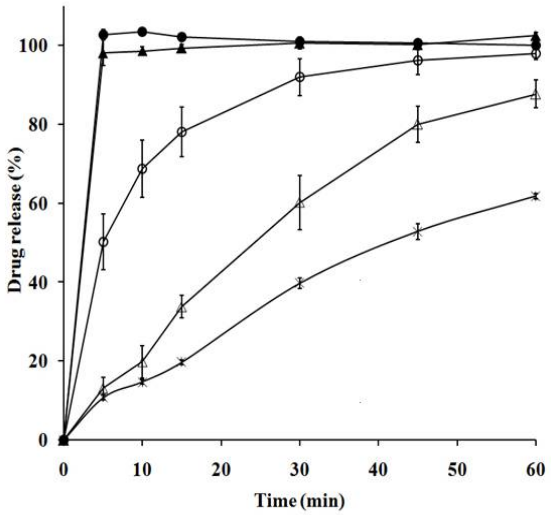

Figure 6: Drug release from propranolol hydrochloride tablets containing SSG at 2.5 (△) and 10 % (▲); and from poly(MAA-co-EGD) in Na form at 2.5 (○), 10 % (●) and without disintegrant (▪)

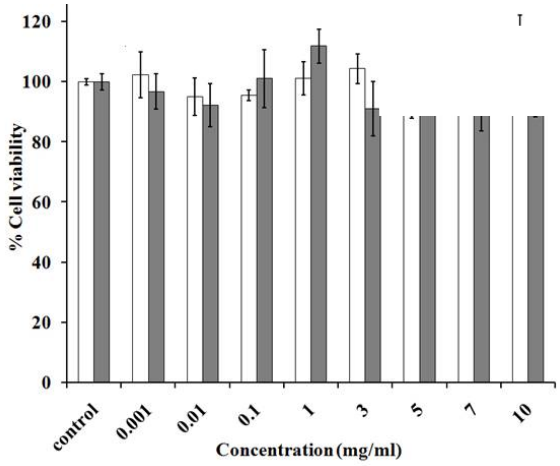

Figure 7: Viabilities of Caco-2 cells incubated with SSG (clear bar) and poly(MAA-co-EGD) (dark bar) in Na form for 24 h

DISCUSSION

The results from spectral analyses indicated successful preparation of poly(MAA-co-EGD) in H and Na forms. The polymers behaved like hydrogels which were able to adsorb water and swell because of the presence of ionizable carboxyl or carboxylate groups. In the aqueous environment, these groups ionized, generating ionic (H^+, Na^+ and $-COO^-$) solutions, and hence osmotic pressure inside the polymer network that acted as semi-permeable membrane. The resultant osmotic pressure brought about the adsorption of water and hence expansion of the polymer network (swelling). When the osmotic pressure became balanced, maximum swelling capacity was attained [9,10]. The polymers in Na form provided greater osmotic pressure and hence swelling capacity than those in H form because the carboxylate group ionizes better [17]. It has been shown that crosslinking hinders the expansion of the polymer chains [9]. Thus, in this study, the swelling capacity of the polymers decreased with increase in the amount of cross-linker.

The disintegrating efficiencies of polymers in Na form were higher than those in H form, corresponding to their higher swelling capacities, except for polymers crosslinked at 0.25 % EGD. The higher hardness of the resultant tablet might be responsible for the lower disintegrating efficiency of the polymer in Na form at 0.25 % of cross-linker in spite of having a higher swelling capacity. The effect of amounts of cross-linker on the disintegration efficiency was different between polymers in H and Na forms. The disintegrating efficiency of polymers in H form decreased with increasing the amount of cross-linker, leading to decreased swelling capacity. This dependency implies that the swelling action accounted for the disintegrating efficiency of the polymers in H form.

On the other hand, the disintegrating efficiency of polymers in Na forms was not influenced by the amount of cross-linker or swelling capacity. This might indicate that the disintegrating property of polymers in Na form did not solely result from the swelling action. A particle repulsion theory has been proposed by Guyot-Hermann [1,18]. In this proposal, it was postulated that electrical repulsive forces between particles cause the disintegrating action of non-swelling disintegrants. Perhaps, this mechanism also accounted for the disintegrating property of the polymers in Na form, which had a propensity for ionization, and hence electrostatic repulsion between particles.

The drug content of formulated propranolol hydrochloride tablets ranged from 95.1 to 101.5 % of the label claim. The drug tablets had comparable hardness, except for one containing 10 % of the polymer which provided a relatively lower hardness. Nonetheless, it was considered hard enough for handling, as indicated by the fact that its low friability was comparable to those of other polymer. Drug tablets without disintegrant took one hour and a half to disintegrate, whereas tablets with the polymer took less than 10 min. This indicated that the polymer acted effectively as a disintegrant for the tablet formulations. Similar to SSG, the disintegrating efficiency of the polymer was concentration-dependent, which is in agreement with results obtained in previous studies [2,6].

Drug release from tablets at 2.5 % polymer was faster than drug release from tablets with SSG and without disintegrant, corresponding to the shorter time required for tablet disintegration. At this concentration, only the drug tablet containing the polymer met the USP dissolution specification for propranolol hydrochloride tablet, which requires that the amount of drug released from each tablet should not be less than 80 % in 30 min [19]. Increasing the concentration from 2.5 to 10 % resulted in the enhancement of drug release from the propranolol hydrochloride tablets containing the polymer and SSG because of the faster disintegration of tablets. Drug tablets with 10 % of the polymer and SSG satisfied the USP dissolution specification for propranolol hydrochloride tablet by providing complete drug release within 5 min. In contrast, the drug tablet without disintegrant had only 61.8 % of drug release at the end of release testing (60 min).

There was no significant decrease in the viability of Caco-2 cells after exposure to the polymer. A similar result was obtained with SGG. Moreover, the viability of the Caco-2 cells incubated with the polymer was not significantly different from that obtained from SSG exposure. These results indicate that the polymeric disintegrant was as safe as SSG.

CONCLUSION

Poly(MAA-co-EGD) has been successfully developed as an efficient tablet disintegrant. The results show that its disintegrating efficiency is influenced by the amount of EGD, and its salt forms. Poly(MAA-co-EGD) possesses disintegration and dissolution attributes that are superior to those of sodium starch glycolate. Thus, this polymeric material has potentials for use as a new super-disintegrant for tablet formulations. However, appropriate investigations have to be carried out first to ascertain its safety profile.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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