SYNTHESIS AND EVALUATION OF CROSS-LINKED POLYMETHACRYLIC ACID AS ALTERNATIVE SUPERDISINTEGRANT

By

Miss Siraprapa Chansatidkosol

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree

Master of Sciences Program in Pharmaceutical Sciences

Department of Pharmaceutical Technology

Graduate School, Silpakorn University

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การสังเคราะห์และการประเมินพอลิเมทาคริลิกแอซิดชนิดเชื่อมโยงข้ามเพื่อใช้เป็นสารช่วยแตกตัวยวดยิ่งทางเลือก

โดย

นางสาวศิรประภา ชาญสถิตโกศล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต

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The graduate school, Silpakorn University accepted thesis entitled “Synthesis and evaluation of cross-linked polymethacrylic acid as alternative superdisintegrant” by Miss Siraprapa Chansatidkosol in partial fulfillment of the requirements for the degree master of sciences program in pharmaceutical sciences.

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SIRAPRAPA CHANSATIDKOSOL : SYNTHESIS AND EVALUATION OF CROSS-LINKED POLYMETHACRYLIC ACID AS ALTERNATIVE SUPERDISINTEGRANT. THESIS ADVISORS : ASSOC. PROF. PRASERT AKKARAMONGKOLPORN, Ph.D., ASSOC. PROF. PRANEET OPANASOPIT, Ph.D. 133 pp.

Two derivatives of crosslinked polymethacrylic acid (resin) i.e. poly(methacrylic acid-co-divinylbenzene) and poly(methacrylic acid-co-ethylene glycol dimethacrylate) at concentration of 0.25-16% crosslinker were prepared by free radical polymerization using benzoyl peroxide as an initiator. The obtained resins were in acid form (H), which was prepared to salt forms (Na and K) by treatment with the aqueous solutions of sodium hydroxide and potassium hydroxide, respectively. Both of the resins in various crosslinks and salt forms were determined for Fourier transform infrared spectroscopy (FTIR), water uptake, swelling and disintegrating efficiency. Further, various factors regarding the tablet manufacture (i.e. amount of resin, tableting force, tablet weight, type of tablet filler and amount of magnesium stearate) affecting the disintegrating efficiency were studied with the promising resins selected from each derivative. Finally, the effect of resins in comparison with sodium starch glycolate on drug release was determined using propranolol hydrochloride tablet as the model formulation. According to FTIR spectra, both of the resins in various crosslinks and salt forms were successfully produced by the used synthetic method, which provided 14-66 % in yields. The poly(methacrylic acid-co-divinylbenzene) resins appeared white to faint yellow, while that of poly(methacrylic acid-co-ethylene glycol dimethacrylate) resins appeared white to off white. In contact with water, the resins did not dissolve, but adsorbed water and swelled to different extents. The resins in low crosslinker or in salt forms (Na and K) would adsorb water and swell to a greater extent than those in high crosslinker or in acid form (H). As tested with microcrystalline cellulose tablet, both of the resins accelerated disintegration, where the disintegrating efficiency and mechanism depended on the crosslink and salt form of resins. From this finding, it appeared that both resins at concentration of 16 % crosslinker in Na salt form were promising candidates for selection as disintegrant. The disintegrating efficiency of resins was also influenced by the manufacturing factors including the amount of resin, tableting force, tablet weight, type of filler and amount of magnesium stearate. The amount of resin revealed that the propranolol hydrochloride tablet containing 10 % resin as disintegrant displayed faster disintegration and greater drug release than 2.5 % resin. At each concentration, poly(methacrylic acid-co-ethylene glycol dimethacrylate) resin promoted the tablet disintegration and drug release more effectively than poly(methacrylic acid-co-divinylbenzene) resin and sodium starch glycolate, respectively. From the results, it was concluded that the derivatives of crosslinked polymethacrylic acid had potential to be a new superdisintegrant in tablet formulations. Poly(methacrylic acid-co-ethylene glycol dimethacrylate) resin at 16 % crosslinker in Na form was considered the optimal candidate as disintegrant; as low as concentration of 2.5 % disintegrant sufficiently allowed the propranolol hydrochloride tablet to achieve the compendial specification in the disintegration and dissolution.

Pharmaceutical Sciences Graduate School, Silpakorn University

Student's signature……. Academic Year 2015

Thesis Advisors' signature 1. …….……..……..…... 2……..…….

55361205 : สาขาวิชาวิทยาการทางเภสัชศาสตร์ (วท.ม.)
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ศิรประภา ชาญสถิตโกศล: การสังเคราะห์และการประเมินพอลิเมทาคริลิกแอซิดชนิดเชื่อมโยงข้ามเพื่อใช้เป็นสารช่วยแตกตัวยวดยิ่งทางเลือก. อาจารย์ที่ปรึกษาวิทยานิพนธ์: รศ. ดร. ประเสริฐ อัครมงคลพร และ รศ. ดร. ปราณีต โอปณะโสภิต. 133 หน้า.

อนุพันธ์ของพอลิเมทาคริลิกแอซิดชนิดเชื่อมโยงข้าม (เรซิน) 2 ชนิดได้แก่ พอลิเมทาคริลิกแอซิดโคไดไวนิลเบนซีนและพอลิเมทาคริลิกแอซิดโคเอทิลีนไกลคอลไดเมทาคริเลตที่ระดับการเชื่อมโยงข้ามร้อยละ 0.25-16 สังเคราะห์โดยวิธีฟรีเรดิคอลพอลิเมอร์ไรเซชันโดยใช้เบนโซอิลเปอร์ออกไซด์เป็นตัวเร่งปฏิกิริยา เรซินที่สังเคราะห์ได้จะอยู่ในรูปกรด (ไฮโดรเจน) นำไปเตรียมให้อยู่ในรูปเกลือ (โซเดียมและโพแทสเซียม) โดยการแช่ในสารละลายโซเดียมไฮดรอกไซด์และโพแทสเซียมไฮดรอกไซด์ ตามลำดับ จากนั้นนำเรซินทั้งสองที่มีระดับการเชื่อมโยงข้ามและรูปเกลือต่างๆ ประเมินสมบัติต่างๆ ได้แก่ ฟูเรียร์ทรานสฟอร์มอินฟราเรดสเปกโทรสโกปี (เอฟทีไออาร์) การดูดน้ำ การพองตัว และประสิทธิภาพการเป็นสารช่วยแตกตัว นอกจากนี้ปัจจัยต่างๆ ของการเตรียมยาเม็ด (ได้แก่ ปริมาณสารช่วยแตกตัว แรงที่ใช้ตอกอัด น้ำหนักของเม็ดยา ชนิดของสารเพิ่มปริมาณ และปริมาณแมกนีเซียมสเตียเรต) ที่มีผลต่อประสิทธิภาพในการเป็นสารช่วยแตกตัวของเรซินทั้งสอง สุดท้ายศึกษาผลของเรซินทั้งสองเปรียบเทียบกับโซเดียมสตาร์ชไกลโคเลตต่อการปลดปล่อยยาโดยใช้ยาเม็ดโพรพราโนลอลไฮโดรคลอไรด์เป็นตำรับต้นแบบ ผลของเอฟทีไออาร์สเปกตราพบว่าวิธีการสังเคราะห์ที่ใช้สามารถเตรียมเรซินทั้งสองที่มีระดับการเชื่อมโยงข้ามและรูปเกลือต่างๆ ได้สำเร็จ และได้ปริมาณเรซินร้อยละ 14-66 เรซินพอลิเมทาคริลิกแอซิดโคไดไวนิลเบนซีนที่ได้ มีสีขาวถึงเหลืองอ่อน ส่วนเรซินพอลิเมทาคริลิกแอซิดโคเอทิลีนไกลคอลไดเมทาคริเลตที่ได้มีสีขาว เมื่อนำเรซินทั้งสองชนิดสัมผัสกับน้ำพบว่าไม่ละลายน้ำแต่สามารถดูดซับและพองตัวได้หลายระดับ โดยเรซินที่มีปริมาณตัวเชื่อมโยงข้ามต่ำหรืออยู่ในรูปเกลือ (โซเดียมและโพแทสเซียม) จะดูดซับน้ำและพองตัวได้มากกว่าเรซินที่มีปริมาณตัวเชื่อมโยงข้ามสูงหรืออยู่ในรูปกรด (ไฮโดรเจน) เรซินทั้งสองชนิดสามารถช่วยให้ยาเม็ดที่เตรียมจากไมโครคริสตัลลีนเซลลูโลสแตกตัวเร็วขึ้น โดยประสิทธิภาพและกลไกในการช่วยแตกตัวขึ้นอยู่กับปริมาณตัวเชื่อมโยงข้ามและรูปเกลือของเรซิน จากผลที่ได้พบว่าเรซินทั้งสองชนิดที่ปริมาณตัวเชื่อมโยงข้ามร้อยละ 16 และเตรียมในรูปเกลือโซเดียมเป็นเรซินที่เหมาะสมในการเลือกใช้เป็นสารช่วยแตกตัว ประสิทธิภาพในการเป็นสารช่วยแตกตัวของเรซินทั้งสองชนิดขึ้นอยู่กับปัจจัยต่างๆ ในการเตรียมยาเม็ด ได้แก่ ปริมาณสารช่วยแตกตัว แรงที่ใช้ตอกอัด น้ำหนักของเม็ดยา ชนิดของสารเพิ่มปริมาณ และปริมาณแมกนีเซียมสเตียเรต ผลของปริมาณสารช่วยแตกตัวพบว่ายาเม็ดโพรพราโนลอลไฮโดรคลอไรด์ที่ใช้เรซินเป็นสารช่วยแตกตัวปริมาณร้อยละ 10 จะแตกตัวและปลดปล่อยยาได้เร็วกว่าที่ใช้เรซินร้อยละ 2.5 โดยที่พอลิเมทาคริลิกแอซิดโคเอทิลีนไกลคอลไดเมทาคริเลตทุกความเข้มข้น ทำให้ยาเม็ดแตกตัวและปลดปล่อยยาได้เร็วกว่าพอลิเมทาคริลิกแอซิดโคไดไวนิลเบนซีนและโซเดียมสตาร์ชไกลโคเลตตามลำดับ ผลการวิจัยสรุปได้ว่าอนุพันธ์ของพอลิเมทาคริลิกแอซิดชนิดเชื่อมโยงข้ามนี้มีศักยภาพที่จะใช้เป็นสารช่วยแตกตัวยวดยิ่งชนิดใหม่สำหรับยาเม็ดได้ พอลิเมทาคริลิกแอซิดโคเอทิลีนไกลคอลไดเมทาคริเลตเรซินที่มีปริมาณตัวเชื่อมโยงข้ามร้อยละ 16 ในรูปเกลือโซเดียมเป็นเรซินที่ดีที่สุดในการเป็นสารช่วยแตกตัวในยาเม็ด โดยที่ปริมาณร้อยละ 2.5 เพียงพอทำให้ยาเม็ดโพรพราโนลอลไฮโดรคลอไรด์มีการแตกตัวและปลดปล่อยยาได้มาตรฐานตามเภสัชตำรับ

สาขาวิชาวิทยาการทางเภสัชศาสตร์ บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร
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ลายมือชื่ออาจารย์ที่ปรึกษาวิทยานิพนธ์ 1. ..... 2. .....

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%w/w	percent weight by weight
°C	degree Celsius
®	registered Trademark
cm^{-1}	reciprocal centimeter (or wavenumber)
e.g.	exemplī grātiā (Latin) ; for example
i.e.	id est (Latin) ; that is, in other word(s)
g	gram(s)
h	hour(s)
kg_F	kilogram-force
M	molar(s)
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
nm	nanometer(s)
pH	potentia hydrogenii (Latin); potential of hydrogen
rpm	round per minute
r^2	coefficient of determination
s	second(s)
S.D.	standard deviation

CHAPTER 1
INTRODUCTION

1.1 Statement and significance of the research problem

The pharmaceutical products typically involve a mixture of active ingredients (drug components) and inactive ingredients (excipients). An active ingredient is a pharmaceutically active substance, while an inactive ingredient may also be referred to as an inert substance or excipient, which generally has no pharmacological effect [1]. It is added during the manufacturing process of pharmaceutical products, combining with active ingredients either to meet desired properties of formulated products or to facilitate drug transport in the body [2]. The quality of the final dosage form depends not only on the active principles and production processes, but also the performance of excipients [3-4].

Depending on the route of administration, dosage forms come in several types. Tablet is recognized as one of the most preferred dosage forms [5-8]. It is convenient, easy to use, long shelf-life and less expensive to manufacture than other oral dosage forms. It can be made in many sizes and shapes and deliver the intended dose with a high degree of accuracy [9]. There are two main methods used for preparing tablets namely granulation and direct compression. In the granulation, two types of technologies are employed namely wet granulation and dry granulation. The greatest disadvantage of wet granulation is its cost. It is an expensive process because of more labor, time, equipment, energy, and space requirement. During granulating and drying processes, moreover, high moisture and elevated temperature can have adverse effect on the drug stability [10-11].

In the direct compression, tablets are compressed directly from powder blends of the active ingredient and suitable excipients. The most obvious advantage of direct compression is economy [12]. It is safe in a number of areas, including reduced processing time and thus reduced labor costs, fewer manufacturing steps and pieces of equipment such as the absence of granulators and dryers in preparing tablets, less process validation and lower consumption of power. In terms of the tablet quality, the most advantages are processing tablets without the need for moisture and heat, and avoiding the high compaction pressures involved in producing tablets by slugging or roller compaction [10]. Tablets of moisture and heat-labile drugs are recommended to be manufactured by direct compression technique.

The development and formulation of tablets always challenges with major problems of unaccepted disintegration and dissolution of drug, particularly those manufactured by the direct compression method [13]. The start of disintegration and dissolution is often delayed by the poor wettability of the tablet surface and/or slow liquid penetration into the tablet matrix. This causes increased disintegration time and retarded drug release [14]. To overcome these problems, tablet formulations have to accompany with disintegrant, which is a substance or mixture of substances added in the formulations to facilitate the disintegration of tablets into smaller fragments for more dissolution of delivered drugs. Two groups of disintegrants namely traditional and superdisintegrant have been categorized so far. The former mostly based on linear or uncrosslinked hydrophilic cellulosic polymers (e.g., starch, gum and mucilage) imparts effective disintegration at relatively high concentrations. Owing to its accompanying adhesive property this disintegrant can cause lump formation that may oppose the water entry and hence desired property of assisting disintegration. The latter is chemically derived from crosslinked hydrophilic polymers, e.g., sodium starch glycolate, croscarmellose sodium, crospovidone and last but not least ion-exchange based polacrilin [15]. This superdisintegrant possesses higher disintegrating efficiency and lower adhesive property, resulting in decreased use concentrations. Since both groups contain hydrophilic hydroxyl groups in the structure, swelling and wicking (capillary action) are the two mechanisms most frequently favored to explain tablet disintegration [16].

Though many usable superdisintegrants are sold in markets, the search for alternative superdisintegrants or modified forms has been ongoing to serve individual need of different tablet formulations. New disintegrants can be received by various ways. Some are naturally received and used in native form, while others are partially modified prior to use or even fully synthesized. For instance, Breadfruit starch extracted from *Atrocapus communis* was found to be a potential disintegration due to significant hydration capacity [17]. When tested with paracetamol tablet formulation, the time required for disintegration was shorter than those without a disintegrant. The hardness of tablets using breadfruit starch was slightly increased from the starting tablets, indicating breadfruit starch quite compressible. Several works investigated the disintegrant property of mucilages from various origins [17,18]. One was the mucilage obtained from *Mimosa pudica* [18]. Hydrochlorothiazide tablets formulated with different concentrations of mucilage showed a better disintegration compared with those without a disintegrant. At low range of mucilage concentration, there was an increase in the rate and extent of water uptake and swelling, which reflected in the obviously shorter disintegration time. Nonetheless, at high concentration was not as good as at low concentration. The very viscous layer of mucilage covering the tablet surface slowed down the water entry into the tablet and hence reduced the disintegrant efficiency. Yam starches obtained from two species i.e. *Dioscorea rotundata L.* and *Dioscorea alata L.* were acid-hydrolyzed and determined for disintegrant property with paracetamol tablets [16]. Due to enhanced swelling, the modified yam starches enabled the tablet to break up and the drug to release much faster than those with native starches or without a disintegrant. Somewhat low compactibility of these alternative disintegrants however still persisted, causing the deterioration on tablet strength. In case of a fully synthetic disintegrant, there was an evaluation of disintegrating property for a crosslinked polyalkylammonium polymer along with three other superdisintegrants i.e. Ac-Di-Sol®, Crospovidone® and Explotab®, using hydrochlorothaizide and aspirin tablets as the model formulations [19]. This polymeric material was expected to be a possible disintegrant because of its excellent water uptake and swelling properties [20]. The disintegration and dissolution tests showed that the crosslinked polyalkylammonium polymer possessed the effective disintegrant property for both of the tablets tested. From physical testing, the lowest

hardness, but not significantly different, was observed with the tablets using the crosslinked polyalkylammonium polymer as a disintegrant.

Polacrilin potassium is only a practically usable superdisintegrant that bases on ion-exchange resins. Chemically, it is made from repeated units of potassium methacrylate and divinylbenzene (Figure 1.1) of which however the concentration of crosslinker (the ratio of y in Figure 1.1) has yet been revealed. The resin is an efficient disintegrant at low concentration in various tablet formulations, including highly hydrophobic formulations where standard disintegrants are poorly effective [21]. Concentrations of 2–10 %w/w have been used as disintegrant, although 2% w/w of polacrilin potassium may be sufficient. It swells on hydration, but does not dissolve or become cohesive, a feature commonly encountered with gums. Moreover, it facilitates tablet compression for greater hardness. Some products of polacrilin potassium available in markets include Amberlite® IRP88, Doshion P544 DS®, Indion 294®, Tulsion 339® [21,11] and Indion 414® [22].

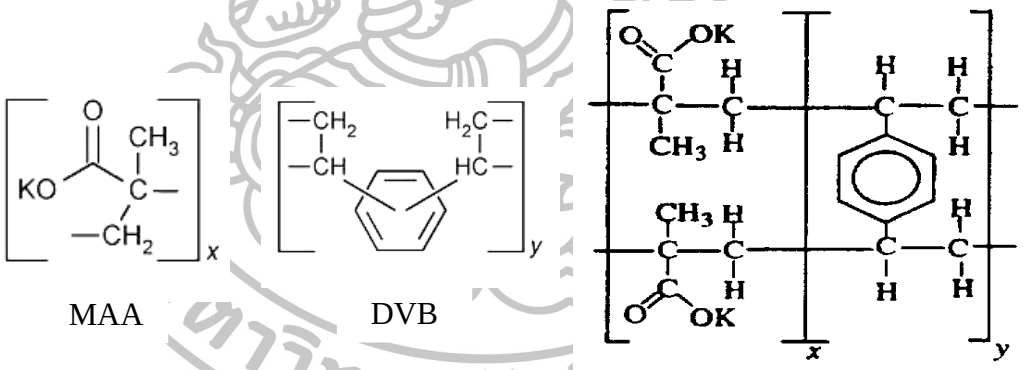

Figure 1.1 Chemical structure of polacrilin potassium.

According to limited choice for selection of ion-exchange based disintegrant, this research is aimed at raising numbers of ion-exchange resins applicable as alternative disintegrants. The utilized approach is to structurally modify polacrilin potassium via 1) alteration of crosslinkage, 2) salt form and 3) replacement of hydrophobic (divinylbenezene) with hydrophilic crosslinkers (ethylene glycol dimethacrylate). The top derived resins exhibiting desired properties (disintegration time and tablet hardness) are picked up, and further investigated for their disintegrating efficiency as well as tablet property under variation of various factors

i.e. disintegrant concentration, tableting force, tablet size, type of tablet filler and presence of hydrophobic lubricant (magnesium stearate). Due to ion-exchange nature, finally, whether the developed resin disintegrants adversely affects drug release is demonstrated with a tablet formulation of propranolol hydrochloride, a cationic model drug [11]. More choices for selection of ion-exchange based disintegrants with good or better disintegrating action along with their technical information are expected to be outcomes from this research.

1.2 Research objectives

1.2.1 To develop alternative ion-exchange based disintegrants structurally modified from polarcrilin potassium via alteration of crosslinkage, salt form and replacement of hydrophobic (divinylbenezene) with hydrophilic crosslinker (ethylene glycol dimethacrylate).

1.2.2 To investigate the performances of developed disintegrant resins under various conditions i.e. disintegrant concentration, tableting force, tablet size, type of tablet filler and presence of hydrophobic lubricant (magnesium stearate).

1.2.3 To determine the ion-exchange effect of developed disintegrant resins on drug release.

1.3 Research hypotheses

1.3.1 Alternative ion-exchange based disintegrants with good or superior disintegrating action can be structurally modified from potassium polarcrilin via alteration of crosslikage, salt form and replacement of hydrophobic (divinylbenezene) with hydrophilic crosslinker (ethylene glycol dimethacrylate).

1.3.2 Efficiency of developed ion-exchange based disintegrants depends on various conditions i.e. disintegrant concentration, tableting force, tablet size, type of tablet filler and presence of hydrophobic lubricant (magnesium stearate).

1.3.3 Ion-exchange based disintegrants do not have an adverse effect on drug release.

1.4 Scope of study

1.4.1 Preparation and evaluation of ion-exchange based disintegrants derived from poly(methacrylic acid-divinylbenzene (DVB)

1.4.1.1 Alteration of crosslink: 0.25, 2, 8 and 16 % DVB

1.4.1.2 Alteration of salt form: H, Na, K

1.4.2 Preparation and evaluation of ion-exchange based disintegrants derived from poly(methacrylic acid-ethylene glycol dimethacrylate (EGDMA)

1.4.2.1 Alteration of crosslink: 0.25, 2, 8 and 16 % EGDMA

1.4.2.2 Alteration of salt form: H, Na, K

1.4.3 Factors affecting the disintegrant efficiency

Study selected resins from 1.4.1 and 1.4.2 each

1.4.4 Determination of ion-exchange effect on drug release

Study selected resins from 1.4.1 and 1.4.2 each

The scope of study can be schematically depicted as shown in **Figure 1.2**.

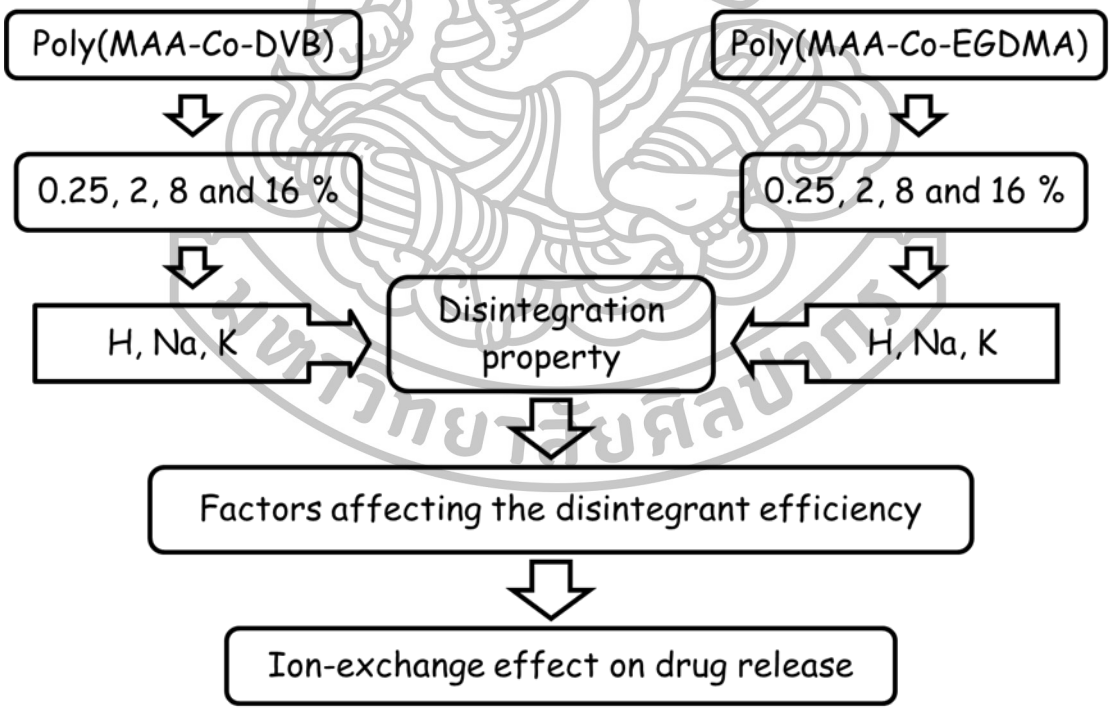

Figure 1.2 Scope of study.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction of the dosage forms

The dosage forms are essentially pharmaceutical products in the form in which they are marketed for use. Depending on the route of administration, they include many kinds of solid, liquid, and semisolid dosage forms. Solid oral dosage forms have been the most popular route due to ease of ingestion, pain avoidance, versatility and patient compliance. Overall of solid dosage forms, tablet is one of the most preferred dosage forms for a number of reasons [5-8]. They are simple, easy to use, long shelf-life, convenient in packaging, shipping and dispensing [13], less expensive to manufacture than other oral dosage forms. In addition, they can be made in many sizes and shapes with a variety of properties and deliver the intended dose with a high degree of accuracy [9].

2.2 Tablet formulation

A tablet is a pharmaceutical solid dosage form, which typically involves a mixture of active ingredients (drug components) and inactive ingredients. An active ingredient is a pharmaceutically active substance, while an inactive ingredient may also be referred to as an inert substance or excipient, and generally have no pharmacological effect [1]. They are added during the manufacturing process of tablets, that combine with active ingredients either to meet desired properties of formulated products or to facilitate drug transport in the body [2]. The quality of the final tablets depends not only on the active principles and production processes but also the performance of excipients [3-4].

2.3 Pharmaceutical excipient

Additives are usually divided into six major excipient categories such as diluent or filler, binder, disintegrant, lubricant (anti-adherent and glidant included), color, and sweetener (flavor included). They are classified according to the primary function they perform in the tablet. Many additives also have secondary function, which may or may not be beneficial to the formulated dosage forms. Some fillers or diluents facilitate tablet dissolution, which is beneficial, while others may impair disintegration and dissolution. The effective lubricants e.g. magnesium stearate are typically water repellent by their nature, which may retard both disintegration and dissolution [23]. The various types of excipients are shown as follows:

2.3.1 Diluent or filler

Diluents are inert substances, which are added to increase the bulk in order to make the tablet a practical size for compression. Diluents used for this purpose include dibasic calcium phosphate (Emcompress®), calcium sulfate, spray dried lactose (Tablettose®), cellulose and its derivatives e.g. microcrystalline cellulose (Avicel®), kaolin, mannitol, sodium chloride, dry starch and powdered sugar. In addition, it is important to note that many excipients can possess multi-functionality, which is dependent upon the concentration at which they are employed. For example, microcrystalline cellulose is usually used as a diluent (20–90%) in direct-compression formulas [24]. However, it can be used as an anti-adherent (5–20%) and a disintegrant (5–15%) at low concentrations [25]. Many ingredients are used for several different purposes, even within the same formulation; e.g. corn starch can be used in paste form as binder, while in dry form as disintegrant.

2.3.2 Binder

Binders or adhesives are agents used to impart cohesive qualities to the powdered material to insure the tablet remaining intact after compression as well as improve the free-flowing qualities of granules for the formulation of tablets. The direct-compression method for preparing tablets requires a material that is not only free-flowing but also sufficiently cohesive to act as a binder. The quantity of binder used has considerable influence on the characteristics of the compressed tablets. Excess of binder will make such a hard tablet that may not disintegrate easily and probably cause attachment to the punch and die [26]. Commonly used binders include starch, gelatin, sugars such as sucrose, glucose, dextrose, lactose, natural and synthetic gums namely acacia, veegum, sodium alginate, carboxy-methylcellulose, methylcellulose and polyvinyl pyrrolidone.

2.3.3 Disintegrant

Disintegrants are agents added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Aside from having good disintegrating property, ideal disintegrants should have safety, poor solubility, poor gel formation, good hydration capacity, high compressibility, good flow properties and compatibility with actives and other excipients (no tendency to form complexes). Materials serving as disintegrants have been classified according to their chemical origin as starches, clays, celluloses, algins, gums, natural and synthesized cross-linked polymers [18,27]. Frequently, they are also categorized into traditional and superdisintegrant [28]. Traditional disintegrants (>10%) are less effective and thus require higher concentrations to exert fast disintegration than superdisintegrants (2-10%). Disintegrants cause the tablet to disintegrate via many possible mechanisms i.e. swelling and wicking (capillary action), deformation, particle repulsion, etc. [16]. More details of properties and mechanism of actions for common disintegrants are presented in 2.5 and 2.6 respestively.

2.3.4 Lubricant, anti-adherent and glidant

The primary function of tablet lubricants is to reduce the friction arising at the interface of tablet and die wall during compression and ejection. The lubricants may also possess anti-adherent or glidant properties. Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can waterproof tablets, resulting in poor tablet disintegration and delayed dissolution of the drug substance. The examples of lubricants used in tablet formulation are talcum, magnesium stearate, calcium stearate and stearic acid. They are used in concentrations less than 1% [29,30]. Anti-adherents such as colloidal silica are used to reduce sticking and adhesion of the tablet granulation or powder to the faces of the punches or to the die walls. Glidants such as talcum are used to promote the flow of the tablet granulation or powder materials by reducing friction among particles.

2.3.5 Other excipients

A Colorant is used in tablet formulation to produce a more elegant tablets and also provide the user product identification. Sweeteners and flavors are usually used only with chewable tablets or orally fast disintegrating or dissolving tablets for masking unfavorable taste. Examples of sweeteners are mannitol, lactose, saccharin and aspartame.

2.4 Tablet preparation

A suitable manufacture is necessary to obtain satisfactory tablets. There are three main methods for tablet preparation i.e. wet granulation, dry granulation and direct compression. Direct compression is the simplest method and should be evaluated for new products. Wet granulation is the oldest method and still the most widely used, while the dry granulation method is limited to situations where neither wet granulation nor direct compression can be used [23].

2.4.1 Direct compression

Direct compression is the simplest method for tablet manufacture which requires fewer unit operations compared with various processes that involve granulation. It is used to define the process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved [12]. Since no solvent or water is used in the process, drying is avoided during manufacturing. This is critical for preparing tablet of actives that are sensitive to heat or moisture. Another obvious advantage of direct compression is economy [23]. It is save in a number of areas, including reduced processing time and labor costs, fewer manufacturing steps and pieces of equipment such as granulators and dryers needed in preparing tablets by wet granulation, less process validation, and a lower consumption of power [31]. Last but not least, fewer excipients are generally required in a direct compression tablet.

2.4.2 Wet granulation

Wet granulation is the most widely used method for tablet manufacture because of the great probability that the granulation will meet all the physical requirements for the compression of good tablets. The procedure is carried out by wet-massing the material and then making the wetted material into granules. It provides better control of content uniformity at low drug concentrations as well as control of product bulk density and ultimately compactibility (brittle fracture), even for high drug contents [32], and improves the flow characteristics of formulations consisting of cohesive powders [33], reduces dust problems and prevents segregation of formulation components [34]. However, this granulation method has several problems. The greatest disadvantage of wet granulation is its cost. It is an expensive process because of more labor, time, equipment, energy, and space requirement. On drying and blending processes, the effect of temperature, time and rate of drying on drug stability and distribution during the drying process must be intensively investigated [10, 35]. Moisture content remaining in granules can affect the tableting characteristics and the stability of actives. Thus, this process is not suitable for moisture and heat sensitive drugs.

2.4.3 Dry granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, slugging may be used to prepare granules. This process is generally consisted of three steps; blending of ingredients, slugging without water and sieving. Roll compactor and tablet press can be used to create slugs, which are following treated by milling and sieving to form dry granules. This method allows the granulation of materials sensitive to moisture and heat. Aspirin is a good example of moisture and heat sensitive drugs where slugging is satisfactory. Another major advantage is the continuous production of granules leading to a reduction of costs [36, 37]. In addition, dry granulation is one of the options used to reduce capping tendency [23].

2.5 Disintegrant for tablet

Various types of disintegrants are available in markets. Common materials used as disintegrants can be chemically classified as follows:

2.5.1 Starch

Starch is one of the most widely used excipients in pharmaceutical formulations. It is referred to as a group of polysaccharides found in plants that the molecule consists of many glucose joined by α linkages (see in Figure 2.1, Notice that the bridging oxygen atom is opposite the CH_2OH groups). It can be used both as a disintegrant and as a binder depending on the specific attributes necessary for the formulation. As a disintegrant, the mechanism of action of starch is wicking–the imbibitions of water into the tablet matrix via capillary action. The subsequent interaction between water and starch granules also leads to stress relaxation (or deformation). However, it does not regain their original shape when moistened with water [38-39]. Some starches recognized as applicable disintegrants are corn and potato starches [17].

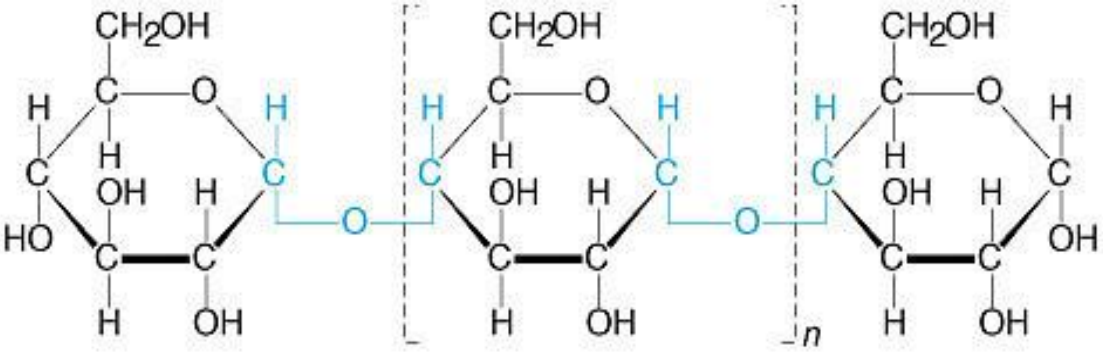

Figure 2.1 Chemical structure of starch.

Source : **Carbohydrates**, accessed January 25, 2015, available from http://wps.prenhall.com/wps/media/objects/3085/3159329/ blb2508.html.

2.5.2 Starch derivatives

A modified starch with dramatic disintegrating property recently available is sodium starch glycolate (Primojel® and Explotab®). It is a superdisintegrant made from cross-linking sodium carboxymethyl starch **(**Figure 2.2). The mechanism involves rapid absorption of water leading to an enormous increase in volume of granules resulting fast and uniform disintegration. The disintegrant efficiency of sodium starch glycolate is unimpaired in the presence of hydrophobic excipients, such as lubricants unlike many other disintegrants. Increasing the tablet compression pressure also appears to have no effect on disintegration time. It is used in tablets prepared by direct compression as well as wet granulation processes. The usual concentration employed in a formulation is between 2 and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. While pre-dried natural starches swell in water to the extent of 10 to 25%, this modified starch increases in volume by 200 to 300% in water [40-42].

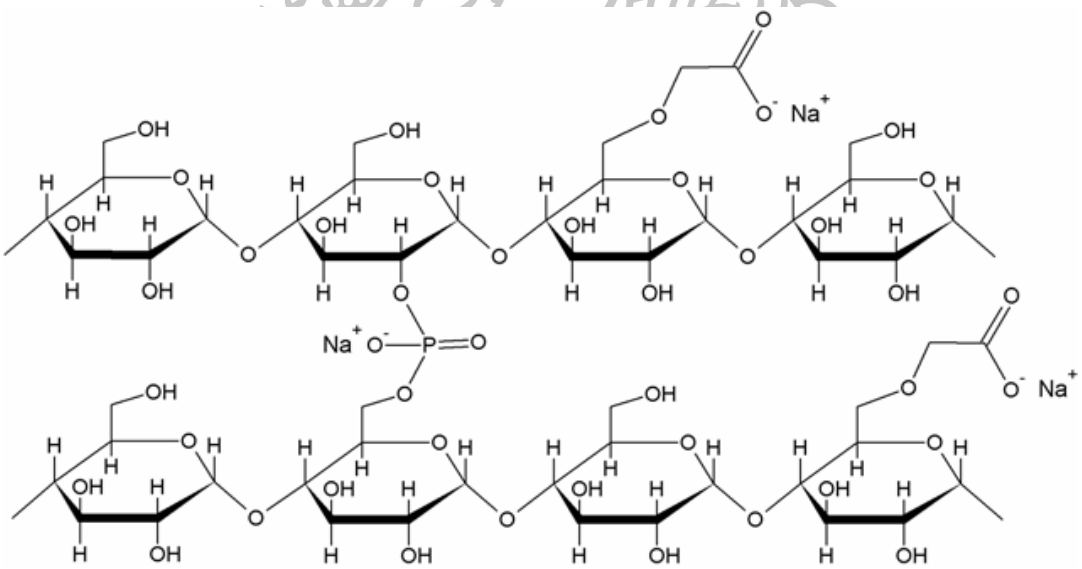

Figure 2.2 Chemical structure of sodium starch glycolate.

Source : **The quality signature of superdisintegrants**, accessed January 25, 2015, available from http://www.dfepharma.com/en.

2.5.3 Cellulose

Celluloses have been evaluated as disintegrants but have not found widespread acceptance. The structure of cellulose is shown in Figure 2.3; the molecule consists of a repeating unit of glucoses joined by the β linkage, which is different from that in starch. Microcrystalline cellulose (Avicel®) exhibits good disintegrant property when present at a level as low as 10%. It functions by allowing water to enter the tablet matrix by means of capillary action, which breaks the hydrogen bonding between adjacent bundles of cellulose microcrystal. However, MCC loses its disintegrant property at high levels of incorporated content. Placebo tablets prepared from MCC show a very slow rate of disintegration [43]. MCC-based pellets without disintegrant do not disintegrate and slow drug release occurs via diffusion through an insoluble matrix [44].

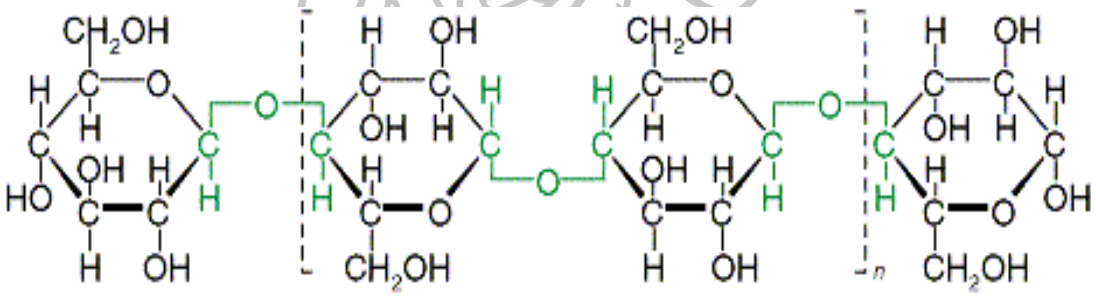

Figure 2.3 Chemical structure of cellulose.

Source : **Carbohydrate**, accessed January 25, 2015, available from http://wps.prenhall.com/wps/media/objects/3085/ 3159329/blb2508.html.

2.5.4 Cellulose derivatives

Croscarmellose sodium (Ac-Di-Sol®, Primellose®) is derived from internally cross-linking a cellulose ether (Figure 2.4), sodium carboxymethylcellulose which is a water soluble polymer. Cross-linking makes it to be an insoluble, hydrophilic and highly absorbent material, which has excellent swelling property [25]. In addition, the unique fibrous nature gives it excellent water wicking capability. Croscarmellose sodium at concentrations up to 2-5% w/w is sufficient to act as a tablet disintegrant [18].

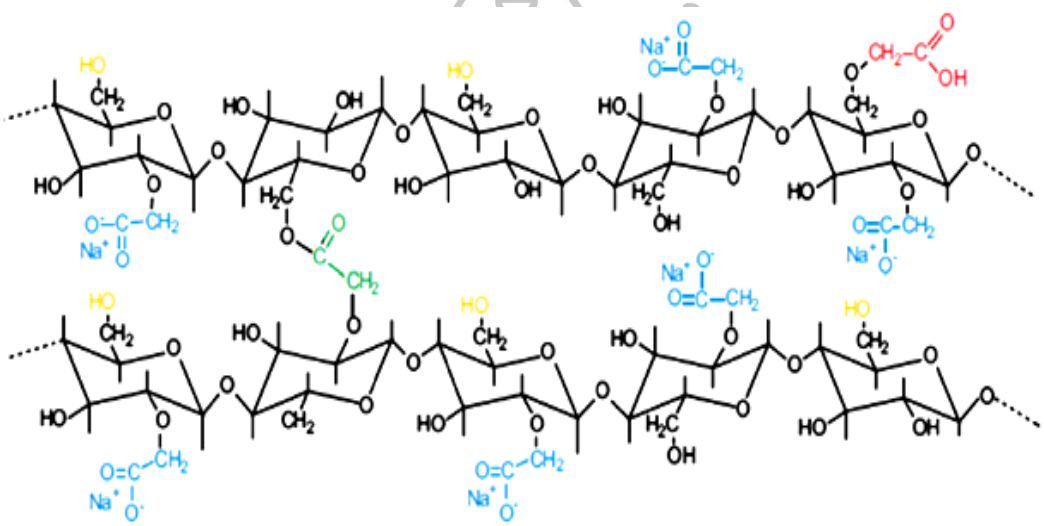

Figure 2.4 Chemical structure of croscarmellose sodium.
Source : **JRS Pharma**, Rosenberg, Germany.

2.5.5 Cross-linked polyvinylpyrrolidone

Polyvinylpyrrolidone or crospovidone (Polyplasdone®) is a synthetic, crosslinked homopolymer of N-vinyl-2-pyrrolidone (Figure 2.5). It is a water-insoluble tablet disintegrant typically used at 2–5% concentration in tablets prepared by direct compression or wet and dry granulation methods. It exhibits high capillary and pronounced hydration capabilities, with little tendency to form sticky gels. When examined under a scanning electron microscope [25], crospovidone particles appear granular and highly porous. This unique porous character facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. During tablet compression, the crospovidone particles become highly deformed. As the deformed particles come in direct contact with water, the particles recover their normal structure and swell resulting in volume expansion and hydrostatic pressure that cause tablet disintegration.

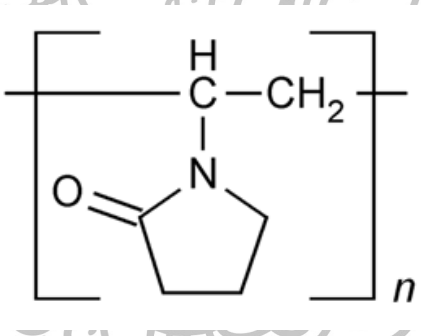

Figure 2.5 Chemical structure of crospovidone.

Source : Modified from Mukharya, A., et al. (2012). **Int. J. Pharm. Invest.**, 2, 2: 90-96.

2.5.6 Ion exchange resin based disintegrant

Ion-exchange resins are water insoluble crosslinked copolymer that contains acidic or basic functional groups in a repeating pattern [23]. The resins are organized into two main types depending upon the charge of counterions for which they exchange (Figure 2.6). The cationic exchange resin contains the negatively ionizable group such as sulfonic or carboxyl groups, which is capable of interchanging a positively charged or cationic counterion. The anionic exchange resin interchanges a negatively charged or anionic counterion due to the existence of the positively ionizable group such as a quaternary ammonium groups [45-46].

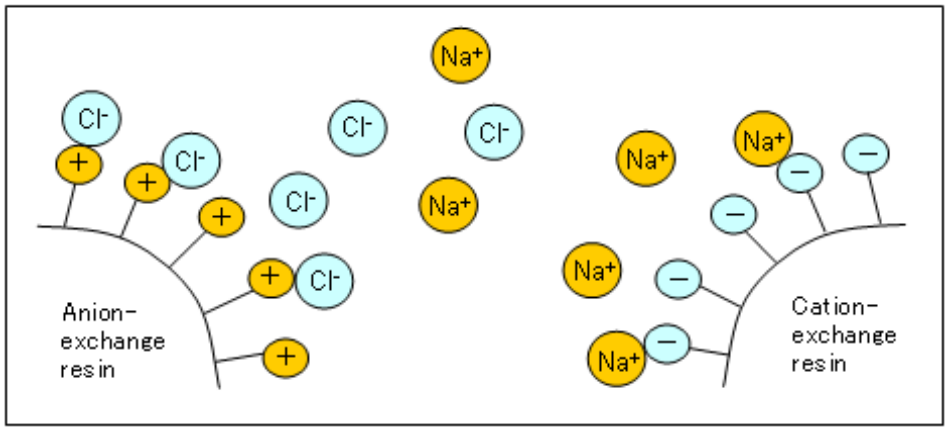

Figure 2.6 Ion exchange resin mode.

Source : **Ion exchange mode**, accessed April 04, 2015, available from http://www.hitachi-hightech.com.

Polacrilin potassium is a superdisintegrant that bases on cationic exchange resins. Chemically, it is prepared by the copolymerization of methacrylic acid and divinylbenzene (Figure 1.1) and subsequently neutralized with potassium hydroxide. The resin is an efficient disintegrant at low concentration in various tablet formulations, including highly hydrophobic formulations where standard disintegrants are poorly effective [4]. Concentrations of 2–10% w/w have been used as disintegrant, although 2% w/w of polacrilin potassium may be sufficient. It swells on hydration, but does not dissolve or become cohesive, a feature commonly encountered with

gums. Moreover, it facilitates tablet compression for greater hardness. Several commercial products of polacrilin potassium are produced and sold in markets including Amberlite® IRP88, Doshion P544 DS®, Indion 294® and Tulsion 339® [21]. Other types of ion-exchange resins are also found to have the disintegrant property acting via the swelling and capillary or wicking. The ethylcellulose tablets containing a sulfonated cationic exchange resin whose the matrix copolymer was derived from styrene and divinylbenzene (Amberlite® IRP69) display a rapid breakup [47]. Some styrenic anionic exchange resins (Dowex® 1W) enable the MCC tablets to rapidly disintegrate, where the disintegrating efficiency decreases with increasing the crosslink of resins [48]. However, these styrenic resins (Amberlite® IRP69 and Dowex® 1W) are poorly compressible.

In another way, disintegrants may be categorized into traditional and superdisintegrant [41]. The former imparts effective disintegration at relatively high concentrations, which mostly bases on linear or uncrosslinked hydrophilic cellulosic polymers (e.g., starch, gum and mucilage). Owing to its accompanying adhesive property this disintegrant can cause lump formation that may oppose the water entry and hence desired property of assisting disintegration. The latter is chemically derived from crosslinked hydrophilic polymers e.g. sodium starch glycolate, croscarmellose sodium, crospovidone and polacrilin potassium [48]. This superdisintegrant possesses higher disintegration efficiency, resulting in decreased concentrations for pracitcal use. Almost superdisintegrants exhibit either high capillary or swelling property, but have little tendency to form sticky gels because of its cross-linked structure. Some superdisintegrants commonly used are summarized in Table 2.1.

Table 2.1 Examples of superdisintegrants and their properties.

Superdisintegrants	**Commercially available grades**	**Mechanism of action**	**Special comment**
Crosslinked cellulose	Crosscarmellose® Ac-Di-Sol®, Nymce ZSX® Primellose®, Solutab®, Vivasol®, L-HPC	Swells 4-8 folds in < 10 seconds. Swelling and wicking. Acts by capillary action	swelling in both tabletting method, direct compression or granulation
Crosslinked PVP	Crosspovidon M® Kollidon® Polyplasdone®	Swells very little and returns to original size after compression.	Water insoluble and spongy in nature so get porous tablet.
Crosslinked starch	Explotab® Primogel®	Swells 7-12 folds in < 30 seconds	Swells in high level
Crosslinked alginic acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Polacrilin potassium	Amberlite® Doshion®, Indion® Tulsion®	Swells on hydration, but does not dissolve or become cohesive	2–10% w/w have been used as disintegrant

Source : Mohanachandran, P.S., et al. (2011). Superdisintegrants : an overview. **Inter. J. Pharm.Sci.** 1, 6: 105-109.

2.6 Mechanisms of tablet disintegration

The mechanism of action for tablet disintegrants has been widely researched [18,32]. There are several major mechanisms describing tablet disintegration as follows:

2.6.1 Swelling

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism by which certain disintegrating agents impart the disintegrating effect. By swelling, the binding of ingredients in a tablet is overcome causing the tablet to fall apart (Figure 2.7) [4]. The efficiency of this mechanism depends upon the tablet porosity. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. However, if the packing fraction is so high, fluid is unable to penetrate into the tablet and disintegration can be delayed [49]. Some disintegrants using the swelling mechanism [22] for tablet disintegration include starch, sodium starch glycolate and natural gum-mucilage.

Figure 2.7 Swelling mechanism of a disintegrant.

Source : **Disintegrant**, accessed May 22, 2014, available from http://www.pharmatutor.org.

2.6.2 Capillary or wicking action

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action [50] and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles (Figure 2.8). Crospovidone and croscarmellose are examples of disintegrants for the capillary or wicking action.

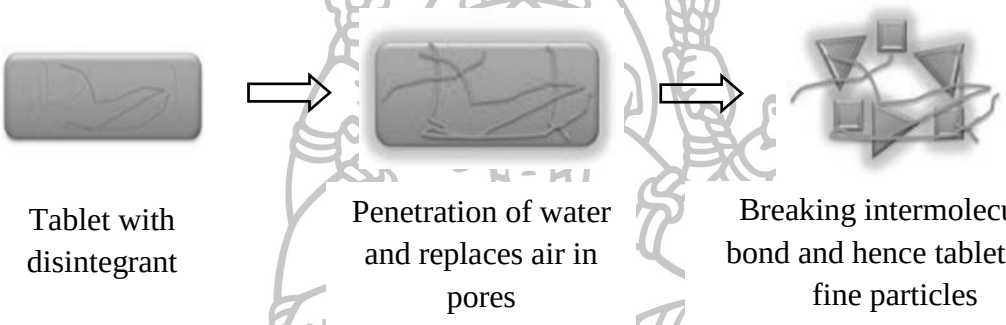

Figure 2.8 Capillary or wicking action of a disintegrant.
Source : **Disintegrant**, accessed May 22, 2014, available from http://www.pharmatutor.org.

2.6.3 Deformation

During tablet compression, disintegrant particles get deformed and these deformed particles get to their normal structure when they come in contact with aqueous media or water. This increase in size of the deformed particles produces a breakup of the tablet (Figure 2.9). Starch grains are generally thought to be "elastic" in nature. Under relatively high compression forces in tableting, the starch grains are believed to be deformed temporarily and are said to be "energy rich". Once exposure to water, the stored energy releases and the grains that are deformed under pressure will return to their original shape [22]. Occasionally, the swelling action of starch is improved when granules are extensively deformed during compression.

Tablet containing deformed disintegrant

Disintegrant recovers original form when placed in water

Disintegration of tablet

Figure 2.9 Deformation mechanism of a disintegrant.

Source : **Disintegrant**, accessed May 22, 2014, available from http://www.pharmatutor.org.

2.6.4 Particle/particle (inter-particle) repulsive forces

Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particles also cause disintegration of tablets (Figure 2.10). By this mechanism, the disintegrants can dissociate or protonate into electric charged species upon exposure to aqueous media or water. In close contact, the charged disintegrants push one another, by the electric repulsive forces that break the tablet into fine particles [22]. It is believed that the inter-particle repulsion is secondary to the capillary or wicking action.

Tablet containing non-swellable disintegrant

Repulsion between disintegrant when placed in solvent

Disintegration of tablet due to repulsion of disintegrant

Figure 2.10 Repulsion mechanism of a disintegrant.

Source : **Disintegrant**, accessed May 22, 2014, available from http://www.pharmatutor.org.

2.6.5 Miscellaneous

The tablet disintegration can be created by the release of gas (carbon dioxide) due to the effervescent reaction between a pair of acids and bases e.g. citric or tartaric acids and bicarbonate or carbonate salts. The reaction takes place in contact with aqueous liquid, producing carbon dioxide inside tablets. The accumulating gas leads to the increasing pressure (force) that can be sufficient for tablet breaking [51]. Enzymes present in the body can act as disintegrants. These enzymes weaken the binding action of binder and help in disintegration [22]. Some amino acids such as glycine can also make tablet disintegration by promoting the wettability of tablets into which water can enter more conveniently [52]. These substances may be classified as monomeric disintegrants.

From reviewing, it seems no single mechanism responsible for the action of disintegrants. For most disintegrants, either swelling or wicking (capillary) action is frequently found to account for tablet disintegration [16].

2.7 Factors affecting the disintegration properties

Certainly, the disintegrant property varies according to the chemistry of disintegrant. The disintegrants derived from linear or uncrosslinked hydrophilic cellulosic polymers (e.g., starch, gum and mucilage) in contact with water can rapidly hydrate and swell, allowing them to exert tablet disintegration mainly via swelling action. However, these linear or uncrosslinked disintegrants dissolve in water at certain extent and also possess adhesive property which can cause a viscous lump barrier covering the tablet surface that may deter the water entry and hence desired property of assisting disintegration. On the other hand, the crosslinked hydrophilic disintegrants (e.g. sodium starch glycolate, croscarmellose sodium, crospovidone and polacrilin potassium) exhibit both capillary and swelling properties, which activity is prevalent depending upon concentration of crosslinker. The more crosslink the less swelling action is likely to govern tablet disintegration. In addition, they have little tendency to form the viscous lump barrier because of their crosslinked structure. This advantage may explain why most of crosslinked disintegrants require less effective

concentrations for tablet disintegration than the linear or uncrosslinked ones. The monomeric disintegrant does not have swelling and wicking activities; therefore, the disintegrant action solely accords to their inherently physicochemical or chemical properties. Glycine makes tablet disintegration by wetting promotion [52-53], while a mixture of bicarbonate salt and citric acid allows the tablet to disintegrate by effervescent reaction [51]. In addition to the chemistry, the particle size, shape, crystal morphology and moisture content of a disintegrant can more or less influence the disintegrating action [14, 17, 23, 45-46].

Disintegrants are an excipient for tablets. Therefore, relevant conditions for making tablet formulations inevitably influence the disintegrant property. This issue has been widely investigated. The disintegrating efficiency for most disintegrants is concentration-dependent [18]. An increased concentration causes an accelerated disintegration of tablets. However, this pattern does not always obey with mucilage-like disintegrants which, when used at high concentrations, may slow down tablet disintegration owing to the formation of a viscous lump barrier. The effect of compression force on the disintegrant efficiency is another factor of interest [15]. There is a tendency of a decreased disintegration as the tableting force is increased [14-17, 45]. It is generally attributed to the reduction of tablet porosity, which makes difficulty for water entry into tablets. In addition, stronger tablets are more difficult to disintegrate due to higher consolidation.

There are studies which report the type of drug added in the tablet formulation affecting the disintegrant efficiency. Fukami et al. investigated the effect of ethenzamide (poorly water soluble) and ascorbic acid (water soluble) on disintegration times of the tablet formulations using glycine and carboxymethylcellulose as disintegrants [52]. The ascorbic acid tablet provided a longer disintegration time than the ethenzamide tablet. The possible cause might be due to the rapid solubilization of ascorbic acid, which became a viscous barrier obstructing the water entry into tablets. Chang et al. determined the disintegration time of hydrochlorothiazide and aspirin tablets separately using four kinds of disintegrants [19]. At equivalent amounts of disintegrants used and comparable

crushing strengths obtained, the aspirin tablet took more time to disintegrate than the hydrochlorothiazide tablet.

For the tablets prepared by wet granulation, the efficiency of disintegrants may depend upon mode of disintegrant incorporation that a disintegrant is added intragranularly or extragranularly in tablets. It is reported that an intragranular disintegrant is most likely not as effective as an extragranular one due to the fact that the former is exposed to wetting and drying which reduces the activity of disintegrants [17,19,53].

Storage condition affecting disintegrating property is also reported. High relative humidity can shorten disintegration time, or in other words apparently increase disintegrant efficiency, because moisture from the environment penetrates and softens tablets [14].

2.8 Evaluation of tablet disintegration

There are several methods developed for the measurement of tablet disintegration. The typical approach involves the utility of conventional disintegration apparatus as specified in Pharmacopoeia [54]. The apparatus consists of a basket made of transparent plastic materials, containing six tubes in the same basket with equal diameter. The bottom of each tube is attached by wire screen made of stainless steel with uniform mesh size. In testing, the basket-rack assembly is moved repeatedly downward and upward by a reciprocating motor into a vessel containing a disintegration medium maintained at a desired temperature. The disintegration time is the moment that tested tablets completely disintegrate and pass through the assembly screen.

The above official method is not always suitable for all types of tablet. Therefore, many researchers are attempting to develop alternative methods that are expected to obtain more accurate results from disintegration test. For instance, a method modified from the official dissolution apparatus has been proposed as shown in Figure 2.11 [55-56]. A basket sinker containing tested tablets is placed just below the surface of a disintegration medium maintained at a desired temperature and speed of revision. The disintegration time is determined when the tablets completely disintegrate and pass through the screen of the sinker.

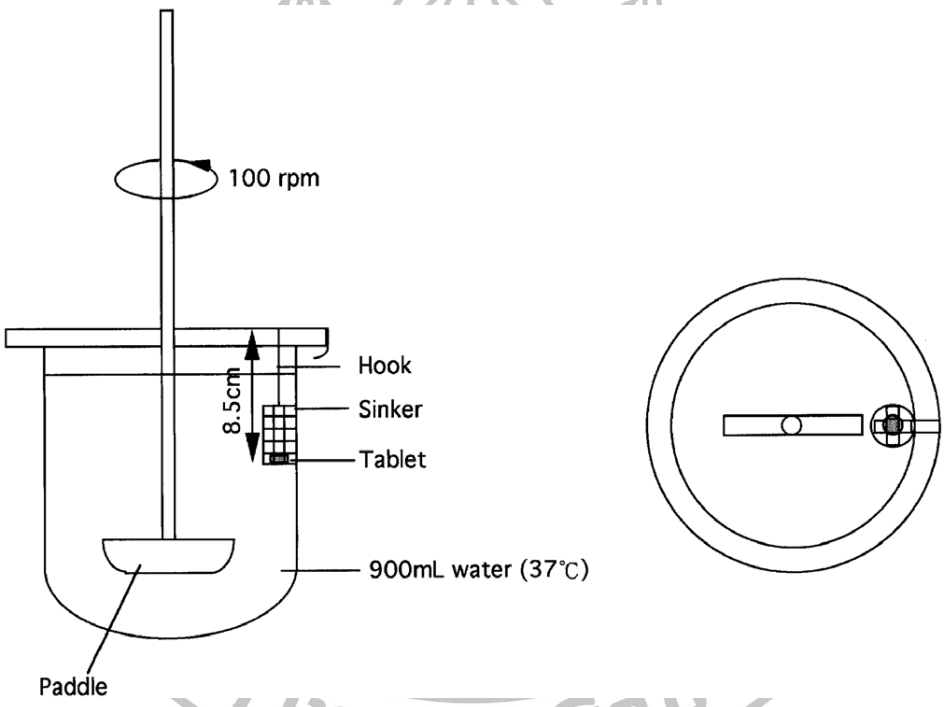

Figure 2.11 Schematic view of modified dissolution apparatus for disintegration test.

Morita et al. [57] developed a disintegration test apparatus equipped with a CCD camera. This apparatus is divided into two distinct sections, a disintegration component and a measurement device. The mode of measurement involves the continuous monitoring and recording of disintegration time course by obtaining pictures through the CCD camera, which are simultaneously transferred into a computer and stored. The specialty of this apparatus is to combine the detailed pictures obtained by the CCD camera and the calculation capabilities of the computer. The disintegration apparatus consists of a plastic cell partitioned into two parts: one component comprises of an inner tank containing the stirring bar, the grid fabricated from stainless-steel and a disintegration medium; the second component is an outer tank, which functions as a water bath maintained at a desired temperature (Figure 2.12a) via circulation of thermostated water. The grid consists of three hollow areas, equidistant from the center, in which the tablets are positioned using a support to avoid their displacement during the test (Figure 2.12b). The CCD camera is positioned such that the top surface of the three tablets can be seen on the camera's screen.

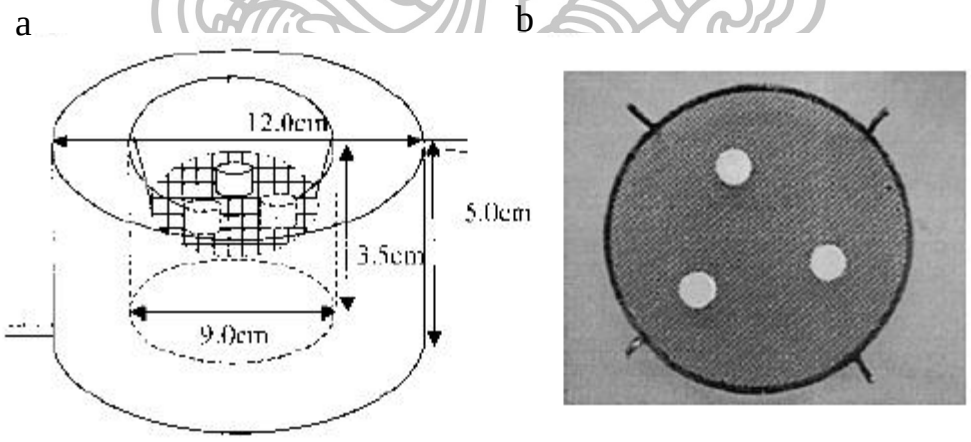

Figure 2.12 (a) Plastic disintegration cell and (b) tablet support grid with three tablets.

Texture analyzer apparatus has been applied to measure tablet disintegration [58]; the setup is shown in Figure 2.13. In this test, a flat-ended cylindrical probe penetrates into the disintegrating tablet immersed in water. The instrument is set to maintain a small force for a determined period of time as the tablet disintegrates. The disintegration profile is plotted from the distance traveled by the probe generated with the instrument's software against time. The plot facilitates calculation of the starting and ending time of disintegration.

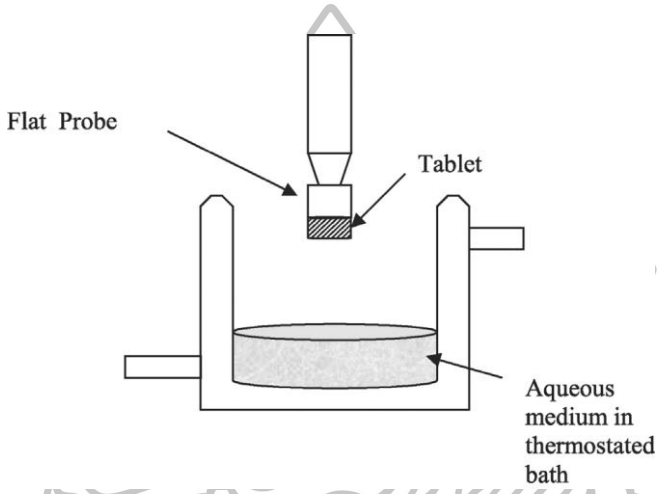

Figure 2.13 Texture analyzer apparatus for disintegration test.

Narazaki et al. [59] developed a disintegration test method using a rotary shaft for fast disintegrating tablets (FDTs) as shown in Figure 2.13. In testing, the FDTs is placed on the wire gauze (D), slightly immersed in test medium, and the rotary shaft (E) is employed to provide mechanical stress on the tablet by means of its rotation and weight. The critical parameters of this method are the rotation speed and the mechanical stress. The compression force can be easily adjusted using the weight (A). The rotary shaft covered with a wetting sponge (C) crushes the FDT which disintegrates into the medium. The endpoint (disintegration time) is measured visually using a stopwatch. Later, Harada et al. [60] modified the apparatus by adding an electric sensor, which can optimize not only rotation speed and mechanical stress of the rotary shaft but also indicate the end point of disintegration test.

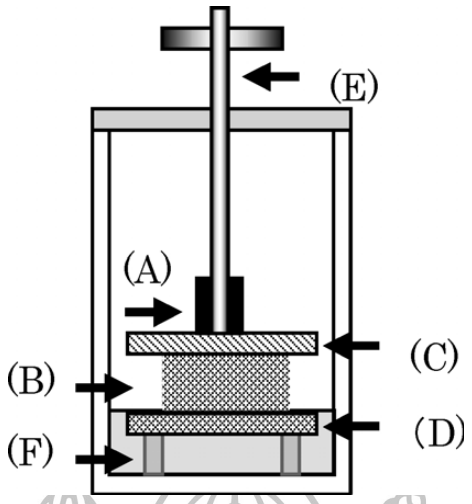

Figure 2.14 Apparatus of rotary shaft method for (A) FDT weight, (B) FDT, (C) wetting sponge, (D) wire gauze, (E) rotary shaft and (F) medium.

In another study, a simple device based on a shaking water bath has been designed to measure the disintegration time of FDTs [61]. The disintegration test is performed by placing the FDTs in a glass cylinder fitted with 10 meshes at its base. This set up is further placed in a shaking water bath operated at desired speed and temperature. After adding a medium, the FDT starts disintegration into small particles and the time at which the particles of the tablet go completely through the sieve is determined visually as the disintegration time. This quick method gives reproducible data that are highly useful in screening various formulations and testing many formulation variables.

Recently, ElectroForce® 3100 (Figure 2.14C) has been applied by the Bose corporation to determine the disintegration of FDTs. It works similarly as the texture analyzer apparatus that monitors the disintegration of tablets via force and displacement as a function of time. However, it requires lower force application, thus providing greater controlled resolution than typically available with moderate to high force test instruments.

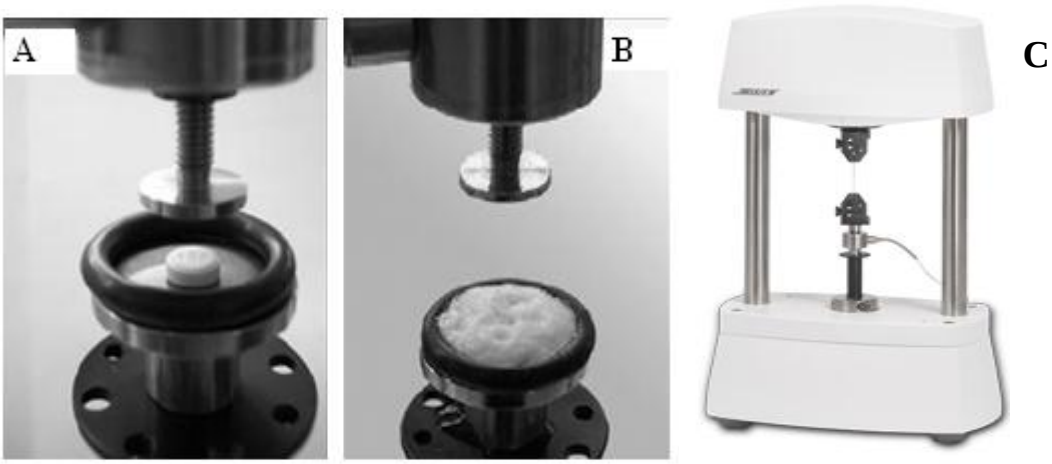

Figure 2.15 FDT mounted on test plate (A) before loading, (B) FDT after completion of disintegration test and (C) ElectroForce® apparatus for disintegration test.

Occasionally, in vitro disintegration testing for FDTs may not reflect the real in vivo disintegration of tablets. For this case, a study on in vivo disintegration test can be employed, which is conducted with volunteers who are usually randomized to receive the treatment in the oral cavity [56]. The disintegration time is directly measured by the human sensory [64]. It should be noted that the results from this type of test typically reveal unsatisfactory reproducibility and are not completely reliable [57]. Furthermore, the in vivo disintegration test has limitations from the perspective of ethics and the safety of volunteers.

2.9 Model drug

Propranolol HCl is a nonselective β-adrenergic blocking agent [65] with the chemical name 1-(1-methylethylamino)-3-(1-naphthyloxy)-propan-2-ol hydrochloride and its structure is shown in Figure 2.15 [66]. It appears white or off white, crystalline powder with a bitter taste and odorless. Melting point and molecular weight are 163-166 °C and 295.8 g/mol ($C_{16}H_{22}ClNO_2$). The pH of 1% solution of propranolol HCl in water lies between 5.0 and 6.0. The pKa is 9.45 [67]. Propranolol HCl is soluble 1 in 20 of water and 1 in 20 of ethanol; slightly soluble in chloroform and practically insoluble in ether. It shows a pH-dependent solubility in the pH range of the gastrointestinal tract [68].

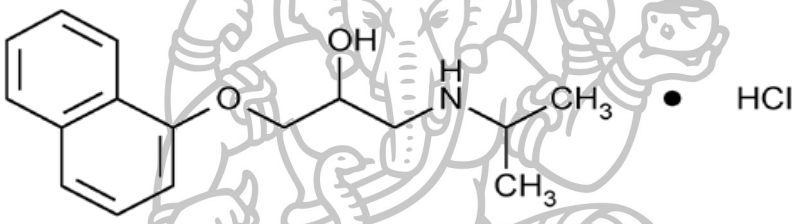

Figure 2.16 Chemical structure of propranolol HCl .

Propranolol HCl is widely used in therapeutics as an antihypertensive, antianginal and antiarrhythmic agent and for the treatment of migraine [69-70]. It is highly lipophilic and almost completely absorbed after oral administration but undergoes high first-pass metabolism by the liver such that only about 25% of drug reaches the systemic circulation. It has a short elimination half life (3–4 h) so is one of candidates for the development of extended-release dosage forms.

Propranolol HCl is a salt of weak base, which dissolves and exists as cationic species in the aqueous solution. This ionic species can adsorb on cationic exchange resins via ion exchange process [71-75].

CHAPTER 3
MATERIALS AND METHODS

3.1 Equipments and chemical reagents

3.1.1 Laboratory equipment and analysis

1. Manual hydraulic press (Specac, P/N 15011/25011, United Kingdom)
2. Analytical balance (Sartorius, Germany)
3. Infrared spectrophotometer (Nicolet, magna4700, USA)
4. Ultraviolet spectrophotometer (PG Instrument, United Kingdom)
5. Hardness testing apparatus (Erweka, Model THB 225TD, Germany)
6. Disintegration testing apparatus (Erweka, Germany)
7. Dissolution testing apparatus, Paddle, Apparatus II (Prolabo, United Kingdom)
8. Friability tester (Erweka, Model TA120, Germany)
9. Hot air oven (Heraeus, Germany)
10. Hot plate (IKA, Germany)
11. Blender (Moulinex, Franch)
13. pH meter (SevenEasy, Mettler-Toledo, Switzerland)
14. Centrifuge
15. Caliper (PEACOCK, Model G (0.01-10mm), Japan)

3.1.2. Chemical reagents

1. Methacrylic acid (MAA) (Aldrich Chemistry, Germany)
2. Divinylbenzene (DVB) (Aldrich Chemistry, Germany)
3. Ethylene glycol dimethacrylate (EGDMA) (Aldrich Chemistry, Germany)
4. Benzoyl peroxide (Aldrich Chemistry, Germany)

5. Amberlite® IRP64 (Aldrich Chemistry, Germany)
6. Microcrystalline cellulose Avicel® PH101
   (FMC Corporation, USA.)
7. Dibasic calcium phosphate (P.C. Drug Center, Thailand)
8. Supertab® 11SD. (Fonterra Ltd., New Zealand)
9. 95% ethanol (QreC, New Zealand)
10. Silicone oil (P.C. Drug Center, Thailand)
11. Magnesium stearate (P.C. Drug Center, Thailand)
12. Sodium hydroxide (P.C. Drug Center, Thailand)
13. Potassium hydroxide (P.C. Drug Center, Thailand)
14. Sodium starch glycolate (P.C. Drug Center, Thailand)
15. Propranolol hydrochloride (P.C. Drug Center, Thailand)

3.2 Experimental methods

3.2.1 Preparation of resin disintegrant

Two series of resins differently crosslinkers as DVB or EGDMA were synthesized as follows. MAA 10 g, crosslinker DVB or EGDMA 0.25 - 16 % mol of MAA and benzoyl peroxide 1 g were mixed in a flask and then 10 ml of deionized water was added to the mixture. The copolymerization was carried out at 85-90 ^{o}C in a silicone oil bath under continuous stirring (Figure 3.1). The copolymer product was cooled to ambient temperature and washed with several times of ethanol and deionized water to remove an excess of MAA and crosslinker DVB or EGDMA, respectively. After washing, the product was dried in a hot air oven at 60 ^{o}C for 4 h, milled and passed through a 80 mesh sieve. Synthetic reaction of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) is depicted in Figure 3.2 and Figure 3.3, respectively.

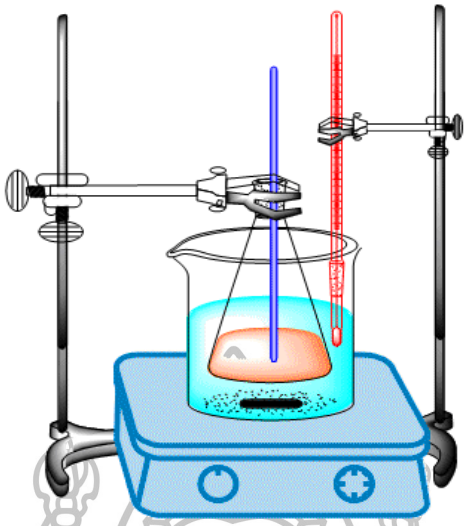

Figure 3.1 Setup of preparing method.

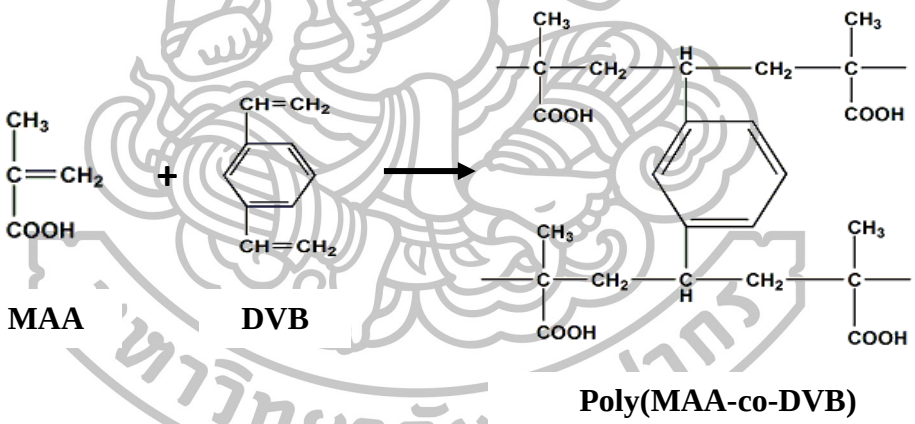

Figure 3.2 Synthesis of poly(MAA-co-DVB).

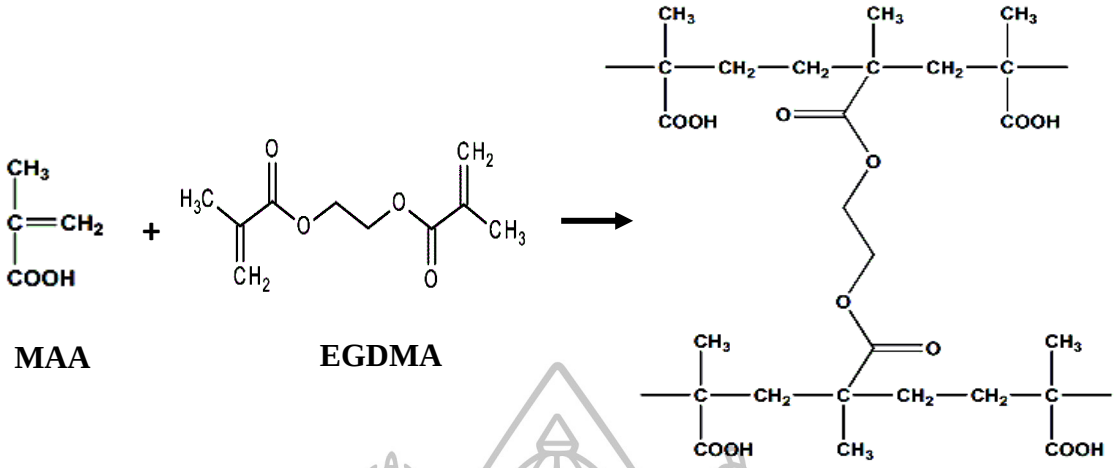

Figure 3.3 Synthesis of poly(MAA-co-EGDMA).

3.2.2 Conversion of disintegrant resins to Na and K salts

Na and K salted resins were individually prepared by suspending 2 g of dry polymer product in 50 ml of 1 M NaOH and KOH for 24 h. Thereafter, the salted resins were collected by filtration and washed several time with distilled water until neutral. The products were dried in a hot air oven at 60-80 ^{o}C for 24 h, milled and passed through a 80 meshes sieve.

3.2.3 Powder characterization

3.2.3.1 Infrared analysis

Infrared spectra of samples were recorded by KBr disc method on Fourier transform infrared spectrometer (Nicolet, magna4700, USA) in the wavelength region of 400 to 4000 cm^{-1}.

3.2.3.2 Water uptake

The water uptake of samples was determined by the method reported previously [39]. In brief, 100 mg (W_1) of each resin weighed quantitatively was transferred into micro centrifuge tubes. 1 mL of deionized water was added and mixed for 30 s. The samples were allowed at ambient temperature for 2 h, centrifuged (6000 rpm, 15 min) and drained for 10 min. The experiment was done in the test tubes weighed (W_2) and the water uptake was calculated as follows:

$$\%\ \text{water uptake} = \frac{W_2 - W_1}{W_1} \times 100$$

3.2.3.3 Swelling

The swelling of samples was determined by the method reported previously [39]. In brief, 0.5 g of each resin was placed into a 10 ml cylinder and tapped several times. The tapped volume of copolymer (V_1) was recorded and an excess amount of deionized water was carefully added into the cylinder. Later 2 h, the volume of swollen copolymer (V_2) was recorded and the experiment was carried out in swelling capacity (%) calculated by the following equation:

$$\%\ \text{swelling} = \frac{V_2 - V_1}{V_1} \times 100$$

3.2.4 Disintegrant property

100 mg MCC tablets containing 10 % w/w of each resin were prepared by flat-faced 6.5 mm punches on a hydraulic press under 1 ton of compression force. The tablets prepared from each batch were determined for disintegration time and hardness, respectively. Tablets with 10 % sodium starch glycolate and without disintegrant were also prepared and evaluated for comparison purpose.

3.2.5 Factors affecting the disintegrant properties

Flat-faced tablets containing selected resin disintegrants were prepared under alteration of various conditions as follows:

3.2.5.1 Concentration of disintegrants and tableting force

100 mg of MCC tablets contained 2.5, 5, 7.5, 10 % w/w of resin disintegrant

Prepared under 0.5, 1 and 2 ton of compression force

3.2.5.2 Tablet size

100, 250, 500 mg of MCC tablets contained 10 % w/w of resin disintegrant

Prepared under 1 ton of compression force

3.2.5.3 Type of tablet filler

100 mg tablets of MCC, dibasic calcium phosphate (DCP) or Supertab® contained 10 % w/w of resin disintegrant

Prepared under 1 ton of compression force

3.2.5.4 The presence of magnesium stearate

100 mg of MCC tablets contained 10 % w/w of resin disintegrant and 0, 0.5, 1 % of magnesium stearate

Prepared under 1 ton of compression force

The tablets prepared from each batch were determined for disintegration time and hardness, respectively.

3.2.6 Determination of ion-exchange effect on drug release

Propranolol hydrochloride tablets containing 2.5 and 10 % of selected resin disintegrants, MCC as a direct compresson filler, 0.5 % magnesium stearate and 1 % fumed silica (glidant) were prepared on a hydraulic press under 1 ton of compression force. The prepared drug tablets were evaluated for drug content, hardness, friability, disintegration time and dissolution test. The drug tablets containing 2.5 and 10% of sodium starch glycolate and without disintegrant were also prepared and evaluated for comparison purpose.

3.2.7 Evaluation of tablet

3.2.7.1 Hardness

The hardness of ten tablets from each batch was measured by a hardness tester.

3.2.7.2 Friability

The friability of tablets from each batch was measured by a friability tester. Ten tablets were weighed (W_1) and placed in the friabilator, which was run at 25 rpm for 4 min. After removal of fines, the tablets were re-weighed (W_2), and the friability (F) was calculated by the following equation.

$$F = \left(\frac{W_1 - W_2}{W_1} \right) \times 100$$

3.2.7.3 Drug content (Assay)

Drug content was determined in triplicate by dissolving the tablet with alcoholic solution in a 100 ml volumetric flask. The mixture was then properly diluted with phosphate buffer pH 6.8, filtered and analyzed the content of propranolol HCl at the wavelength of 290 nm by using a UV/Visible spectrophotometer [76-77].

3.2.7.4 Disintegration

The disintegration time of six tablets was determined by the USP disintegration apparatus in deionized water at 37±0.5 ^{o}C. The disintegration time was defined from the moment that the tablet disintegrated and passed through the assembly screen.

3.2.7.5 *In vitro* dissolution

The dissolution test was carried out using a paddle dissolution apparatus rotating speed at 100 rpm in 900 ml of 0.1 M HCl (pH 1.2), maintained at 37± 0.5 ºC. Samples (5 ml) were withdrawn at different time intervals (i.e. 5, 10, 15, 30, 45 and 60 min) and replaced with fresh medium. Diluted properly if needed and the amount of drug dissolved was determined by using a UV-vis spectrophotometer at the wavelength of 290 nm. Six tablets from each batch were tested for each round of the dissolution test.

CHAPTER 4
RESULTS AND DISSCUSION

4.1 Synthesis of poly(MAA-co-DVB) and poly(MAA-co-EGDMA)

Poly(MAA-co-DVB) crosslinked with 0.25-16 % DVB and poly(MAA-co-EGDMA) crosslinked with 0.25-16 % EGDMA were synthesized by free radical polymerization using benzoyl peroxide as an initiator. The synthetic reaction of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) is presented in chapter 3, which provided the copolymers in H form (Figure 3.2 and Figure 3.3, respectively). The appearance of the two series of copolymer products is shown in Figure 4.1. As seen in the figures, poly(MAA-co-DVB) resins appeared to be white to faint yellow as increasing the amounts of DVB, while poly(MAA-co-EGDMA) resins were randomly white to off white. These intermediate resins were ground and passed through a 80 mesh sieve before further investigations.

In generally, the polymer without crosslinker (poly(MAA)) was also synthesized. During the preparation, the polymerizing mixture of this polymer was very viscous, and finally turned to single plastic-like lump, as shown in Figure 4.1 (a). This lump was so hard that it could not be ground and passed through the sieve. Due to this drawback, the poly(MAA) resin was therefore excluded from investigation. The presence of crosslinker (DVB or EGDMA) in resins decreased the viscosity of polymerizing mixture during the preparation and provided the softer polymers which were easier to be ground and passed through the sieve.

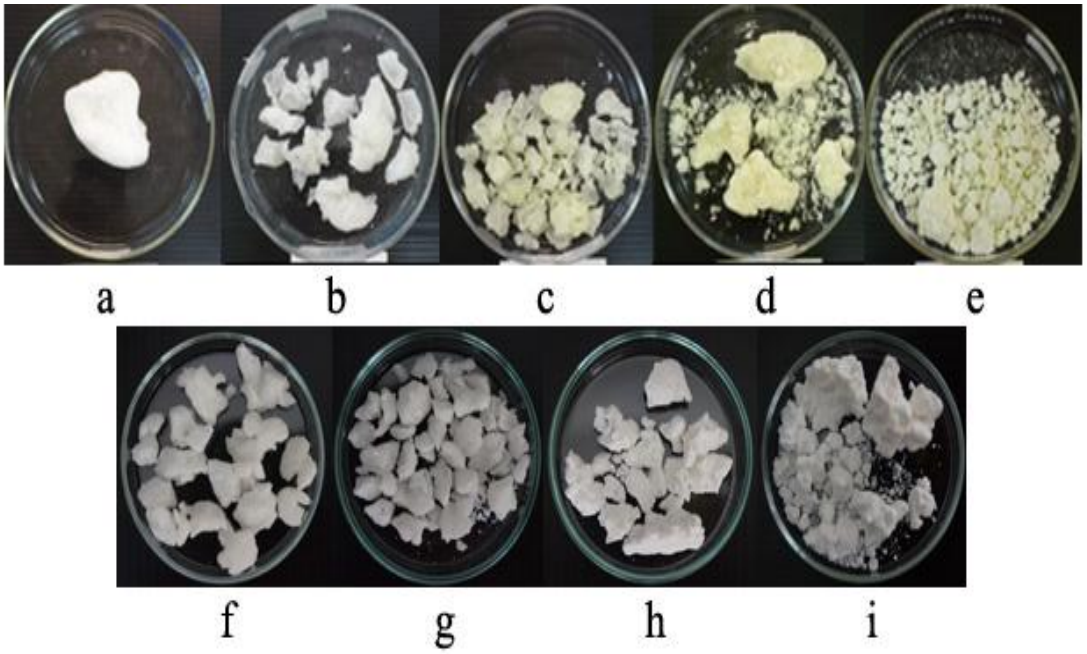

Figure 4.1 Appearance of resin products, (a) poly(MAA), poly(MAA-co-DVB) with (b) 0.25, (c) 2, (d) 8 and (e) 16 % DVB and poly(MAA-co-EGDMA) with (f) 0.25, (g) 2, (h) 8 and (i) 16% EGDMA.

The sodium and potassium salts of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) were prepared by placing the copolymers in H form in the aqueous solutions of sodium hydroxide and potassium hydroxide, respectively. In these basic solutions, the H cation in the copolymer was displaced by the Na and K cations via ion exchange reaction, consequently obtaining the copolymers in Na and K forms, respectively (Figure 4.2 and Figure 4.3). The yields of obtained copolymers were different, which unpredictably dispersed in the range from 14.56 to 66.09 as shown in Figure 4.4.

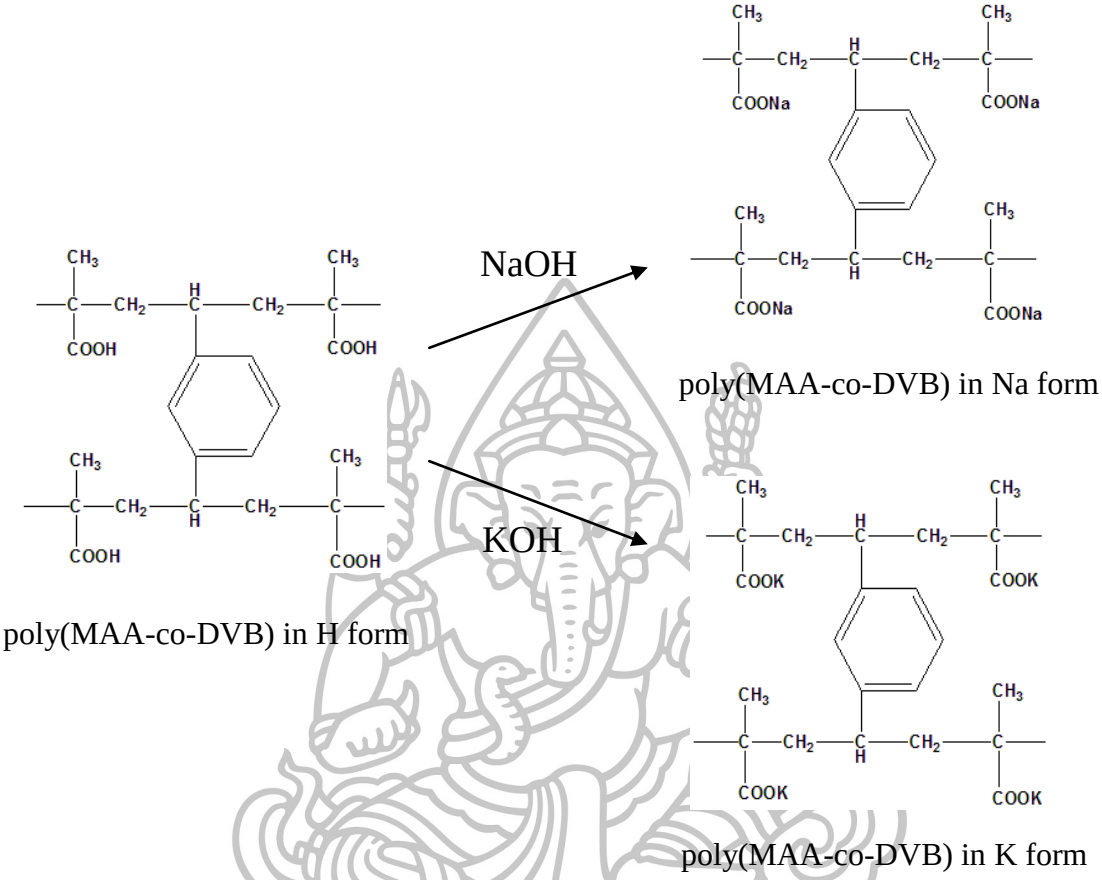

Figure 4.2 Preparation of poly(MAA-co-DVB) in Na and K forms.

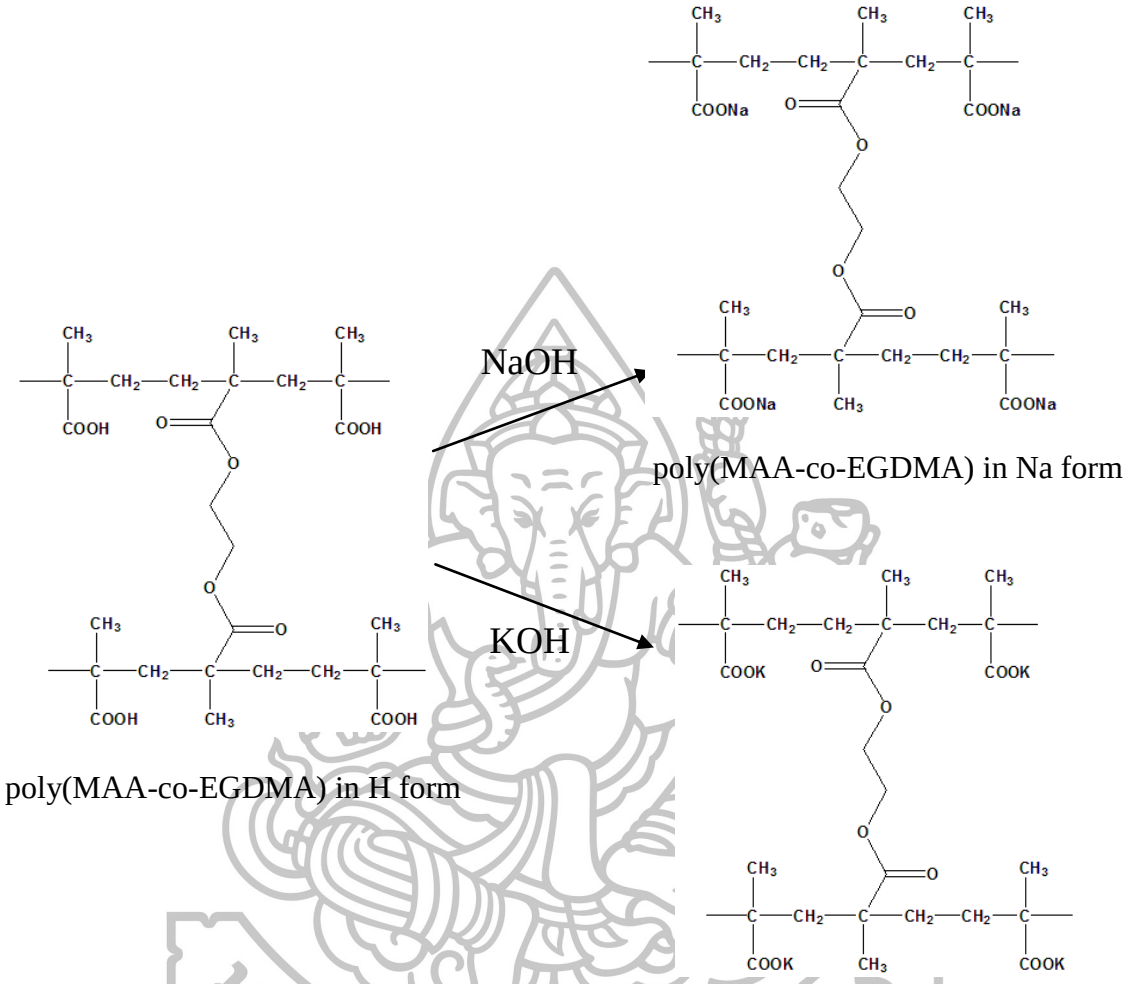

Figure 4.3 Preparation of poly(MAA-co-EGDMA) in Na and K forms.

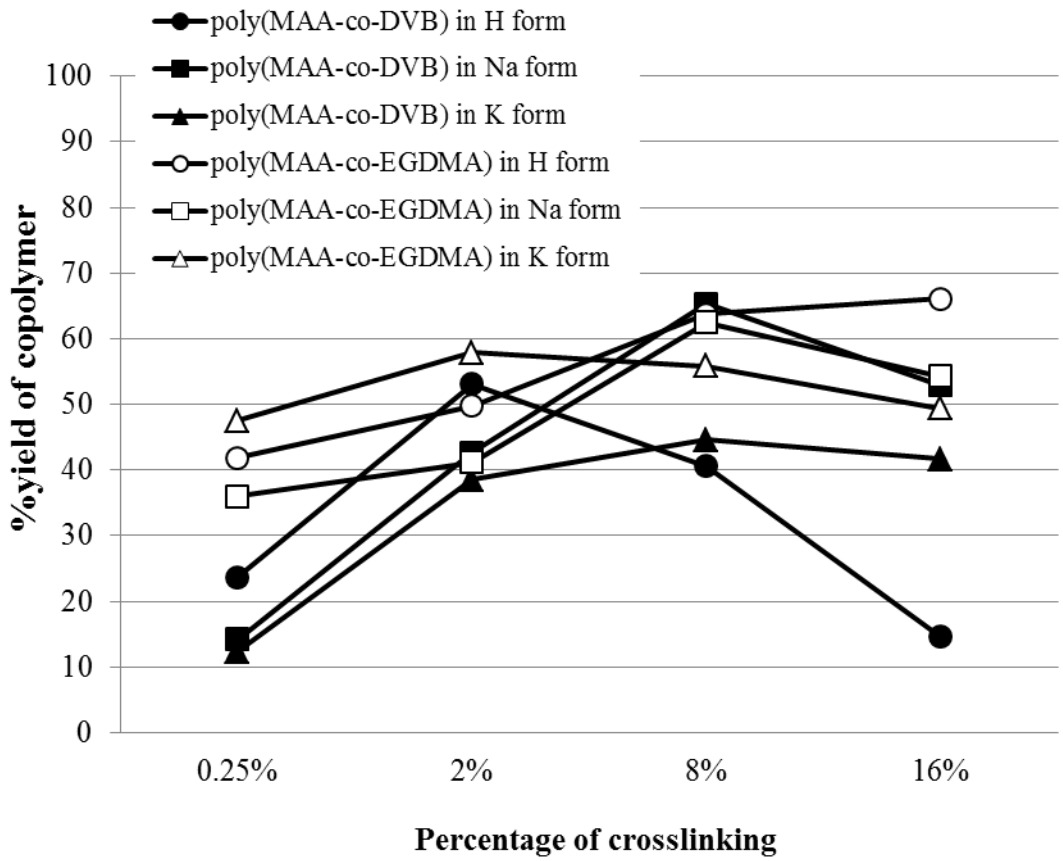

Figure 4.4 Yields of poly(MAA-co-DVB) (filled symbol) and poly(MAA-co-EGDMA) (open symbol) in various crosslinks and salt forms.

4.2 Characterization of copolymer

4.2.1 FT-IR analysis

With the aim to compare, the infrared spectra of DVB and poly(MAA) were firstly determined as presented in Figure 4.5. The main characteristic bands in the spectra of DVB (Figure 4.5 (a)) were at 900 and 675 cm^{-1} assigned for the out-of-plane bending of aromatic C-H bonds, at 1630 cm^{-1} assigned for the aromatic C=C stretching and at 3087 and 2872 cm^{-1} assigned for the aromatic C-H stretching. The poly(MAA) polymer provided several characteristic bands in its IR spectra, which comprised at 3455 cm^{-1} corresponding to the O-H stretching of carboxyl group (COOH), at 1755 cm^{-1} corresponding to the carbonyl stretching of carboxyl group, at 1483 and 1395 cm^{-1} corresponding to the C-H stretching of CH_2 and CH_3 groups and at 1277 and 1174 cm^{-1} corresponding to the C-O stretching of carboxyl group, respectively.

The IR spectra of poly(MAA-co-DVB) in H form at various levels of crosslink are illustrated in Figure 4.5, which looked like a superimpose between the IR spectra of DVB and poly(MAA). The broad peaks at 3469 and 1705 cm^{-1} were assigned for the O-H stretching and carbonyl (C=O) stretching of carboxyl group. The carbonyl peak of poly(MAA-co-DVB) stood at lower wavenumbers than that of poly(MAA) occurring at 1755 cm^{-1}. The peaks at 1479 and 1390 cm^{-1} corresponded to the C-H stretching of CH_2 and CH_3 groups, respectively. The characteristic peaks of C-O stretching were observed at 1274 and 1174 cm^{-1}, confirming the presence of carboxyl group in the copolymer structure. Due to overlapping, only few peaks relating to DVB were observed in the IR spectra. The aromatic C=C stretching of DVB showed as only a small shoulder around 1610 cm^{-1}, which was more evident as the level of crosslink (DVB) increased. The out-of-plane bending peaks of aromatic C-H bonds for DVB were also observed at 834 and 711 cm^{-1}. The functional groups interpreted from the IR spectra complied with the chemical structure of poly(MAA-co-DVB) in H form (Figure 4.2).

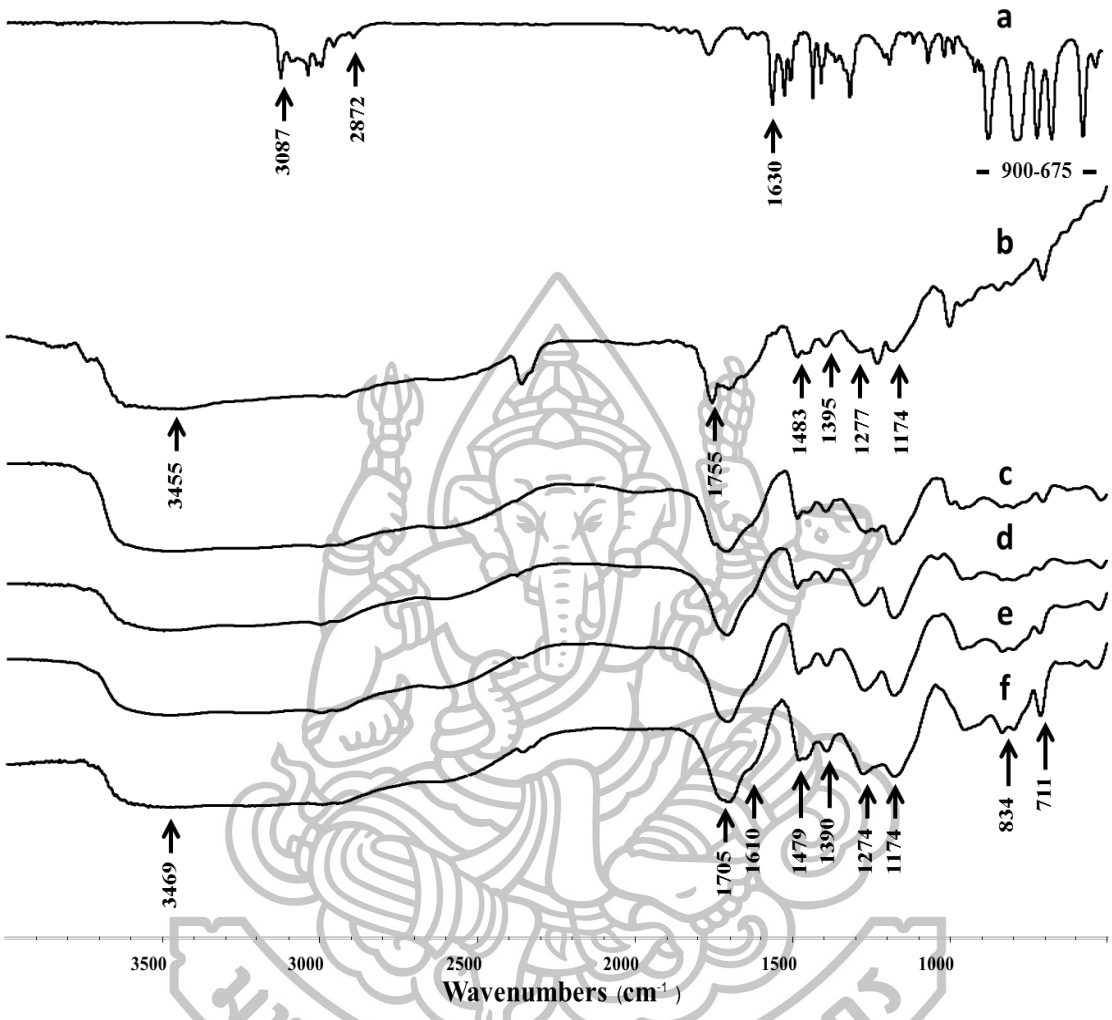

Figure 4.5 Infrared spectra of (a) DVB, (b) poly(MAA), and poly(MAA-co-DVB) with (c) 0.25, (d) 2, (e) 8 and (f) 16 % DVB.

The IR spectra of poly(MAA-co-DVB) in salt forms (Na and K) are illustrated in Figure 4.6 and 4.7, respectively. It was found that the copolymers in Na and K forms provided dramatically different IR spectra from those in acid form, as compared in Figure 4.8. While the peaks of O-H and C=O stretching from the carboxyl group (COOH) significantly diminished, new peaks relating to the asymmetric and symmetric stretching of carboxylate anion (COO^-) (Figure 4.9) occurred at 1558 and 1410 cm^{-1}, respectively [78]. In addition, the C-O stretching peaks of carboxyl group at 1274 and 1174 cm^{-1} disappeared and became single peak around 1207 cm^{-1}. The new peak was assigned for the C-O stretching of carboxylate anion, which its intensity was reduced as increasing the concentration of crosslinker (Figure 4.9). These IR results confirmed that the copolymers in Na or K salt forms were successfully prepared from that in H form. There was no remarkable difference in the FTIR spectra of copolymers between Na and K forms.

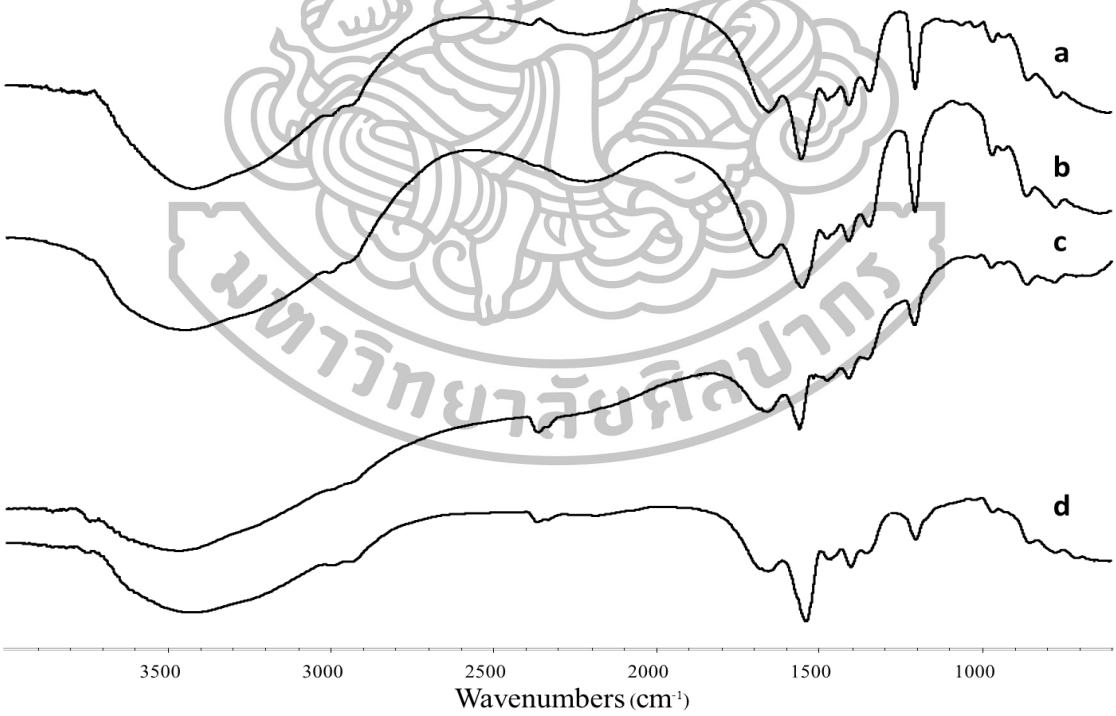

Figure 4.6 Infrared spectra of poly(MAA-co-DVB) in Na form with (a) 0.25, (b) 2,(c) 8 and (d) 16 % DVB.

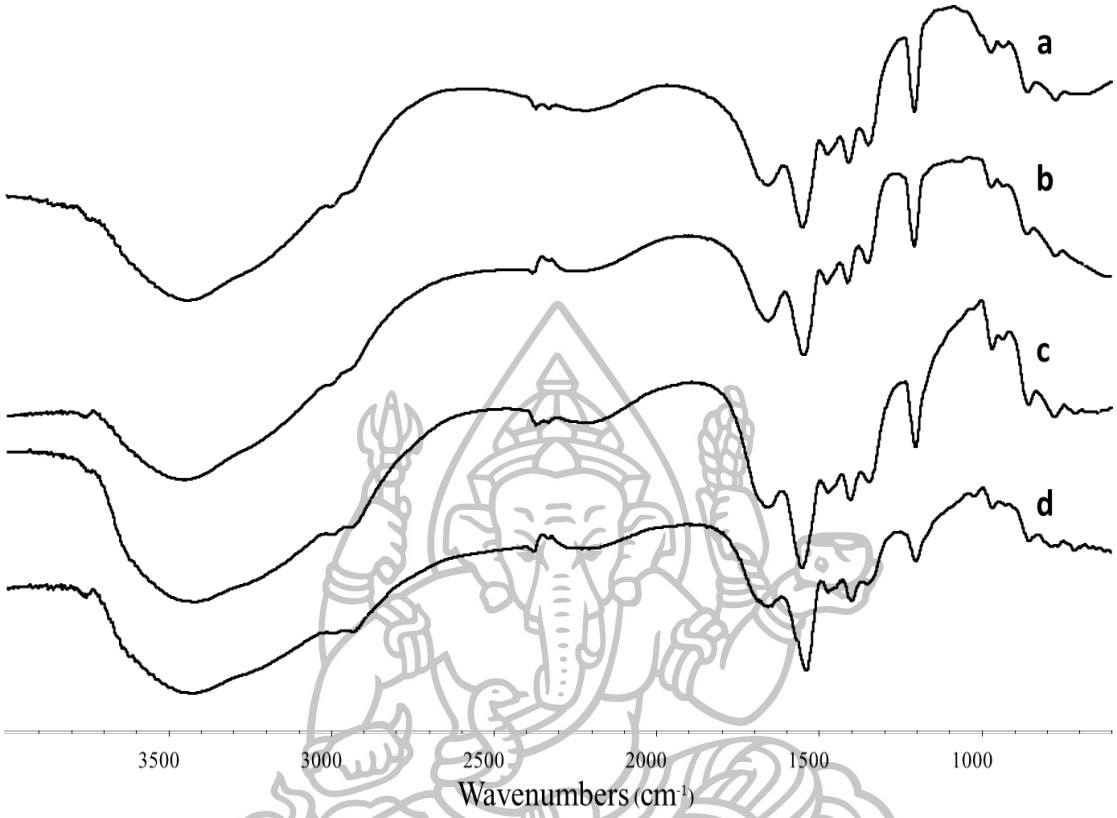

Figure 4.7 Infrared spectra of poly(MAA-co-DVB) in K form with (a) 0.25, (b) 2, (c) 8 and (d) 16 % DVB.

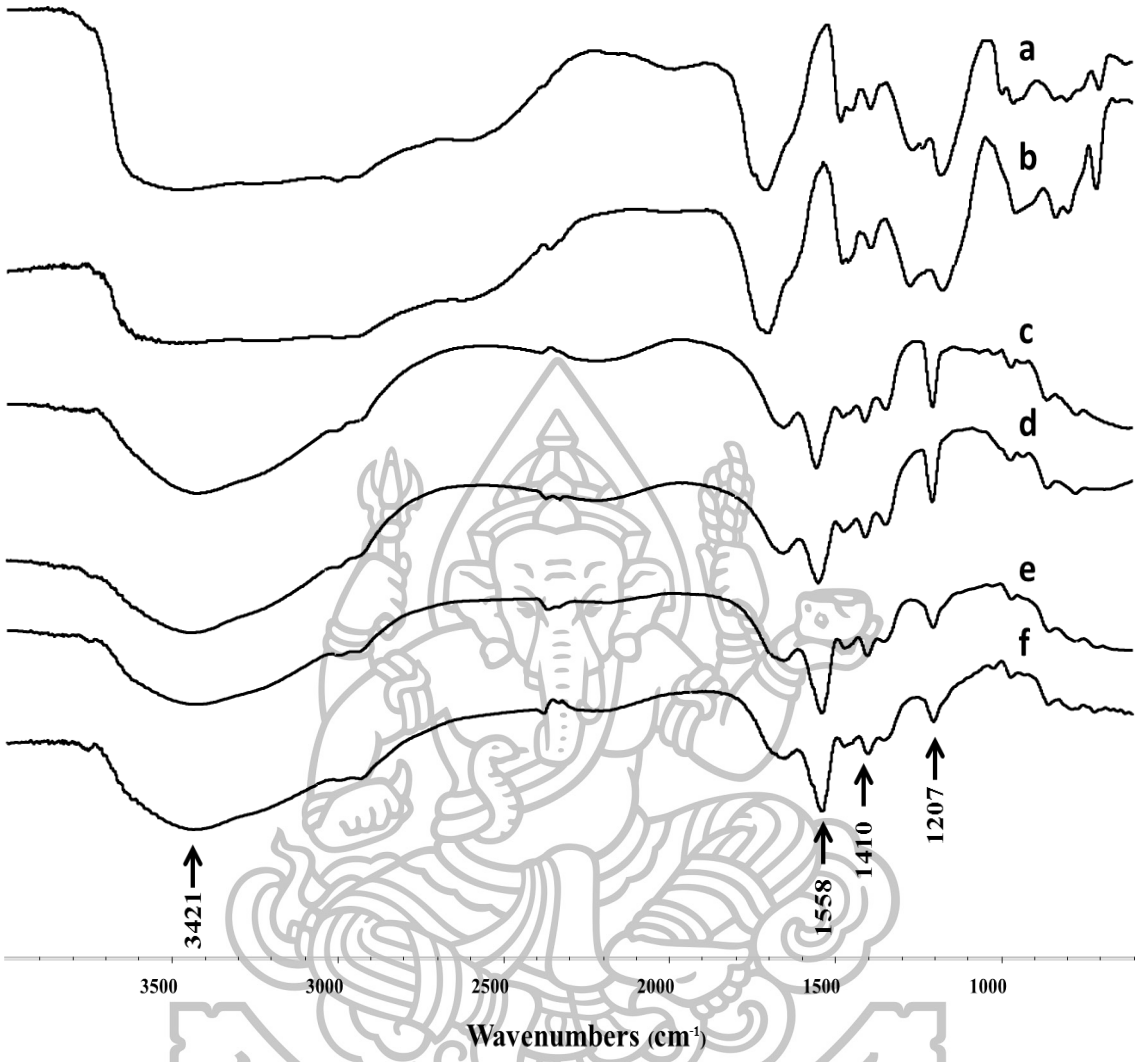

Figure 4.8 Infrared spectra of poly(MAA-co-DVB) in H form with (a) 0.25 and (b) 16 % DVB, with 0.25 % DVB in (c) Na form and (d) K form, with 16 % DVB in (e) Na form and (f) K form.

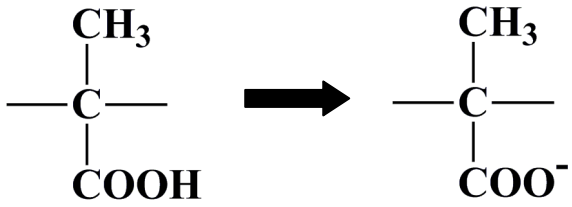

Figure 4.9 Conversion of carboxyl group (H form) to carboxylate anion.

Figure 4.10 presents the IR spectra of poly(MAA-co-EGDMA), together with EGDMA and poly(MAA) for comparison purpose. The IR spectra of EGDMA showed the major peaks at 1718 cm^{-1} assigned for the carbonyl stretching of carboxyl group, at 1630 assigned for the carbonyl stretching of ester group, at 1400-1300 cm^{-1} assigned for the C-H stretching of CH_2 and CH_3 groups, and 1299 and 1133 cm^{-1} assigned for the C-O stretching for carboxyl and ester groups. As previous presented, the poly(MAA) polymer provided several characteristic bands at 3455 cm^{-1} corresponding to the O-H stretching of carboxyl group (COOH), at 1755 cm^{-1} corresponding to the carbonyl stretching of carboxyl group, at 1483 and 1395 cm^{-1} corresponding to the C-H stretching of CH_2 and CH_3 groups and at 1277 and 1174 cm^{-1} corresponding to the C-O stretching of carboxyl group, respectively.

The IR spectra of poly(MAA-co-EGDMA) in H form seemed to be a superimpose between the IR spectra of EGDMA and poly(MAA) (Figure 4.10). The broad peak at 3520 cm^{-1} was assigned for the O-H stretching of carboxyl group. The C=O stretching peaks of carboxyl and ester groups overlapped and happened around 1600-1755 cm^{-1}. The peaks at 1483 and 1395 cm^{-1} corresponded to the C-H stretching of CH_2 and CH_3 groups, respectively. The characteristic peaks of C-O stretching for carboxyl and ester groups occurred at the same positions around 1271 and 1173 cm^{-1}. The functional groups predicted from the IR spectra agreed with the chemical structure of poly(MAA-co-EGDMA) in H form (Figure 4.3).

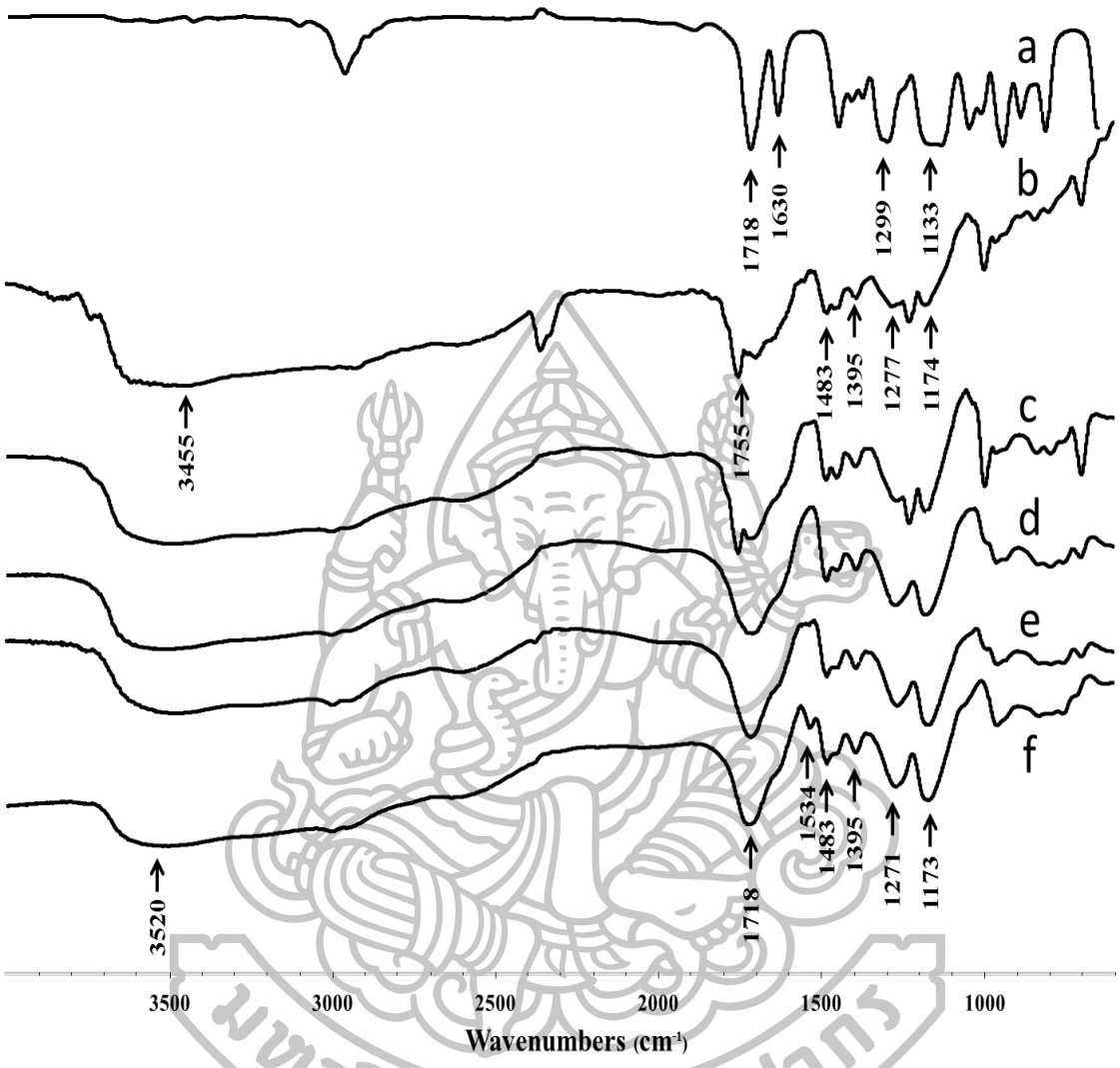

Figure 4.10 Infrared spectra of (a) EGDMA, (b) poly(MAA), and poly(MAA-co-EGDMA with (c) 0.25, (d) 2, (e) 8 and (f) 16 % EGDMA.

The IR spectrum of poly(MAA-co-EGDMA) in Na and K forms is displayed in Figure 4.11 and 4.12, respectively, which dramatically differed from that in acid form as compared in Figure 4.13. The peaks of O-H and C=O stretching from the carboxyl group (COOH) significantly diminished but new peaks relating to the asymmetric and symmetric stretching of carboxylate anion (COO^-) occurred at 1559 and 1413 cm^{-1}, respectively [78]. In addition, the C-O stretching peaks at 1271 and 1174 cm^{-1} disappeared and became single peak around 1198 cm^{-1} due to the formation of carboxylate anion (Figure 4.9). The spectral results clearly indicated the successful preparation of the resins in Na and K from H forms. Similar to poly(MAA-co-DVB), there was no distinct difference in the FTIR spectra of poly(MAA-co-EGDMA) between Na and K forms.

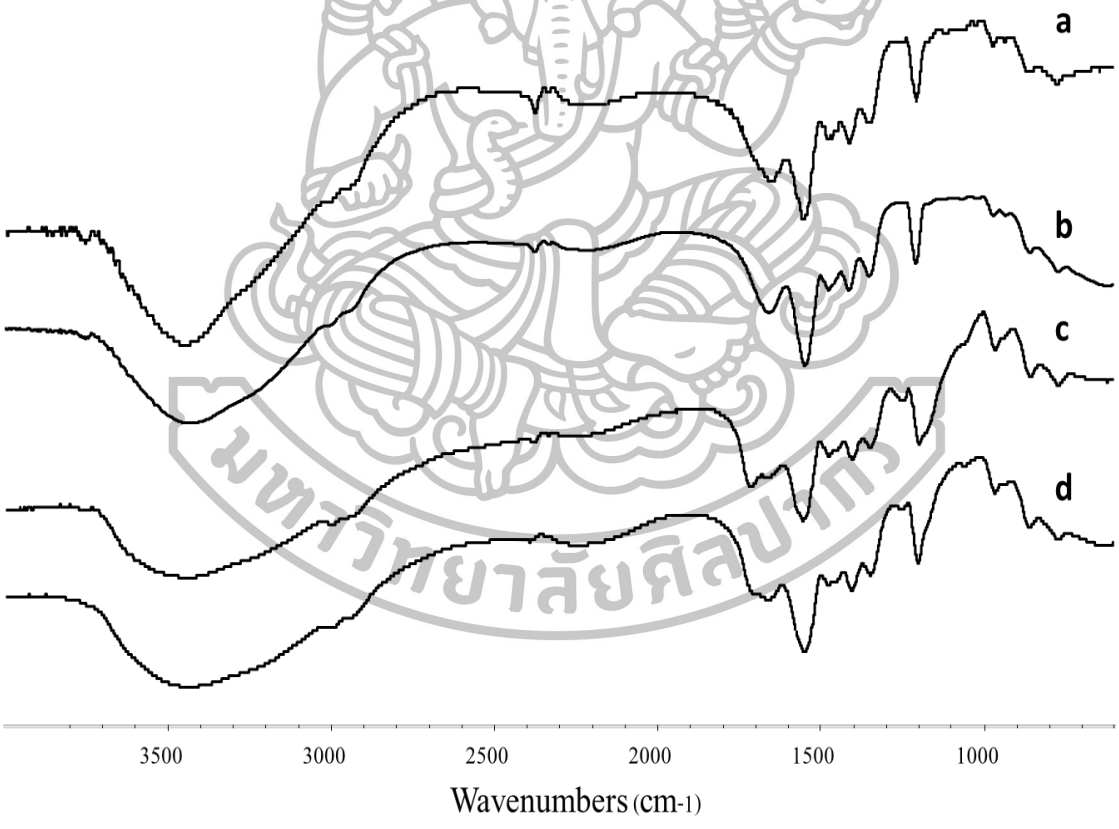

Figure 4.11 Infrared spectra of poly(MAA-co-EGDMA) in Na form with (a) 0.25, (b) 2, (c) 8 and (d) 16 %EGDMA.

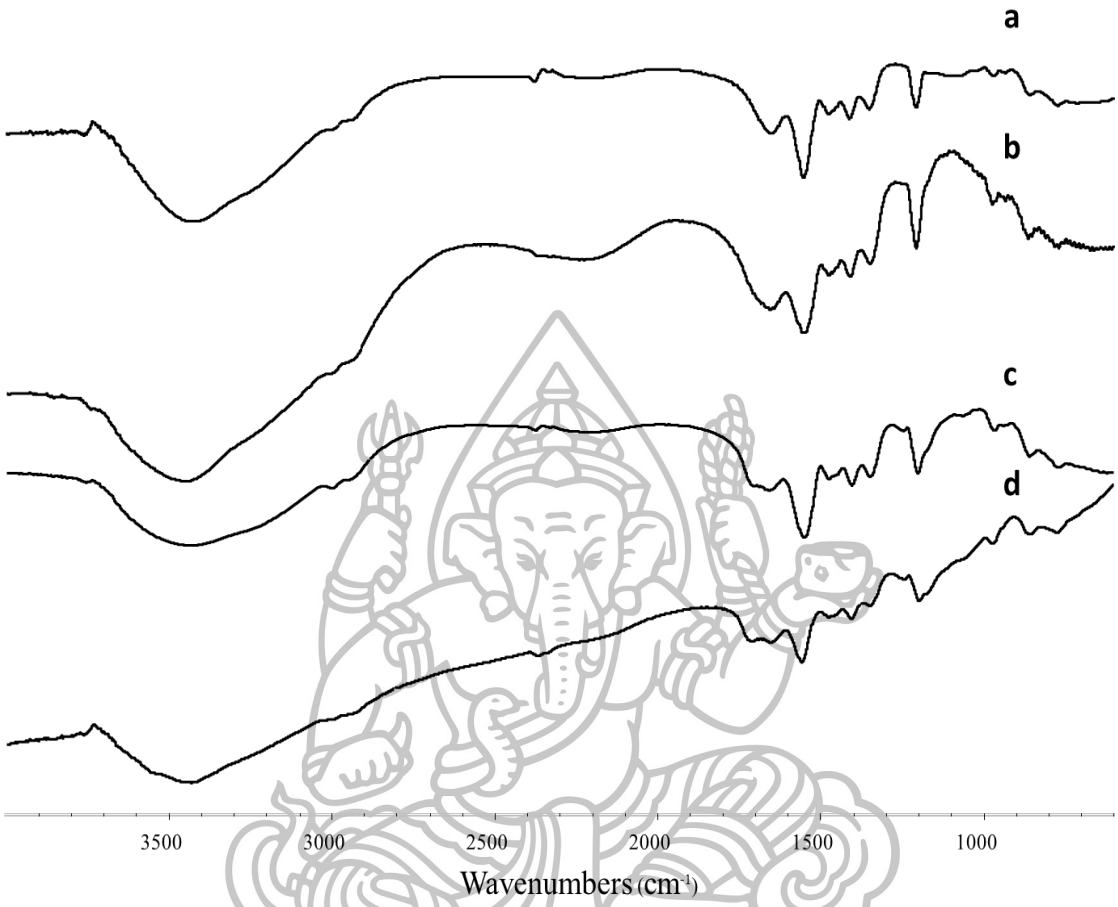

Figure 4.12 Infrared spectra of poly(MAA-co-EGDMA) in K form with (a) 0.25, (b) 2, (c) 8 and (d) 16 %EGDMA.

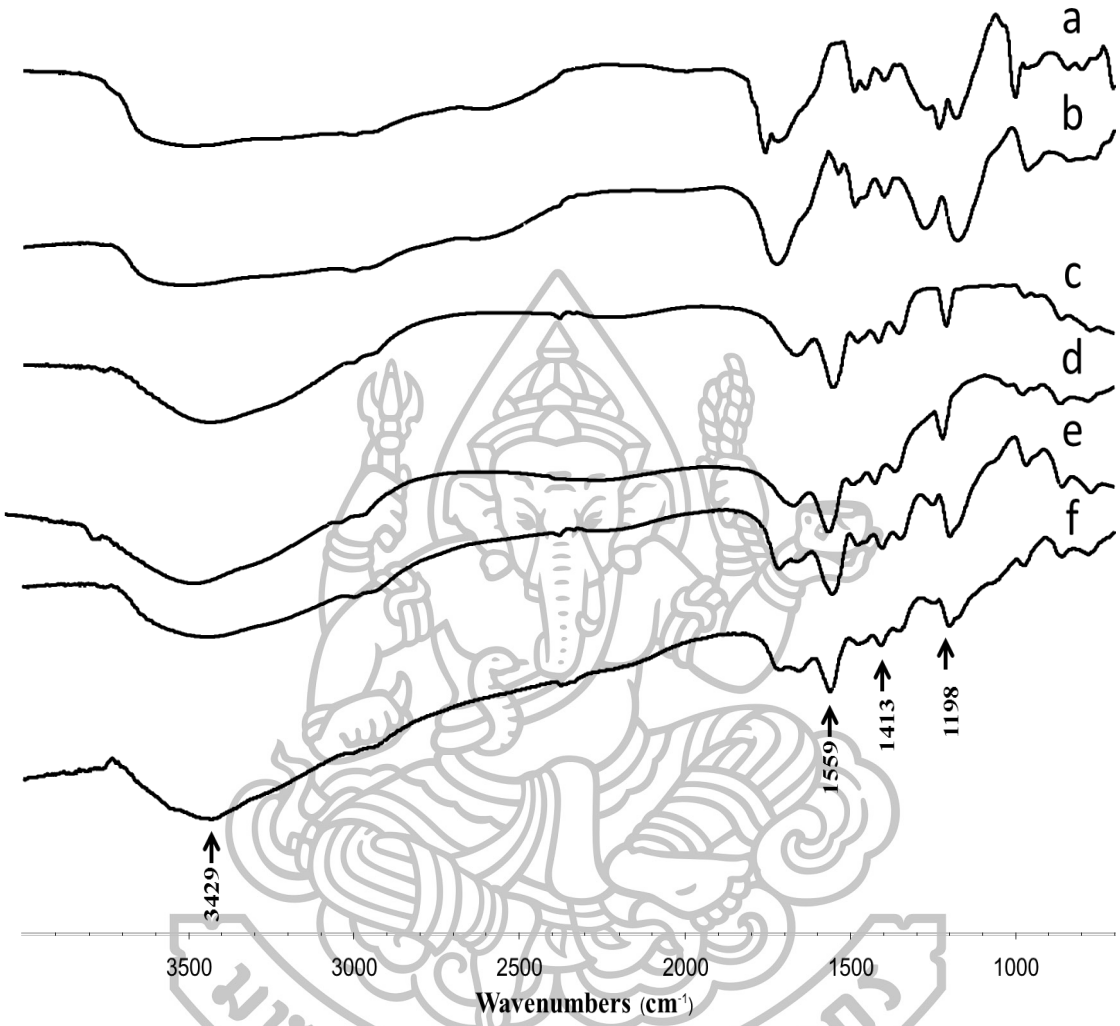

Figure 4.13 Infrared spectra of poly(MAA-co-EGDMA) in H form with (a) 0.25 and (b) 16 % DVB, with 0.25 % DVB in (c) Na form and (d) K form, with 16 % DVB in (e) Na form and (f) K form.

4.2.2 Water uptake and swelling

The water uptake and swelling properties of poly(MAA-co-DVB) were determined as shown in Figure 4.14 and 4.15. It was found that the copolymers behaved like hydrogels, which were able to adsorb water and swell, but did not dissolve, because of the presence of ionizable carboxyl group in the structure. On exposure to water, the carboxyl group ionized, generating an ionic (H^+, Na^+ or K^+ and COO^-) solution and hence osmotic pressure inside the polymer network acting like a semi-permeable membrane. The created osmotic pressure brought about the adsorption of water (water uptake) along with the expansion of polymer network (swelling). When the osmotic pressure was balanced, the water uptake and swelling reached the equilibrium [6]. The swelling property was found to directly relate with the ability for water uptake of copolymers (Figure 4.16).

As shown in Figure 4.14 and 4.15, the capacities of water uptake and swelling depended upon the ionic form and the concentration of crosslinker (DVB) of copolymers. The copolymers in Na and K forms ionized better [79] so they provided the greater osmotic pressure and hence capacities of water uptake and swelling than those in H form. Crosslinking hindered the expansion of polymer network [19,41], thus reducing the water uptake and swelling properties as the concentration of crosslinker of copolymers was increased.

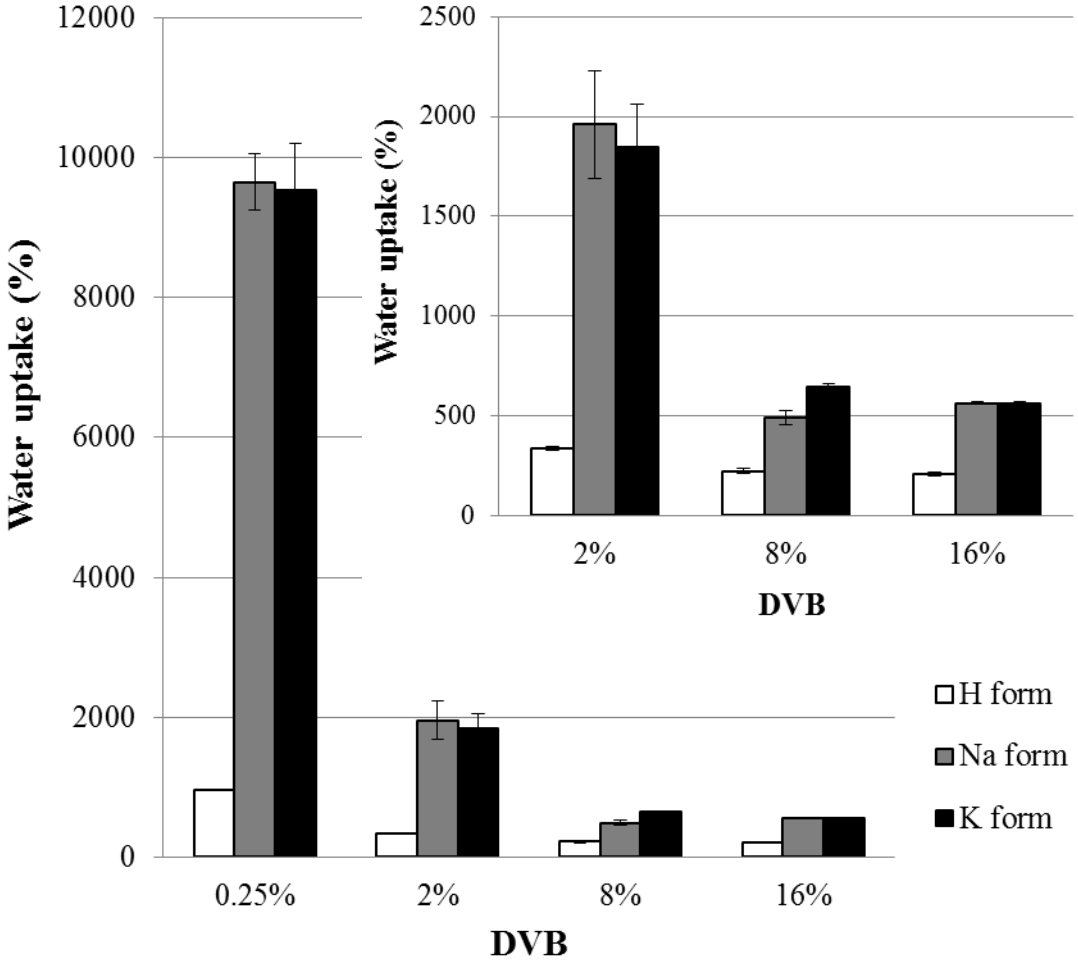

Figure 4.14 Water uptake of poly(MAA-co-DVB); a small figure excludes the copolymer with 0.25 % DVB for clarification.

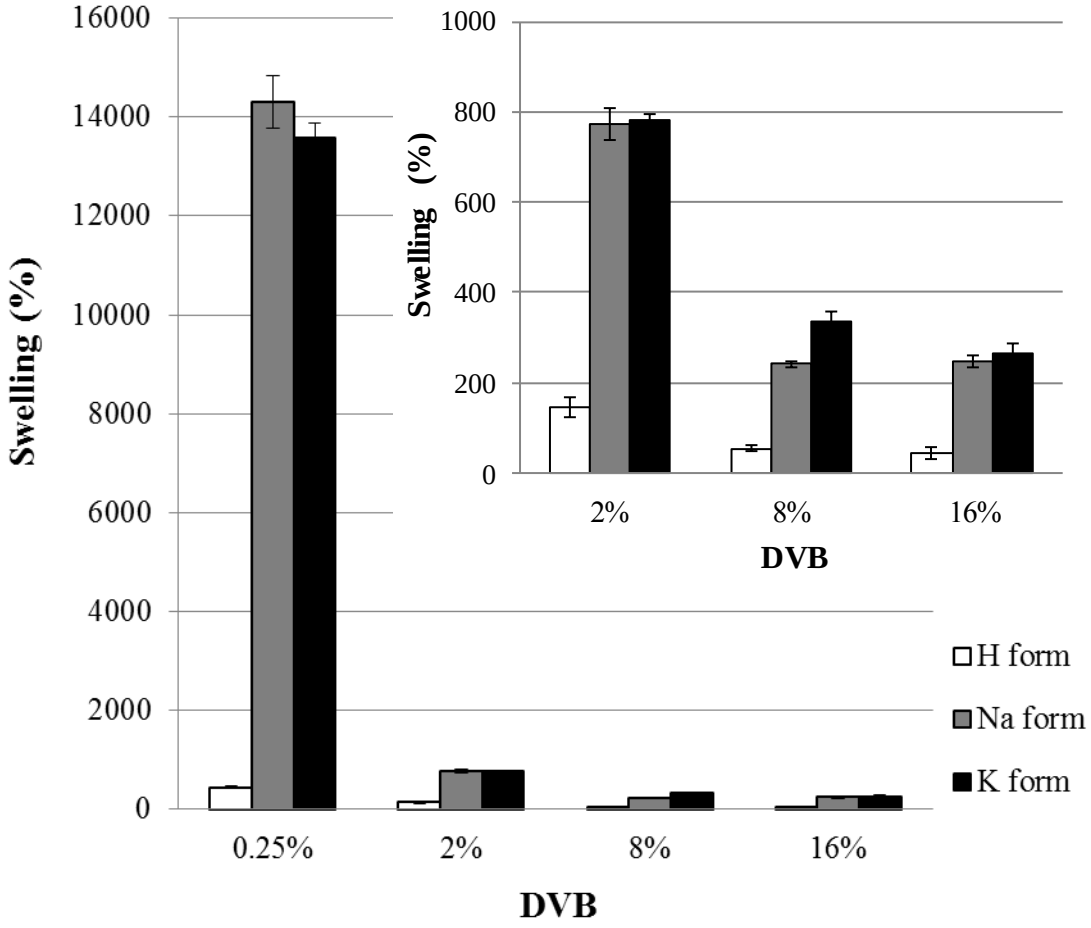

Figure 4.15 Swelling property of poly(MAA-co-DVB); a small figure excludes the copolymer with 0.25 % DVB for clarification.

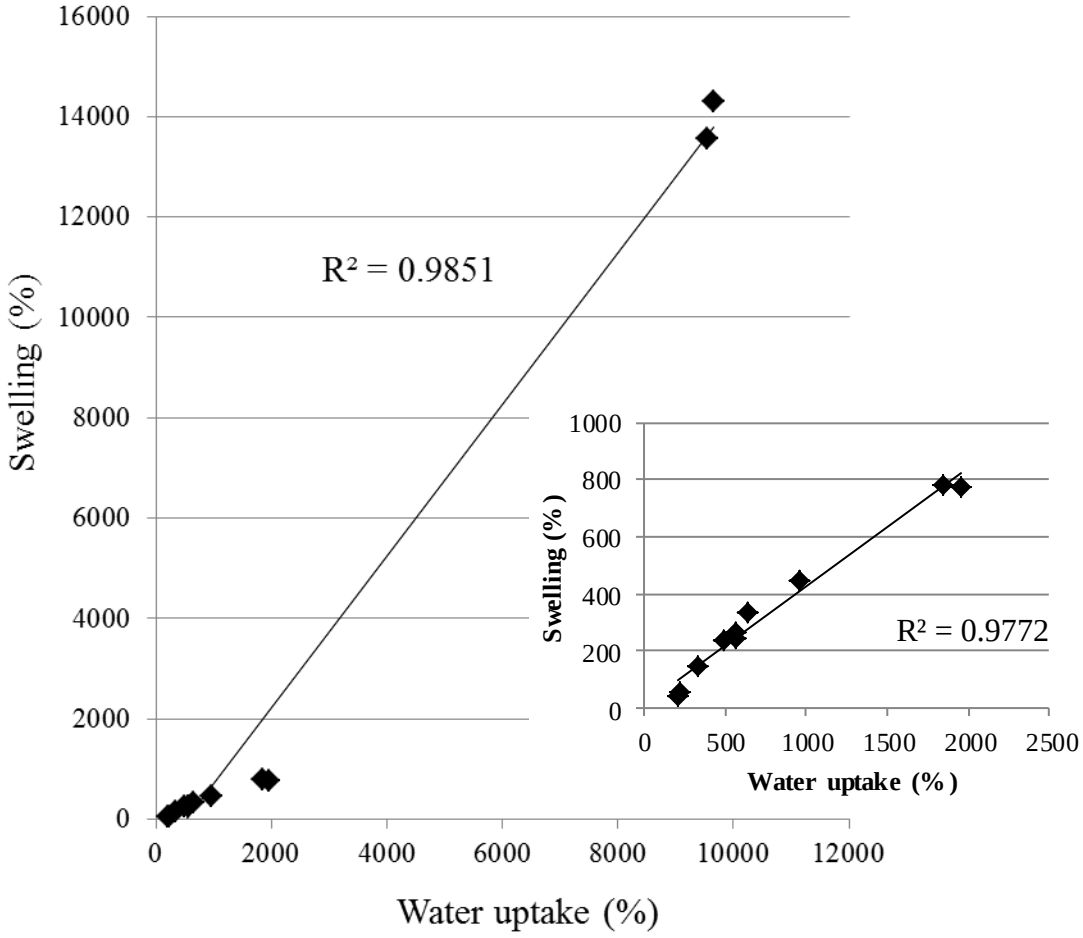

Figure 4.16 Relation between water uptake and swelling of poly(MAA-co-DVB); a small figure excludes the copolymer with 0.25 % DVB in salt forms (Na and K) for clarification.

Figure 4.17 and 4.18 show the water uptake and swelling properties of poly(MAA-co-EGDMA) resins. Similar to the results of poly(MAA-co-DVB), the poly(MAA-co-EGDMA) resins behaved like hydrogels, which adsorbed water and swelled, but did not dissolve after they contacted with water. This property was explained by the same mechanism as that of poly(MAA-co-DVB) mentioned above. In addition, the swelling property correlated with the ability for water uptake of resins (Figure 4.19).

The capacities of water uptake and swelling were substantially affected by the ionic form and the concentration of crosslinker (EGDMA) of copolymers, as shown in Figure 4.17 and 4.18. The copolymers in Na and K forms provided the greater capacities of water uptake and swelling property than those in H form due to the greater ionization of carboxylate than carboxyl groups [79]. The increase of crosslink (EGDMA) hindered the expansion of polymeric network, thus reducing the water uptake and swelling properties of resins.

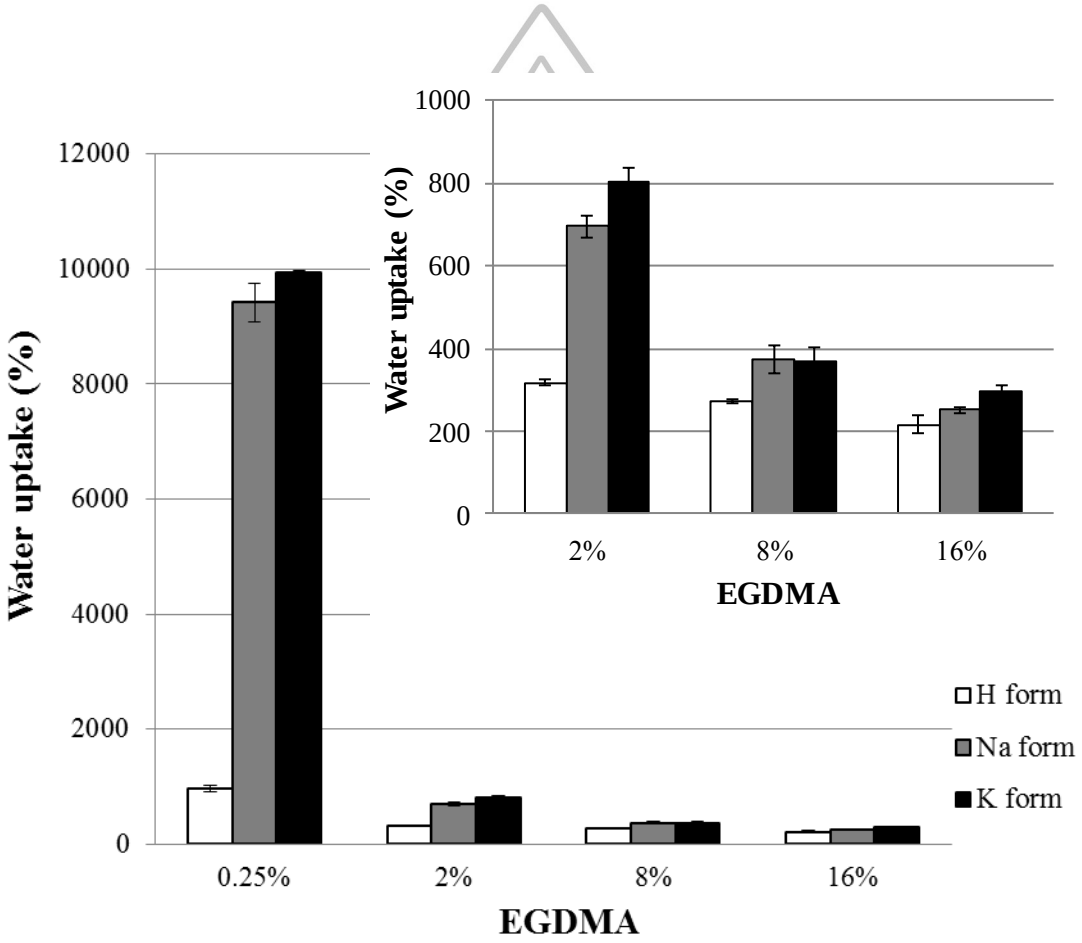

Figure 4.17 Water uptake of poly(MAA-co-EGDMA); a small figure excludes the copolymer with 0.25 % EGDMA for clarification.

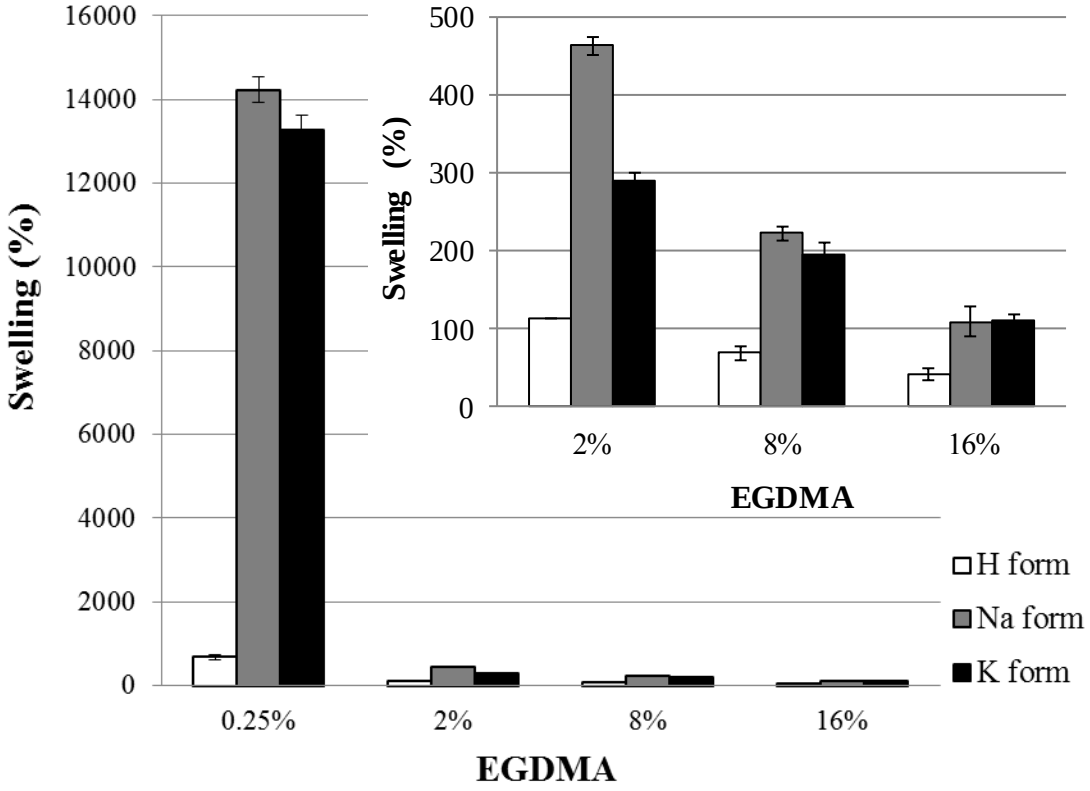

Figure 4.18 Swelling property of poly(MAA-co-EGDMA); a small figure excludes the copolymer with 0.25 % EGDMA for clarification.

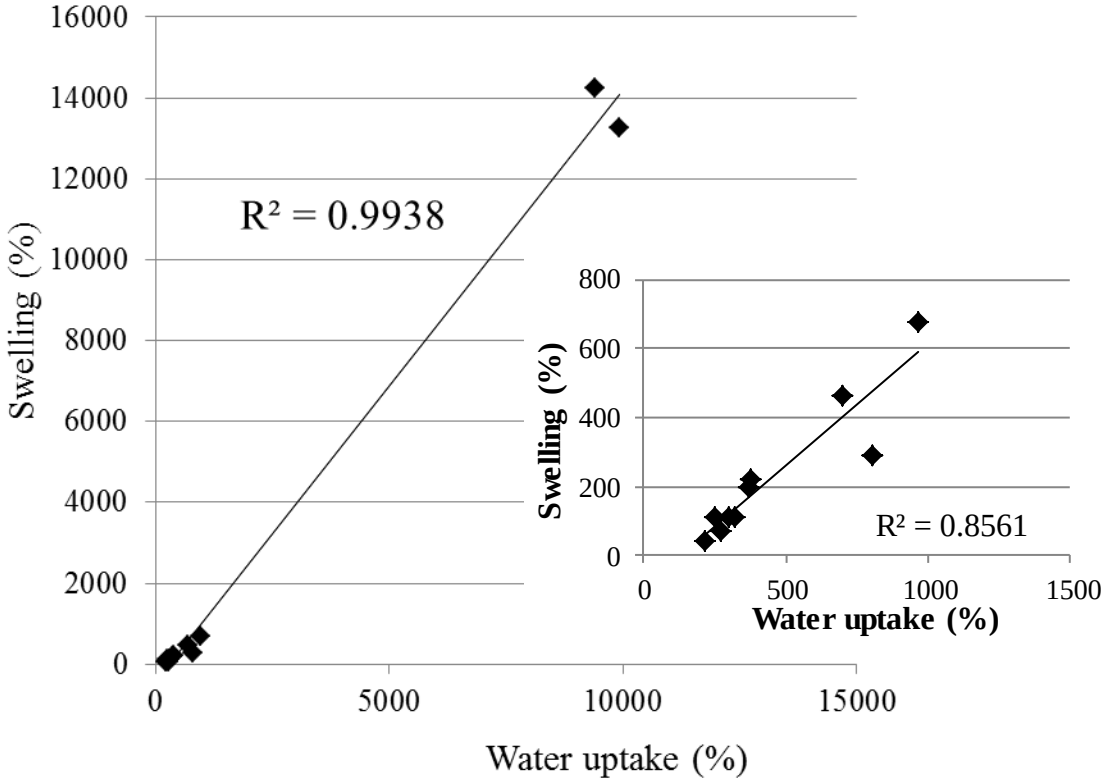

Figure 4.19 Relation between water uptake and swelling of poly(MAA-co-EGDMA); a small figure excludes the copolymer with 0.25 % EGDMA in salt forms (Na and K) for clarification.

To determine the effect of types of crosslinker, the water uptake and swelling properties of poly(MAA-co-EGDMA) were compared to those of poly(MAA-co-DVB), as summarized in Table 4.1. According to the chemical structure, EGDMA was more hydrophilic and water soluble than DVB (Figure 4.2 and Figure 4.3). However, the water uptake and swelling properties of poly(MAA-co-EGDMA) were not higher than those of poly(MAA-co-DVB). Moreover, the difference in the water uptake and swelling properties between poly(MAA-co-EGDMA) and poly(MAA-co-DVB) was unpredictable. This might suggest that the different hydrophilicity of crosslinker had no significant effect on the water uptake and swelling properties of resins.

Table 4.1 Difference in water uptake and swelling properties.

Crosslink	Form	Difference*	
		Water uptake	Swelling
0.25 %	H	8.17	231.37
	Na	-235.33	-66.67
	K	397.33	-300.00
2 %	H	-20.17	-33.80
	Na	-1263.89	-311.06
	K	-1039.77	-493.08
8 %	H	48.31	14.82
	Na	-115.60	-18.43
	K	-273.00	-141.67
16 %	H	5.23	-1.12
	Na	-310.69	-136.85
	K	-266.37	-156.32

** between poly(MAA-co-EGDMA) and poly(MAA-co-DVB)*

4.2.3 Disintegrant properties

Poly(MAA-co-DVB) and poly(MAA-co-EGDMA) resins were evaluated as a disintegrant using MCC tablets without therapeutic agents. MCC was used as a compression filler because of its excellent compactibility [25], giving a hard tablet. Enabling to break up the MCC tablet thus could postulate that the copolymers will also be an efficient disintegrant for tablets made from other fillers. In this part, MCC tablets incorporated with 10 % w/w of various resins were prepared by a direct compression at a fixed compression force of 1 ton. Also, the MCC tablets with 10 % w/w of sodium starch glycolate (SSG) and without any disintegrant were also prepared and assessed for the comparison purpose. The disintegration time as well as hardness of prepared tablets was determined. The hardness was also investigated

because this parameter governed the binding capacity, porosity and water penetration of tablets, which played a vital role on the disintegrating efficiency [55-56,80].

Figure 4.20 presents the hardness of MCC tablets containing various poly(MAA-co-DVB) resins. The tablet made of MCC alone had the highest hardness (26.61 kg_F). The addition of poly(MAA-co-DVB) resins as well as SSG caused a slight decrease in the hardness of tablets. Nonetheless, the hardness of MCC tablets containing the resins and SSG, which ranged from 18.36-26.46 kg_F, was excessively high for handling.

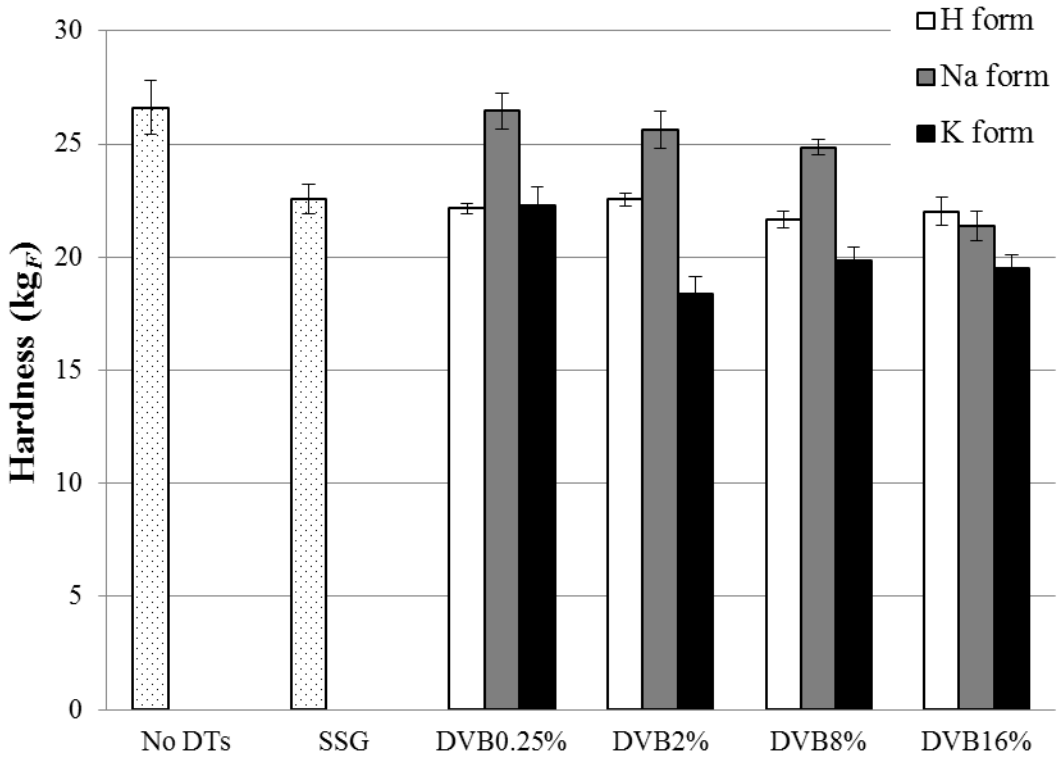

Figure 4.20 Hardness of MCC tablets with or without poly(MAA-co-DVB).

The hardness of MCC tablets containing various poly(MAA-co-EDGMA) resins is depicted in Figure 4.21. The impact of poly(MAA-co-EDGMA) on the hardness of MCC tablets was similar to that of poly(MAA-co-DVB), as described above. The hardness of MCC tablets containing the poly(MAA-co-EDGMA) resins was in the range of 18.40-26.67 kg_F, which was high enough for handling.

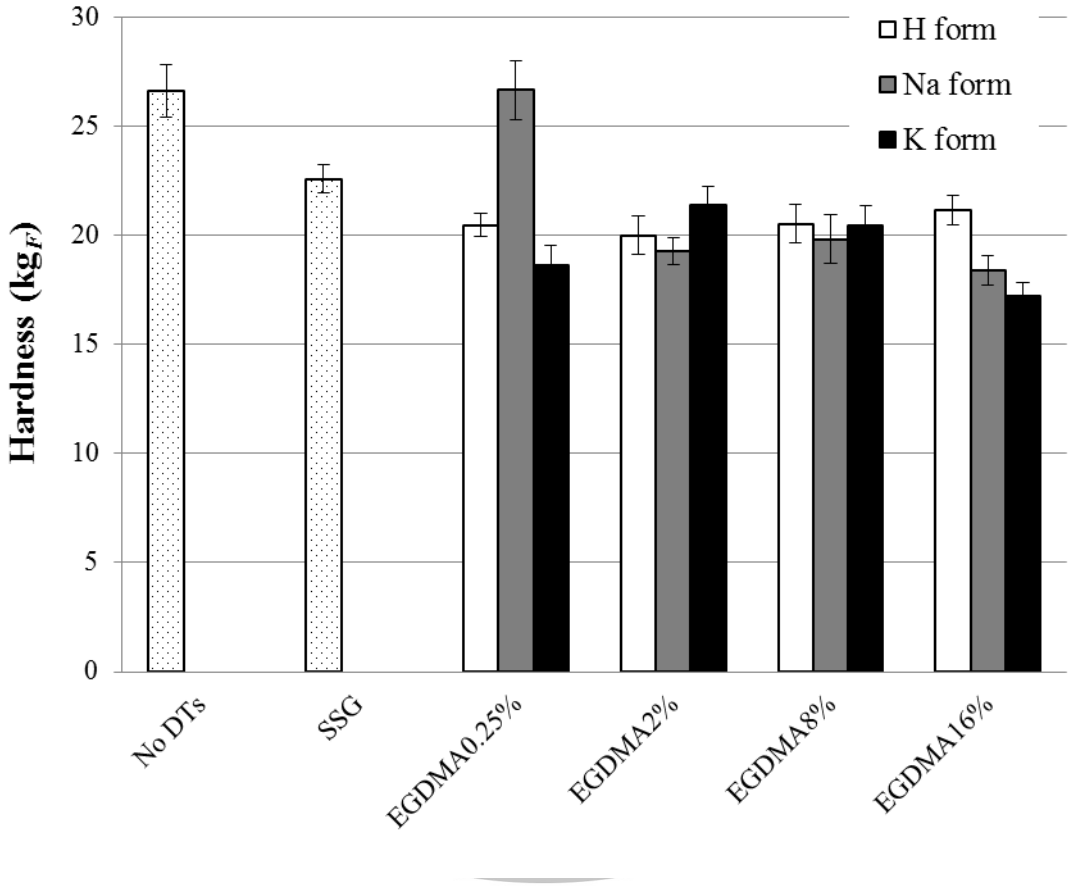

Figure 4.21 Hardness of MCC placebo tablets with or without various disintegrant.

The hardness of MCC tablets containing poly(MAA-co-EGDMA) was compared to that containing poly(MAA-co-DVB), as summarized in Table 4.2. There were no remarkable difference and clear tendency in the hardness between poly(MAA-co-EGDMA) and poly(MAA-co-DVB). It implied that the types of crosslinker did not significantly influence on the compactibility of these resins.

Table 4.2 Difference in hardness and disintegration time (DT).

Crosslink	Form	Difference*	
		Hardness (kg_F)	Disintegration time (s)
0.25 %	H	1.70	0.17
	Na	-0.21	12.83
	K	3.67	10.50
2 %	H	2.55	-13.33
	Na	6.35	20.67
	K	-3.03	0.00
8 %	H	1.13	-773.17
	Na	5.04	-1.83
	K	-0.58	0.00
16 %	H	0.84	-741.33
	Na	2.98	-7.50
	K	2.26	0.00

** between poly(MAA-co-EGDMA) and poly(MAA-co-DVB)*

The disintegration time of MCC tablets containing poly(MAA-co-DVB) or poly(MAA-co-EGDMA) is shown in Figure 4.22 and Figure 4.23. The MCC tablet without any disintegrants took nearly 30 min for disintegration. Indeed, it was observed that the tablet slowly broke apart via erosion rather than disintegration. On the other hand, all MCC tablets with disintegrants including the resins rapidly started to disintegrate after in contact with the disintegrating medium. They provided much shorter time for complete disintegration (< 300 s) most of which met the acceptance criteria of dissolution test for tablets (≤ 15 min). As shown in Figure 4.20 and Figure 4.21, the slightly difference between the hardness of tablets with and without disintegrant was observed and thus it unlikely had considerable effect on the disintegration of tablets. According to this, it could be established that the rapid disintegration of MCC tablets was primarily resulted from the disintegrating property of added resins.

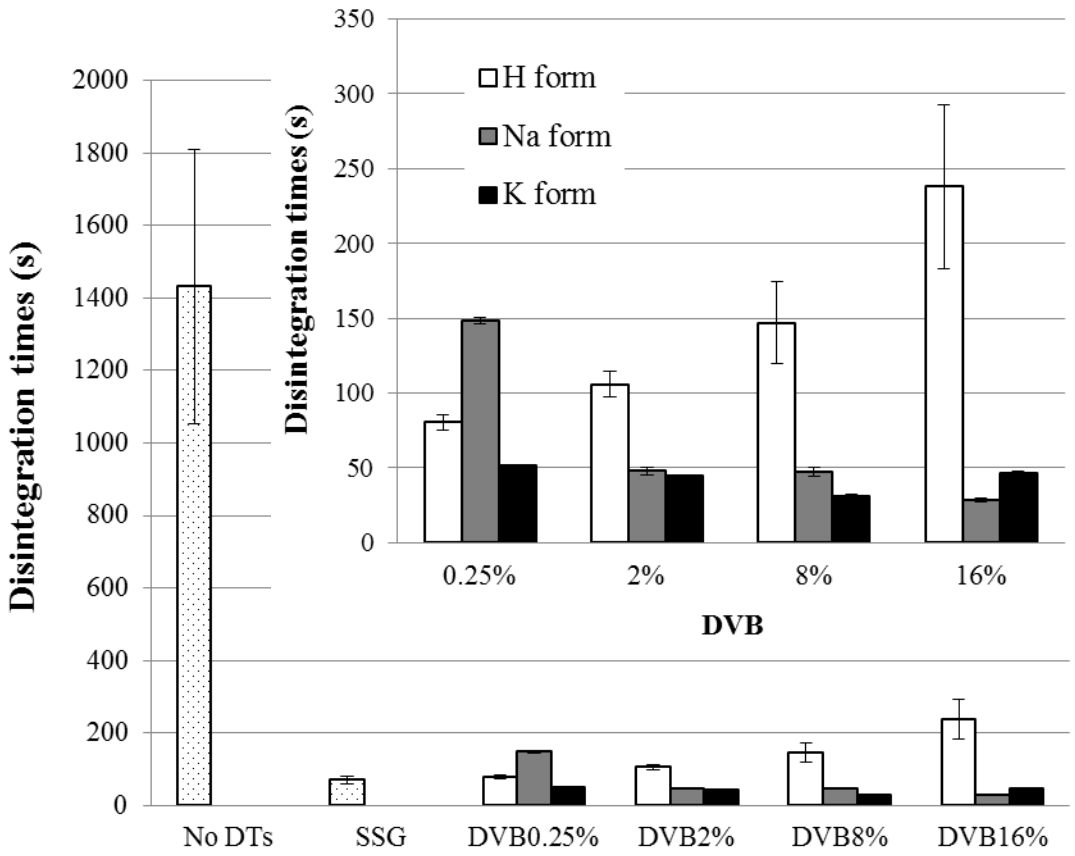

Figure 4.22 Disintegration time of MCC tablets containing poly(MAA-co-DVB); a small figure excludes the tablets with SSG and without disintegrant for clarification.

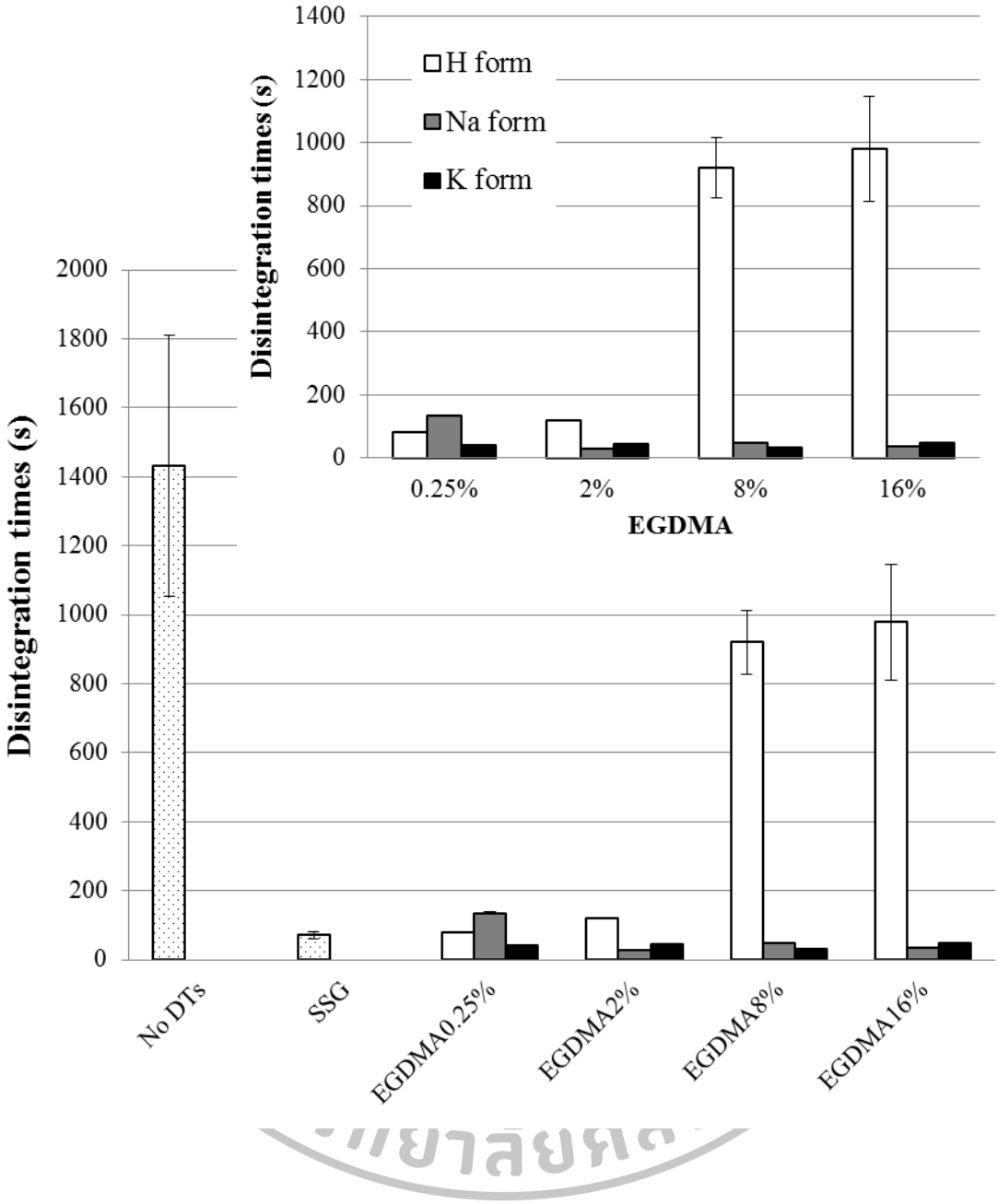

Figure 4.23 Disintegration time of MCC tablets containing poly(MAA-co-EGDMA); a small figure excludes the tablets with SSG and without disintegrant for clarification.

The disintegrating efficiency of both resins was influenced by the salt form and concentration of crosslinker (Figure 4.22 and Figure 4.23). The poly(MAA-co-DVB) and poly(MAA-co-EGDMA) resins in H form were clearly less efficient than Na and K forms, which corresponded to their inferior water uptake and swelling properties (Figure 4.14 – 4.15 and Figure 4.17 - 4.18). The effect of crosslinker on the disintegration property between the resins in acid and salt forms was different. For the resins in H form, the disintegrating efficiency was decreased with increasing the concentration of crosslinker and hence decreasing the water uptake and swelling properties. This dependency could imply that the wicking and swelling actions accounted for the disintegrating action of the resins in H form. In contrast, the disintegration property of copolymers in Na and K forms crosslinked at 2-16 % was rarely affected by the concentration of crosslinker or in other words the water uptake and swelling properties. Furthermore, it appeared that the salted resins at the lowest crosslinker concentration (i.e. the resins in Na form at 0.25 % crosslinker) provided the slowest disintegration in spite of having the greatest capacities of water uptake and swelling. The result might suggest that the disintegrating property of resins in salt form was contributed by other mechanisms apart from the wicking and swelling actions. Guyot-Hermann has proposed a particle repulsion theory in which electric repulsive forces between particles are the disintegrating action for particularly non-swelling disintegrants [40]. This mechanism might also account for the disintegration property of the salted resins, which had the propensity of ionization and hence electric repulsion between particles.

The disintegration time between the MCC tablets containing poly(MAA-co-DVB) and poly(MAA-co-EGDMA) was compared, as summarized in Table 4.2. It was found that the difference in the disintegration time between poly(MAA-co-EGDMA) and poly(MAA-co-DVB) was unpredictable, similar to that in the water uptake and swelling properties of resins as explained previously. This demonstrated that the different types of crosslinker had no significant effect on the disintegranting efficiency of these resins.

From this study, two potential resins poly(MAA-co-DVB) and poly(MAA-co-EGDMA) would be separately selected for further investigation. It was found that the resin with 16 % DVB in Na form provided the fastest disintegration of MCC tablet (28.50 s); as a result, it was selected for further investigation. In case of poly(MAA-co-EGDMA), the resin with 2 % EGDMA in Na form provided the shortest disintegration time (27.17 s) , closely followed by 16 % EGDMA in Na form (36.00 s). However, the resin with 16 % EGDMA in Na form was selected for investigation regarding to easier preparation and greater yield in comparison with those of 2 % EGDMA. In addition, the comparison of determined properties between poly(MAA-co-DVB) and poly(MAA-co-EGDMA) resins in the next investigation could be directly carried out if the resins had the same concentration of crosslinker.

4.3 Factors affecting the disintegrant properties

The disintegrating efficiency of a disingrant is usually influenced by formulation and process factors employed for making a tablet. The relevant factors including the amount of disintegrant, compression force, type of filler, mode of disintegrant addition, etc. [5-10]. The behavior that these variables affect the disintegrating property is important information for successful use of a disintegrant for the tablet formulation. Therefore, the effect of important variables on the disintegrating efficiency of resins i.e. poly(MAA-co-DVB) with 16 % DVB and poly(MAA-co-EGDMA) with 16 % EGDMA in Na form was determined. The hardness of produced tablets was also evaluated because it played a vital role on the disintegrating efficiency [55-56].

4.3.1 Concentration of disintegrants and tableting force

The effect of concentration of disintegrant and compression force on the hardness and disintegration time of MCC tablets containing each of the selected resins as disintegrant is shown in Figure 4.24 and 4.25. It was found that the hardness of tablets was decreased as increasing the concentration of disintegrant, implying that

the compactibility of resins was inferior to MCC. Nonetheless, all tablets containing the resins were sufficiently hard for handling (> 15 kg_F at 0.5 ton of compression force). An increase in the compression force improved the hardness of tablets containing the resins, which was due to the increased contact and hence cohesion of particles in tablets [81-84]. At all concentration and applied forces, the hardness of tablets containing poly(MAA-co-DVB) did not significantly differ from poly(MAA-co-EGDMA), confirming that the compactibility of both resins was similar.

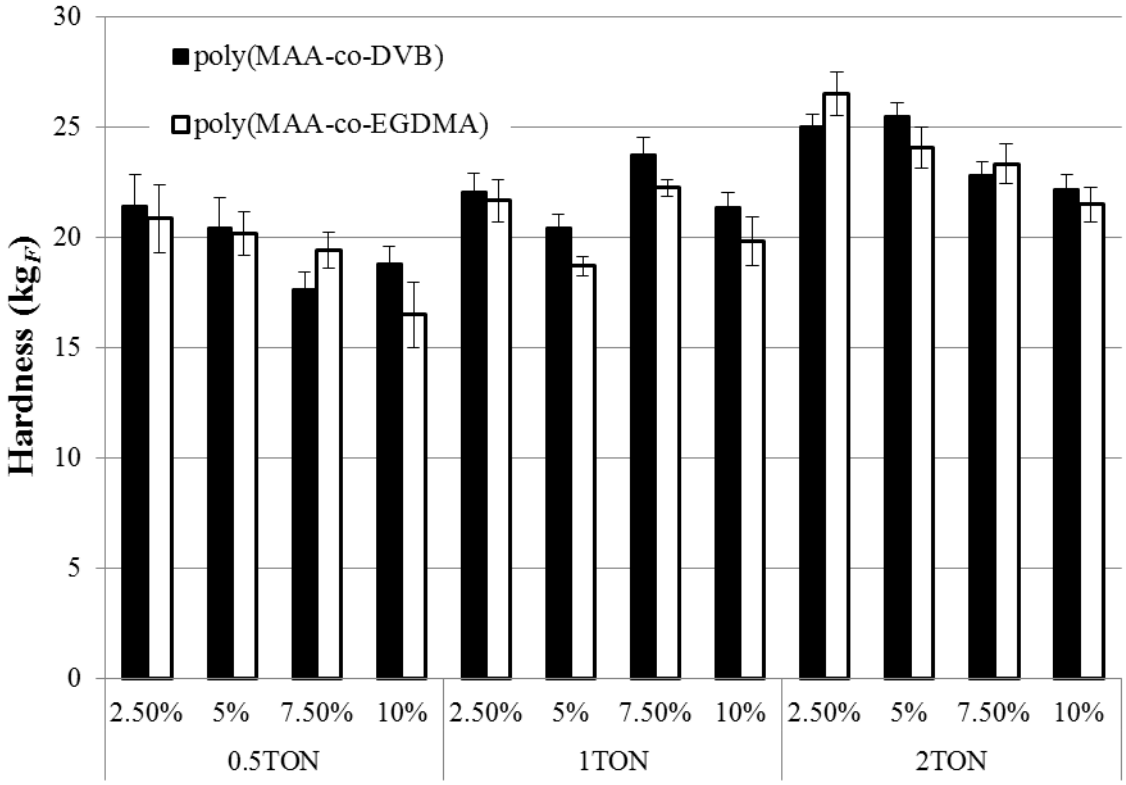

Figure 4.24 Effect of concentration and tableting force on the hardness.

As shown in Figure 4.25, it is seen that the disintegrating efficiency of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) was clearly influenced by the concentration of resins. The increase in concentration of resins, the faster disintegration time was observed. This follows the common tendency that a disintegrant has more disintegrating property as its increased concentration [14]. Surprisingly, there was no clear dependency between the applied force and the disintegrating property of both resins. This unexpected pattern was also found in a previous work [83]. Generally, an increase in the compression force has a direct effect of lowering the disintegrating efficiency because it increases the hardness of tablet and decreases its porosity [20]. At 0.5 and 1 ton of compression force, the disintegrating efficiency of poly(MAA-co-DVB) was higher but at 2 ton was lower than that of poly(MAA-co-EGDMA).

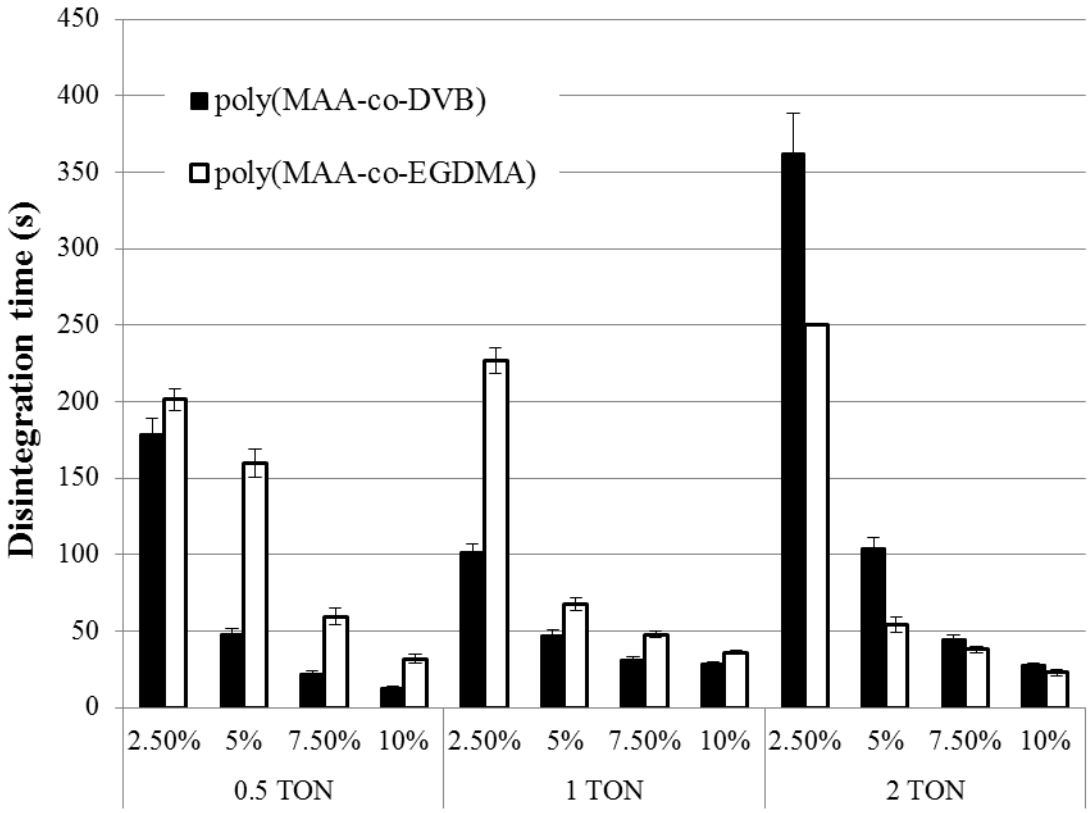

Figure 4.25 Effect of concentration and tableting force on disintegration time.

4.3.2 Tablet weight (size)

The effect of tablet weights i.e. 100, 250 500 mg on the hardness and disintegration time of MCC tablets containing poly(MAA-co-DVB) or poly(MAA-co-EGDMA) as disintegrant is shown in Figure 4.26 and Figure 4.27. These tablets contained 10% w/w of each resin and were made by the same compression force of 1 ton. Both resins displayed the same pattern between the tablet weight and hardness (Figure 4.26). The hardness was considerably increased when the tablet weight was increased from 100 to 250 mg. However, the hardness was lower as the tablet weight was increased to 500 mg. At all tablet weights, the hardness of MCC tablets containing poly(MAA-co-DVB) was comparable to poly(MAA-co-EGDMA), confirming the similar compactibility of two resins as proposed earlier. As shown in Figure 4.27, the effect of tablet weight on the disintegrating efficiency between poly(MAA-co-DVB) and poly(MAA-co-EGDMA) was different. Increasing the tablet weight decreased the disintegration time of tablets containing poly(MAA-co-DVB). In case of poly(MAA-co-EGDMA), the tablets disintegrated around 35 s regardless of the tablet weight. However, all of tablets disintegrated within a very narrow period of time (12-40 s). Based on this, it might be deduced that the tablet weight (100-500 mg) had no practically remarkable effect on the disintegrating efficiency for both resins.

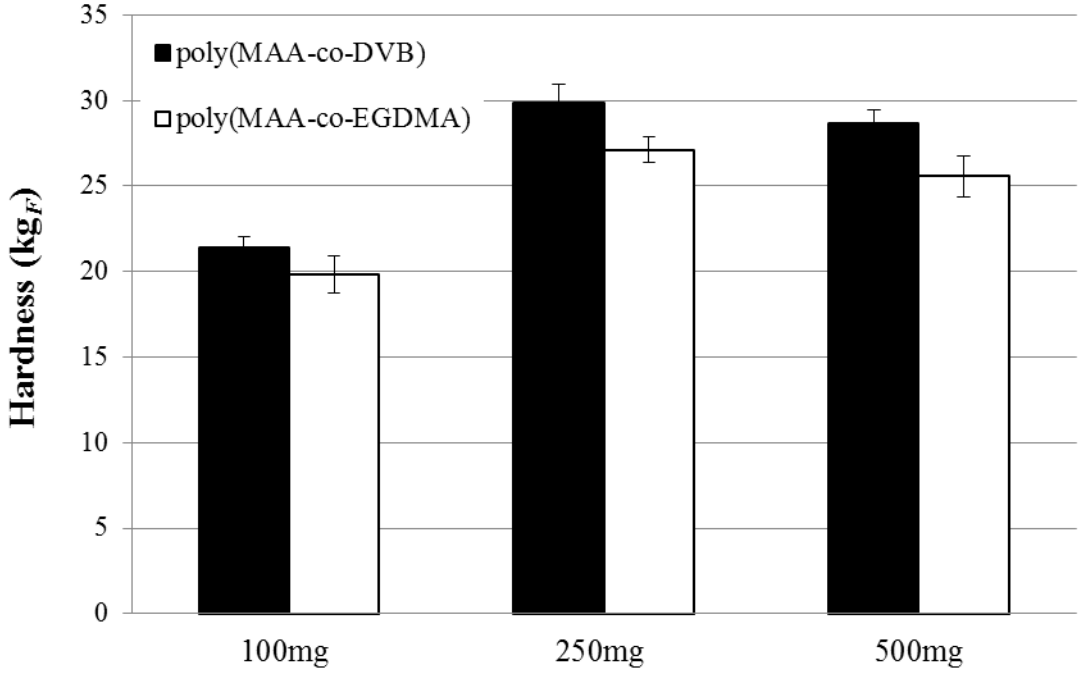

Figure 4.26 Effect of tablet weight on hardness.

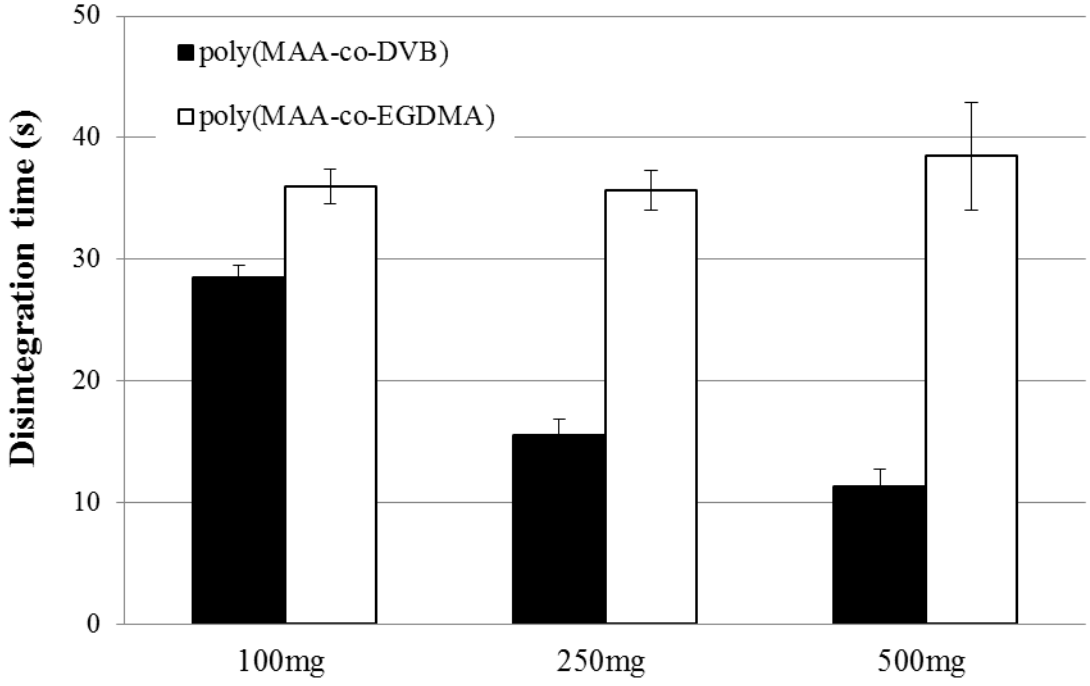

Figure 4.27 Effect of tablet weight on disintegration time.

4.3.3 Type of tablet filler

Aside from MCC, the disintegrating efficiency of poly(MAA-co-DVB) poly(MAA-co-EGDMA) was also comparatively determined with the tablets made from DCP and lactose. These substances are fairly compactible and can be used as tablet fillers although their compactibility is much inferior to MCC. DCP is an absolutely water insoluble filler; whereas, lactose is a freely water soluble filler [3,84-85]. All tablets were incorporated with 10% w/w of each resin and made by the same compression force of 1 ton. The hardness and disintegration time of tablets were determined. In addition, the tablets without resins was made from each filler and used as control tablet.

The hardness of control tablets made from MCC, DCP and lactose was found to be 26.61, 4.06 and 5.98 kg_F, respectively. This finding affirmed the excellent compactibility of MCC, which was followed by lactose and DCP. The incorporation of both resins tended to decrease in the hardness of tablets made from all of fillers, as presented in Figure 4.28.

The control tablets made from MCC, DCP and lactose was found to disintegrate around 1432, 13510 and 16 s, respectively. In spite of having the lowest hardness, the DCP tablet took the longest time for disintegration due to the hydrophobicity and the absence of disintegrating property of filler. MCC is a hydrophilic filler and has the disintrating property [24]. Therefore, the MCC tablet disintegrated faster although it was stronger as compared with the DCP tablet. The tablet made from lactose demanded the shortest time for disintegration due to its high water solubility [3]. Accordingly, the breaking of lactose tablet was likely to proceed via dissolution rather than disintegration [86].

The incorporation of both resins in tablets demonstrated the faster disintegration time as shown in Figure 4.29. For poly(MAA-co-DVB), the disintegration time was decreased from 1432 to 28.50, from 13510 to 1.67 and from 16 to 6.33 s for the tablet made from MCC, DCP and lactose, respectively. Likewise, the addition of poly(MAA-co-EGDMA) reduced the disintegration time of tablet made of MCC, DCP and lactose from to 1432 to 36, from 13510 to 1.67 and from 16 to 6.17 s, respectively. These results indicated that the resins acted more effectively with the tablet made of water insoluble (i.e. MCC and DCP) than water soluble fillers (i.e. lactose). At the same filler, the disintegration times obtained from both resins were not dramatically different (Figure 4.29), implying that their disintegrating efficiency was similar.

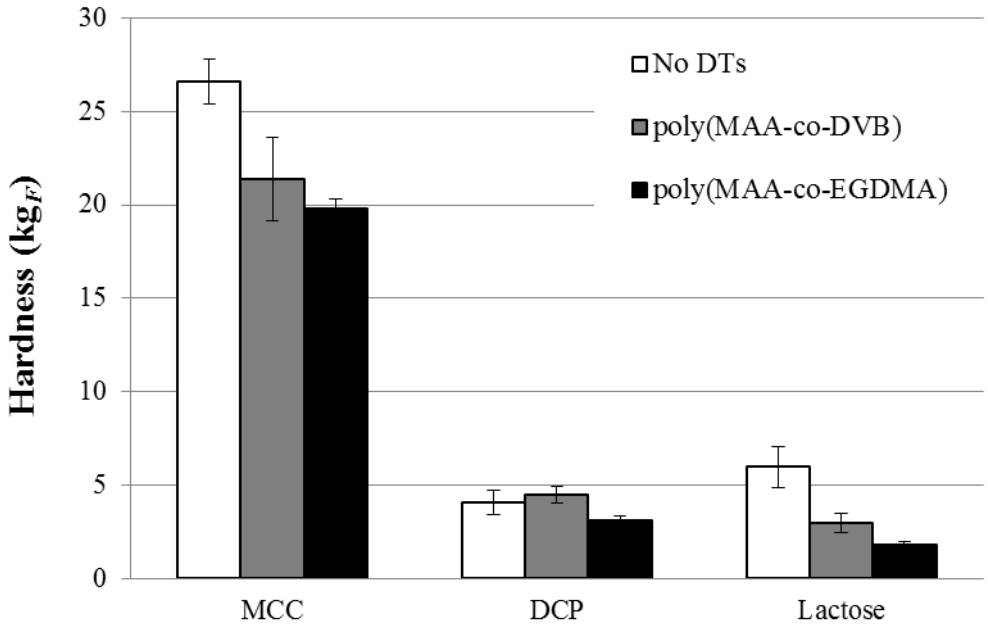

Figure 4.28 Hardness of tablet containing 10 % w/w of resin with various types of tablet fillers.

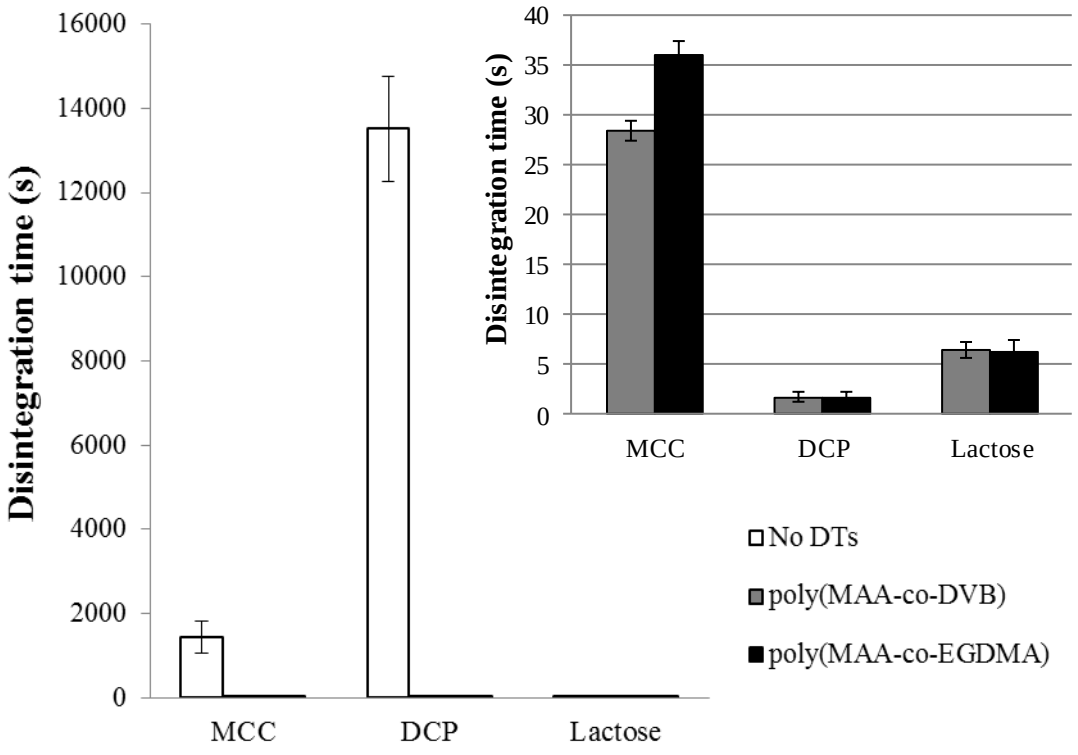

Figure 4.29 Disintegration time of tablet containing 10 % w/w of resin with various types of tablet fillers; a small figure excludes the tablets without disintegrant for clarification.

4.3.4 The presence of magnesium stearate

Magnesium stearate not only affect the hardness but also influenced on the disintegration of tablet is widely known. It resulted from the decrease in tablet cohesion and wettability [87]. In this section, the lubricant sensitivity of MCC tablets using 10 % w/w poly(MAA-co-DVB) or poly(MAA-co-EGDMA) as disintgerant was determined. The tablet was incorporated with 0-1 % w/w magnesium stearate, prepared at the same tableting force of 1 ton and evaluated for hardness and disintegration time. MCC is an example of tablet filler exhibiting high lubricant sensitivity owing to its plastic deformation behavior during compression [88].

As expected, the presence of magnesium stearate tended to decrease the hardness of tablets (Figure 4.30). Additionally, it seemed that this negative effect was concentration dependent. Nonetheless, the lubricated tablets were still strong enough as handling. Surprisingly, the lubrication with magnesium stearate tended to decrease the disintegration time of tablets, as shown in Figure 4.31. It is recognized that the lubrication with magnesium stearate decreases wettability and hence water penetration, which causes a delay in tablet disintegration [87]. But meanwhile, it decreases the cohesion and hence hardness of tablets that allowed for faster water penetration and easier disintegration. With this regard, the final effect of lubrication on disintegrant action depends on the prevalence of these contrary factors. In this case, the enhanced disintegration caused by the reduced hardness probably overruled the deterred disintegration caused by the reduced wettability. As a result, the lubrication with magnesium stearate led to the faster disintegration of tablet.

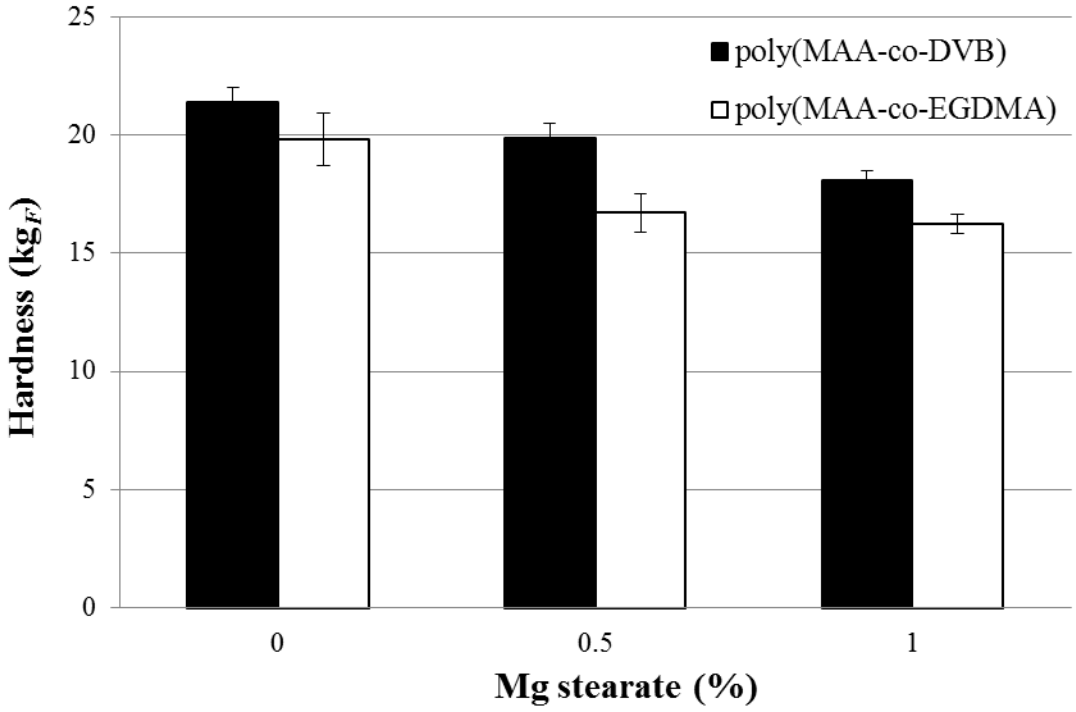

Figure 4.30 Hardness of tablet containing 10 % w/w of resin with various concentrations of magnesium stearate.

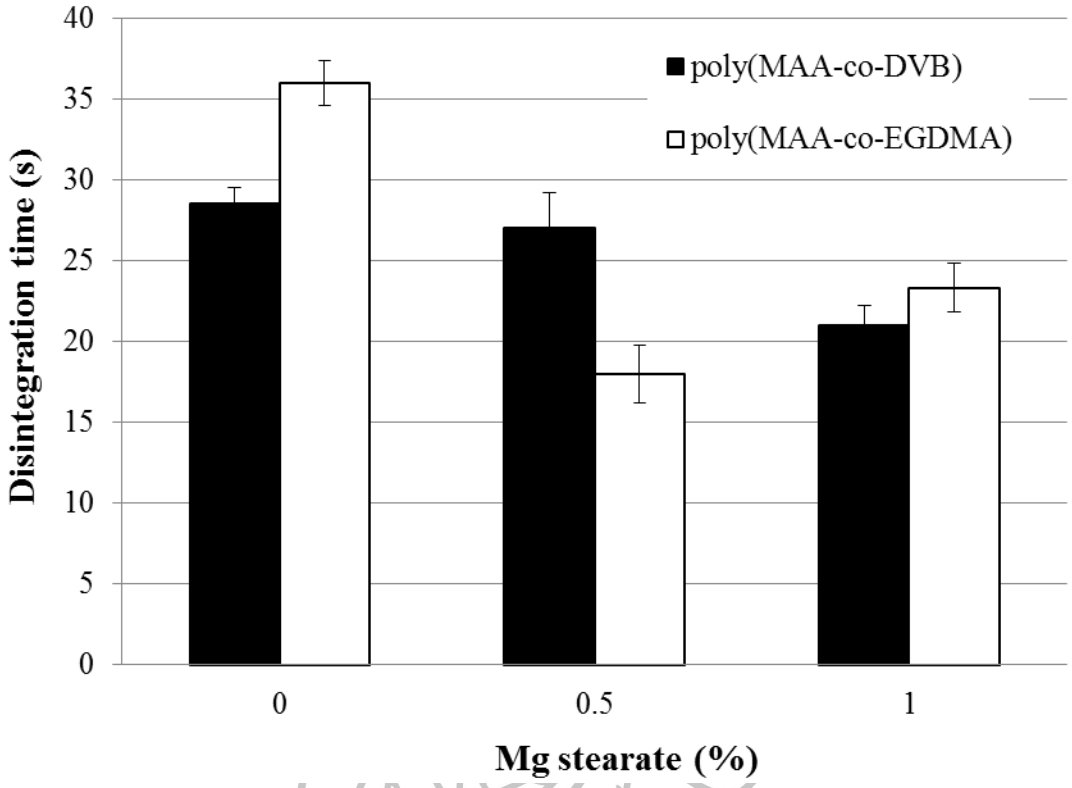

Figure 4.31 Disintegration time of tablet containing 10 % w/w of resin with various concentrations of magnesium stearate.

4.4 Ion-exchange effect on drug release

As shown in Figure 3.2 and Figure 3.3, poly(MAA-co-DVB) and poly(MAA-co-EGDMA) are crosslinked copolymers (R) that contain numerous carboxyl groups (COOH). These dissociable groups bring about the resins cation (C^+) exchangeable via the following reaction [13,47-48].

$$RCOOH + C^+ \leftrightarrow RCOOC + H^+$$

If the ion-exchange effect is high, it possibly leads to the depleted release of cationic drug. According to this concern, the ion-exchange effect of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) at concentration of 2.5 and 10 % of tablet on drug release was determined using propranolol hydrochloride tablets as the model

formulation. Table 4.3 shows the ingredients of tablet formulations which were prepared by 1 ton of compression force. As seen, the drug tablets containing sodium starch glycolate and without disintegrant were also prepared and evaluated for comparison purpose. In this part, the formulated tablets were evaluated for drug content, hardness, friability, disintegration time and dissolution test.

Table 4.3 Ingredients of tablet formulations.

Ingredients	**Amount per tablet (mg/unit)**						
	No-DTs	**2.5%DTs**			**10%DTs**		
Propranolol hydrochloride	20	20	20	20	20	20	20
Microcrystalline cellulose	78.5	76	76	76	68.5	68.5	68.5
Disintegrant							
- Sodium starch glycolate		2.5			10		
- Poly(MAA-co-DVB)			2.5			10	
- Poly(MAA-co-EGDMA)				2.5			10
Silicon dioxide	1	1	1	1	1	1	1
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Figure 4.32 presents the drug content in propranolol hydrochloride tablets, which dispersed in the range of 95.11 to 102.36 %. This could be interpreted that all of the tablet formulations passed the assay specification of USP XXIX requiring that the percentage of drug content for propranolol hydrochloride tablet was not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of propranolol hydrochloride [89].

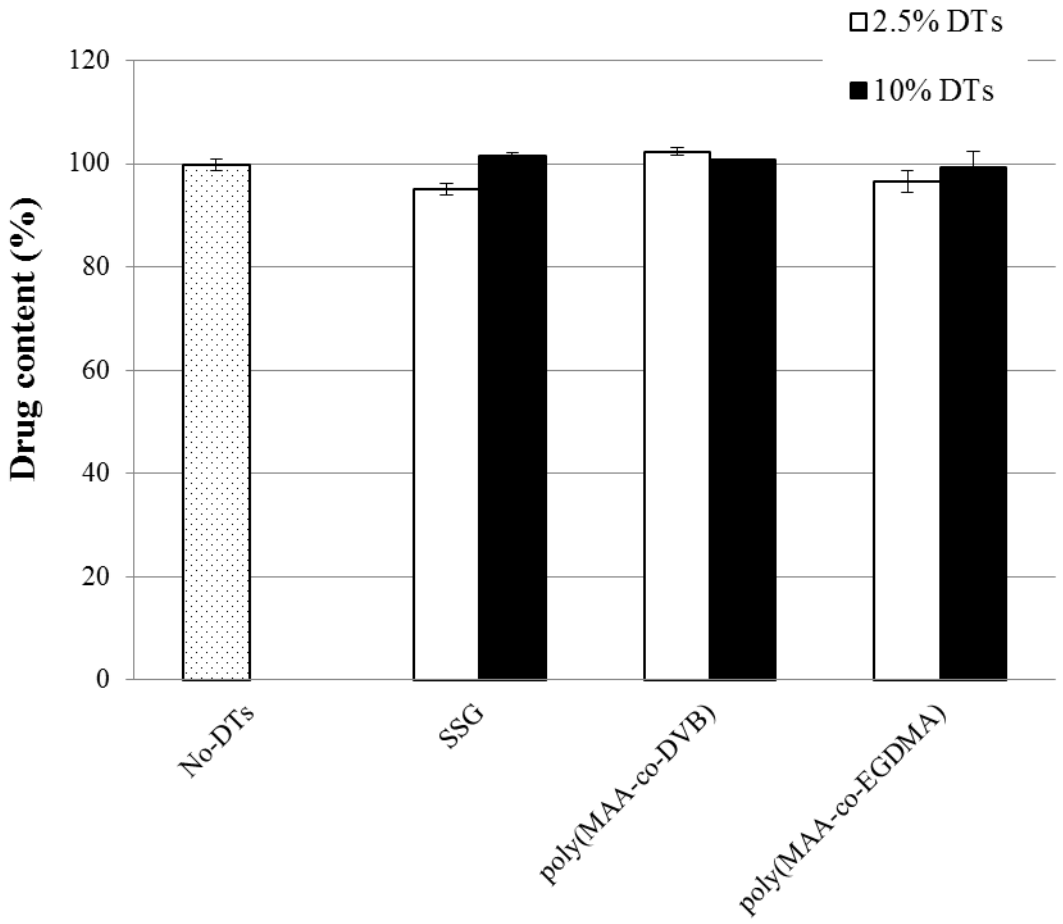

Figure 4.32 Drug content (%) in propranolol hydrochloride tablets.

The hardness of tablet formulations is depicted in Figure 4.33. It appeared that the presence of all disintegrants at 2.5 % had no significant effect on the tablet hardness. However, as the disintegrant concentration was increased to 10 % the hardness of tablets containing especially the resins was lower than that without disintegrant. The hardness was reduced from 16.88 ± 0.36 kg_F (without disintegrant) to 12.56 ± 0.45 and 11.64 ± 0.47 kg_F for the tablets containing poly(MAA-co-DVB) and poly(MAA-co-EGDMA) resins, respectively. In spite of the declined hardness, the tablet formulations containing 10 % of both resins were still hard enough for handling, as confirmed by their very low friability being similar to the others (Table 4.4).

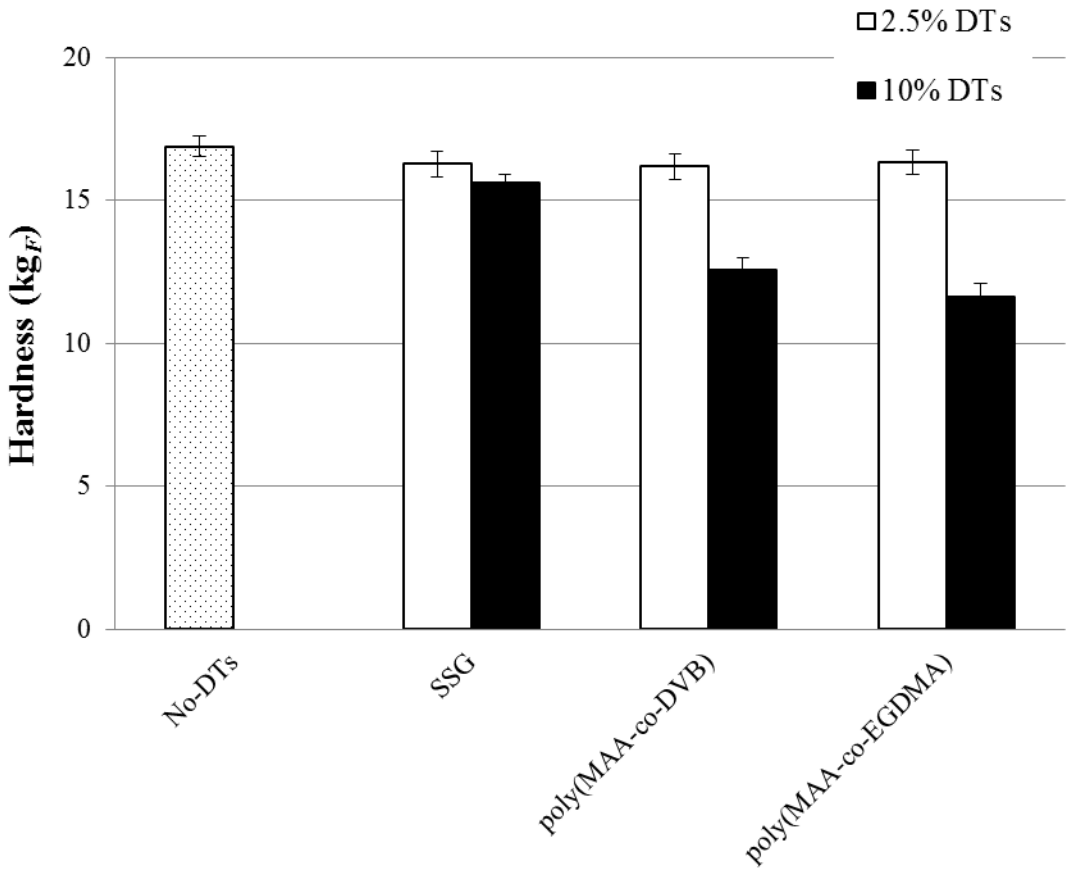

Figure 4.33 Hardness of tablet formulations with and without disintegrant.

Table 4.4 The friability of prepared propranolol hydrochloride tablets.

	No-DTs	Types of disintegrant					
		SSG		DVB		EGDMA	
		2.5%	10%	2.5%	10%	2.5%	10%
% Friability	0.1999	0.2502	0.3291	0.1507	0.0505	0.1509	0.0202

The disintegration time of formulated tablets is illustrated in Figure 4.34. For complete disintegration, the drug tablet without disintegrant took one hour and half; whereas, that with disintgrants took only a few minutes. This indicated the disintegrating property of incorporated disintegrants including both of the resins. The disintegrating efficiency of all disintegrants was found to be concentration-dependent. The higher concentration of disintegrant resulted in the faster disintegration of tablet [14]. At each concentration, the disintegration time from various disintegrants was ranked as SSG > poly(MAA-co-DVB) > poly(MAA-co-EGDMA). It corresponded to the decreasing order of hardness: the tablets containing SSG > poly(MAA-co-DVB) > poly(MAA-co-EGDMA) (Figure 4.33). Softer tablets had lower cohesion and allowed for higher water penetration, thus taking shorter times for disintegration [55].

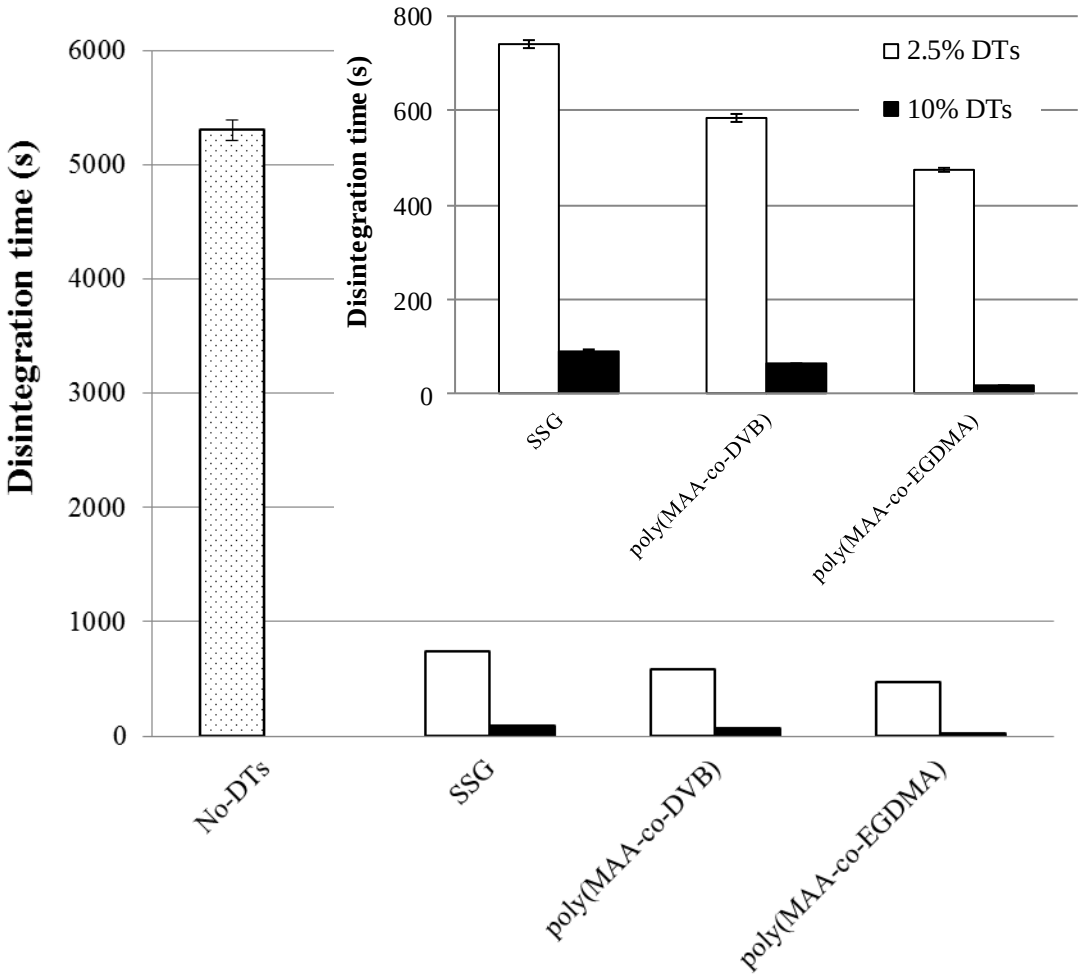

Figure 4.34 Disintegration time of tablet formulations with and without disintegrant.

The dissolution profiles of propranolol hydrochloride from MCC tablet without and with 2.5 % of disintegrants are shown in Figure 4.35. The drug release from the tablet containing poly(MAA-co-EGDMA) was faster than poly(MAA-co-DVB), SSG and no disintegrant, respectively, which corresponded to their faster disintegration as presented above. The faster tablet disintegration generally results in the faster drug dissolution due to the earlier exposure of drug particles with dissolution fluids [46]. It appeared that only the tablet formulation containing poly(MAA-co-EGDMA) met the USP XXIX dissolution specification for propranolol tablet requiring that the percentage of drug release from each tablet was not less than 80 % at 30 min [89].

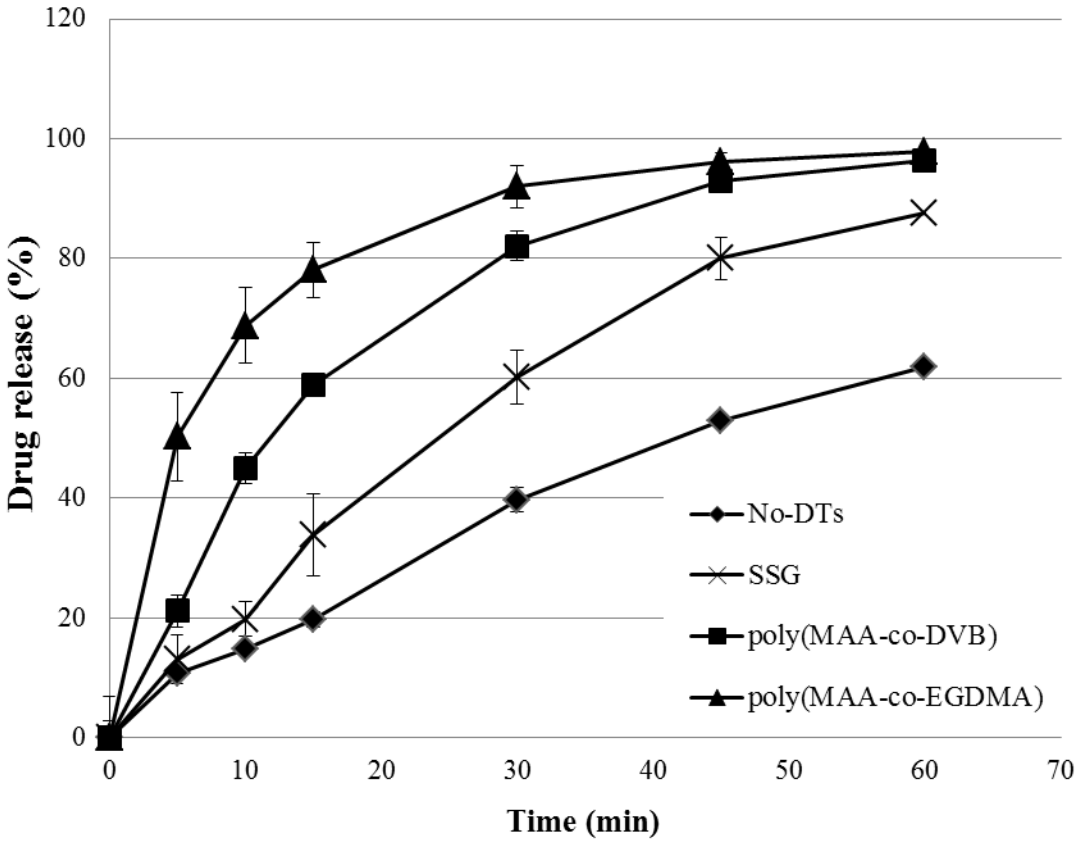

Figure 4.35 Dissolution profiles of propranolol HCl released from tablet formulations without and with 2.5 % disintegrant.

Increasing the concentration of disintegrant from 2.5 to 10 % resulted in the enhancement of drug release (Figure 4.36), which related to the faster disintegration of tablet formulations (Figure 4.34). At 10 % of disntegrant, all of tablet formulations met the USP XXIX dissolution specification for propranolol HCl tablet. They presented 98.79 to 102.49 % of drug release within 5 min; whereas, the drug tablet without disintegrant had only 62 % of drug release after the end of dissolution testing (at 60 min). Like SSG, using poly(MAA-co-DVB) and poly(MAA-co-EGDMA) as disintegrant apparently achieved complete dissolution of the drug, indicating that the ion-exchange effect from both resins on drug release was negligible.

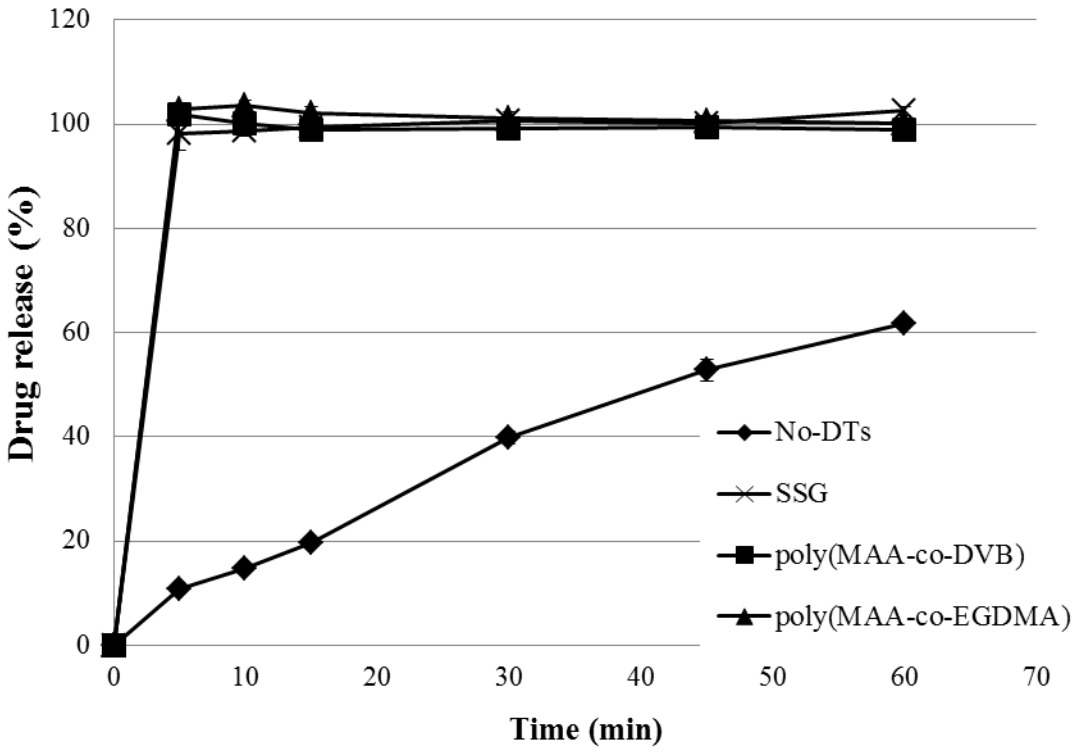

Figure 4.36 Dissolution profiles of propranolol HCl released from tablet formulations without and with 10 % disintegrant.

CHAPTER 5
CONCLUSION

Poly(MAA-co-DVB) and poly(MAA-co-EGDMA) resins at concentration of 0.25-16 % crosslinker in H, Na and K forms were successfully prepared as characterized by FTIR. By the employed synthetic method, the yields of both resins ranged from 14 to 66 %. The two resins were slightly different in color, appearing white to faint yellow. In contact with water, both resins did not dissolve but adsorbed water and swelled to different extents depending on the concentration of crosslinker and salt form. The increase of crosslink had a negative effect on the water uptake and swelling properties. The resins in Na and K forms possessed the greater capacities of water uptake and swelling compared with H form due to their greater ionization. Unexpectedly, the two resins provided comparable water uptake and swelling properties although they contained different types and hence hydrophilicity of crosslinkers in the structure.

As tested with the placebo tablet made of MCC, both resins promoted disintegration. The disintegrating efficiency and mechanism of resins depended on the crosslink and salt form of resins. In comparison with H form, the resins in salted forms (Na and K) provided the greater disintegrating efficiency which was contributed from not only the wicking/swelling action but also electric repulsion. Among the tested resins, it revealed that poly(MAA-co-DVB) and poly(MAA-co-EGDMA) at concentration of 16 % crosslinker in Na form were promising candidates for selection as disintegrant.

The conditions of tablet manufacturing differently affected the disintegrating efficiency of resins. It was found that the disintegrating efficiency of resins was increased as increasing the concentration, but decreased as increasing the compression

force. Both resins promoted the breaking of tablets made from water insoluble fillers (i.e. MCC and DCP) more effectively than water soluble fillers (i.e. lactose). The alteration of tablet weight and the lubrication with magnesium stearate barely affected the disintegrating efficiency of resins. When incorporated as disintegrant at concentration of 2.5 and 10 % in the tablet formulation containing propranolol hydrochloride, the resins at 10 % provided the faster disintegration and drug release than those of 2.5 %. At each concentration, it was apparent that poly(MAA-co-EGDMA) resin promoted the tablet disintegration and drug release more effectively than poly(MAA-co-DVB) resin. At 2.5 %, only the tablet formulation containing poly(MAA-co-EGDMA) resin met the USP dissolution specification for propranolol tablet which required that the percentage of drug release from each tablet was not less than 80 % at 30 min [92]. However, at 10 % the tablet formulations with both resins complied with the USP dissolution specification. Because the drug was totally released (98.79 to 102.49 %) from the tablet formulation it announced that the inherent ion-exchange property of resins had no significant effect on drug release. The effect of resins on the hardness of tablet was also investigated. It was observable that the presence of resins deteriorated the tablet strength. This adverse effect was concentration-dependent. Nonetheless, the acceptable strength and friability of tablets containing the resins could be obtained if the formulation was properly performed by using suitable tablet filler, concentration of resins and compression force.

From all above results, it was concluded that the derivatives of crosslinked polymethacrylic acid had potential to be new superdisintegrants in tablet formulations. Poly(MAA-co-EGDMA) resin at 16 % crosslinker in Na form was considered the optimal candidate as superdisintegrant. As low as concentration of 2.5 % disintegrant, this resin allowed the propranolol hydrochloride tablet to achieve the compendial specification in the disintegration and dissolution.

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APPENDICES

Characterization

1. Synthesis of poly(MAA-co-DVB) and poly(MAA-co-EGDMA)

Table 1 Yields of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) in various crosslinks and salt forms.

Crosslinker	Concentration of crosslinker	% yield		
		H form	Na form	K form
DVB	0.25%	23.65	14.18	12.34
	2%	53.12	42.64	38.56
	8%	40.57	65.30	44.63
	16%	14.56	52.91	41.64
EGDMA	0.25%	41.88	35.97	47.50
	2%	49.74	41.15	57.90
	8%	63.76	62.49	55.83
	16%	66.09	54.23	49.36

2. Characterization of copolymer

Table 2 Water uptake (% w/w) of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) in H form.

Crosslinker	Concentration of crosslinker	Water uptake (% w/w)				
		1	2	3	Average	SD
DVB	0.25%	951.60	970.99	954.50	959.03	10.46
	2%	338.16	343.40	329.47	337.01	7.04
	8%	207.68	227.90	231.20	222.26	12.73
	16%	217.70	200.60	211.67	209.99	8.67
EGDMA	0.25%	1007.00	978.40	916.20	967.20	46.42
	2%	318.72	308.90	322.90	316.84	7.19
	8%	264.74	274.60	272.36	270.57	5.17
	16%	192.50	219.06	234.10	215.22	21.06

Table 3 Water uptake (% w/w) of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) in Na form.

Crosslinker	Concentration of crosslinker	Water uptake (% w/w)				
		1	2	3	Average	SD
DVB	0.25%	9842.00	9195.00	9917.00	9651.33	396.97
	2%	2264.00	1868.00	1745.00	1959.00	271.20
	8%	462.70	529.70	476.80	489.73	35.32
	16%	556.50	562.90	570.03	563.14	6.77
EGDMA	0.25%	9742.00	9074.00	9432.00	9416.00	334.29
	2%	719.66	698.60	667.06	695.11	26.47
	8%	361.40	349.60	411.39	374.13	32.80
	16%	256.30	244.41	256.64	252.45	6.96

Table 4 Water uptake (% w/w) of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) in K form.

Crosslinker	Concentration of crosslinker	Water uptake (% w/w)				
		1	2	3	Average	SD
DVB	0.25%	8769.00	9938.00	9902.00	9536.33	664.77
	2%	1804.00	2077.00	1654.00	1845.00	214.46
	8%	622.50	646.25	661.74	643.50	19.76
	16%	568.10	570.26	554.65	564.34	8.46
EGDMA	0.25%	9953.00	9896.00	9952.00	9933.67	32.62
	2%	767.60	827.40	820.70	805.23	32.76
	8%	405.60	350.80	355.10	370.50	30.47
	16%	310.79	295.00	288.12	297.97	11.62

Table 5 Swelling property (% v/v) of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) in H form.

Crosslinker	Concentration of crosslinker	Swelling property (% v/v)				
		1	2	3	Average	SD
DVB	0.25%	470.00	433.33	440.00	447.78	19.53
	2%	150.00	162.50	122.22	144.91	20.62
	8%	60.00	50.00	50.00	53.33	5.77
	16%	40.00	55.56	30.00	41.85	12.88
EGDMA	0.25%	722.22	626.32	688.89	679.14	48.69
	2%	111.11	111.11	111.11	111.11	0.00
	8%	77.78	60.00	66.67	68.15	8.98
	16%	50.00	38.88	33.33	40.74	8.49

Table 6 Swelling property (% v/v) of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) in Na form.

Crosslinker	Concentration of crosslinker	Swelling property (% v/v)				
		1	2	3	Average	SD
DVB	0.25%	14100.00	13900.00	14900.00	14300.00	529.15
	2%	766.67	744.44	812.50	774.54	34.71
	8%	244.44	244.44	233.33	240.74	6.41
	16%	250.00	255.56	230.00	245.19	13.44
EGDMA	0.25%	13900.00	14500.00	14300.00	14233.33	305.51
	2%	475.00	452.94	462.50	463.48	11.06
	8%	225.00	212.50	229.41	222.30	8.77
	16%	125.00	87.50	112.50	108.33	19.09

Table 7 Swelling property (% v/v) of poly(MAA-co-DVB) and poly(MAA-co-EGDMA) in K form.

Crosslinker	Concentration of crosslinker	Swelling property (% v/v)				
		1	2	3	Average	SD
DVB	0.25%	13500.00	13900.00	13300.00	13566.67	305.51
	2%	800.00	770.59	775.00	781.86	15.86
	8%	350.00	350.00	312.50	337.50	21.65
	16%	255.56	252.94	288.89	265.80	20.04
EGDMA	0.25%	12900.00	13300.00	13600.00	13266.67	351.19
	2%	286.36	300.00	280.00	288.79	10.22
	8%	187.50	212.50	187.50	195.83	14.43
	16%	116.67	111.76	100.00	109.48	8.57

Table 8 Hardness (kg_F) of MCC tablets with or without poly(MAA-co-DVB).

No.	No DTs	SSG	Poly(MAA-co-DVB) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	24.77	22.94	22.22	22.32	21.61	21.51	26.30	24.06	25.18	22.02	21.41	18.25	19.57	19.17
2	27.12	21.20	22.53	22.73	21.30	22.43	26.30	25.38	24.67	21.30	23.55	19.16	19.47	18.92
3	27.10	22.83	21.71	22.22	21.48	23.14	27.52	25.18	25.08	21.30	22.53	16.92	19.88	18.80
4	27.73	23.85	22.02	22.73	21.93	22.72	25.41	25.39	24.97	21.00	21.47	18.14	20.39	20.22
5	27.42	22.63	22.02	22.43	21.67	21.58	26.22	25.38	24.87	22.12	21.63	17.74	18.96	19.88
6	28.13	22.32	22.22	22.32	22.18	22.31	26.32	25.99	24.16	21.00	22.48	18.86	19.37	20.08
7	24.85	22.43	22.12	23.14	21.59	21.42	25.48	24.97	24.73	22.31	22.91	17.82	19.57	20.33
8	25.99	22.73	22.12	22.43	21.44	21.58	27.96	26.50	25.28	21.61	22.76	18.25	20.08	18.76
9	25.71	22.32	22.32	22.71	21.18	21.40	26.40	26.61	24.97	20.18	23.04	18.96	20.39	19.18
10	27.23	22.53	22.32	22.56	22.20	22.06	26.67	26.59	24.67	21.00	21.18	19.47	20.90	19.47
AVG	26.61	22.58	22.16	22.56	21.66	22.02	26.46	25.61	24.86	21.38	22.30	18.36	19.86	19.48
SD	1.19	0.66	0.22	0.28	0.35	0.61	0.79	0.82	0.32	0.65	0.81	0.77	0.58	0.60

Table 9 Diameter (mm) of MCC tablets with or without poly(MAA-co-DVB).

No.	No DTs	SSG	Poly(MAA-co-DVB) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	6.51	6.50	6.54	6.51	6.53	6.49	6.51	6.51	6.52	6.52	6.52	6.53	6.49	6.52
2	6.49	6.51	6.54	6.48	6.50	6.50	6.51	6.51	6.48	6.52	6.49	6.53	6.51	6.51
3	6.48	6.51	6.53	6.51	6.50	6.51	6.51	6.51	6.51	6.49	6.52	6.52	6.50	6.51
4	6.48	6.52	6.52	6.51	6.51	6.50	6.53	6.47	6.51	6.51	6.51	6.52	6.49	6.51
5	6.47	6.48	6.53	6.48	6.50	6.50	6.49	6.51	6.52	6.49	6.51	6.52	6.50	6.50
6	6.47	6.48	6.49	6.52	6.52	6.50	6.49	6.51	6.48	6.52	6.51	6.53	6.50	6.53
7	6.48	6.51	6.48	6.51	6.49	6.50	6.49	6.49	6.51	6.49	6.48	6.52	6.49	6.53
8	6.49	6.52	6.49	6.52	6.50	6.51	6.51	6.52	6.51	6.49	6.49	6.52	6.48	6.52
9	6.48	6.50	6.53	6.49	6.50	6.50	6.50	6.48	6.48	6.52	6.52	6.51	6.48	6.51
10	6.48	6.53	6.53	6.51	6.49	6.49	6.50	6.51	6.51	6.52	6.50	6.51	6.50	6.52
AVG	6.48	6.51	6.52	6.50	6.50	6.50	6.50	6.50	6.50	6.51	6.51	6.52	6.49	6.52
SD	0.01	0.02	0.02	0.02	0.01	0.01	0.01	0.02	0.02	0.01	0.01	0.01	0.01	0.01

Table 10 Thickness (mm) of MCC tablets with or without poly(MAA-co-DVB).

No.	No DTs	SSG	Poly(MAA-co-DVB) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	2.24	2.25	2.27	2.34	2.32	2.33	2.26	2.35	2.30	2.34	2.22	2.28	2.36	2.28
2	2.21	2.26	2.31	2.33	2.34	2.33	2.29	2.27	2.39	2.34	2.31	2.26	2.32	2.25
3	2.22	2.32	2.31	2.35	2.34	2.33	2.33	2.24	2.37	2.34	2.31	2.28	2.28	2.30
4	2.23	2.34	2.24	2.34	2.35	2.34	2.31	2.25	2.32	2.29	2.30	2.33	2.30	2.35
5	2.19	2.27	2.24	2.35	2.33	2.34	2.31	2.29	2.31	2.28	2.30	2.24	2.28	2.27
6	2.25	2.30	2.23	2.35	2.34	2.30	2.28	2.36	2.26	2.35	2.24	2.31	2.28	2.28
7	2.20	2.31	2.25	2.35	2.34	2.33	2.33	2.23	2.31	2.28	2.25	2.34	2.29	2.34
8	2.26	2.25	2.34	2.35	2.33	2.33	2.29	2.25	2.39	2.34	2.25	2.33	2.32	2.30
9	2.24	2.24	2.31	2.34	2.33	2.32	2.28	2.33	2.37	2.25	2.28	2.34	2.37	2.31
10	2.23	2.29	2.30	2.35	2.34	2.33	2.31	2.33	2.36	2.27	2.30	2.30	2.42	2.29
AVG	2.23	2.28	2.28	2.35	2.34	2.33	2.30	2.29	2.34	2.31	2.28	2.30	2.32	2.30
SD	0.02	0.03	0.04	0.01	0.01	0.01	0.02	0.05	0.04	0.04	0.03	0.04	0.05	0.03

Table 11 Disintegration time (s) of MCC tablets with or without poly(MAA-co-DVB).

No.	No DTs	SSG	Poly(MAA-co-DVB) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	1069	57	75	98	111	184	145	45	44	27	50	44	30	45
2	1092	66	77	100	117	204	147	46	45	28	51	44	30	46
3	1237	66	78	100	144	207	148	47	46	28	51	45	31	47
4	1405	71	80	105	165	219	149	48	48	29	52	45	31	47
5	1857	81	85	111	170	296	150	50	50	29	52	45	32	47
6	1934	82	88	120	174	317	150	51	52	30	52	46	33	48
AVG	1432.33	70.50	80.50	105.67	146.83	237.83	148.17	47.83	47.50	28.50	51.33	44.83	31.17	46.67
SD	379.14	9.65	5.01	8.45	27.52	54.77	1.94	2.32	3.08	1.05	0.82	0.75	1.17	1.03

Table 12 Hardness (kg_F) of MCC tablets with or without poly(MAA-co-EGDMA).

No.	No DTs	SSG	Poly(MAA-co-EGDMA) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	24.77	22.94	20.18	18.86	20.90	20.08	25.08	19.78	19.88	18.33	18.14	22.43	20.29	17.43
2	27.12	21.20	21.10	19.57	21.41	21.71	28.64	18.55	21.20	18.35	17.13	21.30	20.80	17.13
3	27.10	22.83	20.39	21.30	19.57	21.92	28.54	18.76	18.45	18.45	17.43	20.18	20.08	17.13
4	27.73	23.85	19.78	20.59	21.10	20.39	26.14	18.45	20.29	18.86	18.93	21.20	20.18	16.72
5	27.42	22.63	20.59	21.00	20.18	21.51	27.09	19.27	18.25	18.65	20.01	21.00	20.90	16.51
6	28.13	22.32	20.49	18.76	22.02	21.71	25.33	19.88	19.67	18.94	19.17	22.02	22.22	18.55
7	24.85	22.43	20.59	19.47	20.90	21.51	25.34	18.86	19.47	17.11	18.64	22.22	18.96	17.74
8	25.99	22.73	19.67	19.67	20.29	20.18	26.15	19.16	21.10	17.92	18.93	22.02	19.28	16.72
9	25.71	22.32	20.39	20.29	19.06	21.41	28.17	19.57	18.76	17.84	19.70	19.98	20.90	17.33
10	27.23	22.53	21.41	20.59	19.88	21.30	26.24	20.29	21.10	19.57	18.18	21.51	20.80	16.92
AVG	26.61	22.58	20.46	20.01	20.53	21.17	26.67	19.26	19.82	18.40	18.63	21.39	20.44	17.22
SD	1.19	0.66	0.53	0.87	0.90	0.69	1.36	0.61	1.11	0.68	0.92	0.83	0.92	0.60

Table 13 Diameter (mm) of MCC tablets with or without poly(MAA-co-EGDMA).

No.	No DTs	SSG	Poly(MAA-co-EGDMA) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	6.51	6.50	6.54	6.53	6.53	6.51	6.51	6.52	6.51	6.52	6.53	6.51	6.52	6.53
2	6.49	6.51	6.53	6.53	6.50	6.48	6.53	6.53	6.51	6.52	6.48	6.51	6.52	6.50
3	6.48	6.51	6.54	6.50	6.52	6.48	6.52	6.50	6.51	6.53	6.52	6.51	6.52	6.52
4	6.48	6.52	6.51	6.54	6.52	6.51	6.50	6.48	6.52	6.51	6.51	6.51	6.51	6.53
5	6.47	6.48	6.53	6.50	6.53	6.52	6.51	6.52	6.52	6.53	6.51	6.49	6.52	6.53
6	6.47	6.48	6.54	6.54	6.53	6.52	6.51	6.51	6.51	6.51	6.51	6.52	6.52	6.52
7	6.48	6.51	6.54	6.54	6.52	6.51	6.49	6.52	6.51	6.52	6.48	6.52	6.51	6.54
8	6.49	6.52	6.54	6.50	6.52	6.51	6.48	6.52	6.51	6.53	6.49	6.51	6.51	6.53
9	6.48	6.50	6.53	6.50	6.52	6.52	6.52	6.52	6.50	6.52	6.52	6.51	6.51	6.53
10	6.48	6.53	6.52	6.50	6.52	6.52	6.52	6.51	6.49	6.53	6.50	6.52	6.52	6.52
AVG	6.48	6.51	6.53	6.52	6.52	6.51	6.51	6.51	6.51	6.52	6.51	6.51	6.52	6.53
SD	0.01	0.02	0.01	0.02	0.01	0.02	0.02	0.01	0.01	0.01	0.02	0.01	0.01	0.01

Table 14 Thickness (mm) of MCC tablets with or without poly(MAA-co-EGDMA).

No.	No DTs	SSG	Poly(MAA-co-EGDMA) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	2.24	2.25	2.31	2.30	2.28	2.33	2.33	2.26	2.33	2.33	2.32	2.35	2.32	2.42
2	2.21	2.26	2.36	2.37	2.29	2.35	2.31	2.28	2.31	2.30	2.35	2.28	2.29	2.44
3	2.22	2.32	2.32	2.32	2.37	2.35	2.34	2.28	2.34	2.32	2.36	2.26	2.30	2.49
4	2.23	2.34	2.33	2.25	2.28	2.38	2.31	2.35	2.30	2.33	2.31	2.32	2.29	2.46
5	2.19	2.27	2.34	2.24	2.26	2.28	2.30	2.27	2.33	2.33	2.32	2.24	2.30	2.42
6	2.25	2.30	2.28	2.25	2.29	2.26	2.30	2.26	2.31	2.34	2.31	2.33	2.32	2.51
7	2.20	2.31	2.32	2.22	2.37	2.39	2.31	2.26	2.33	2.33	2.28	2.22	2.33	2.47
8	2.26	2.25	2.31	2.25	2.26	2.34	2.32	2.36	2.29	2.35	2.34	2.34	2.30	2.40
9	2.24	2.24	2.34	2.30	2.27	2.26	2.31	2.31	2.32	2.33	2.32	2.36	2.34	2.38
10	2.23	2.29	2.36	2.32	2.35	2.32	2.31	2.42	2.34	2.36	2.30	2.22	2.30	2.51
AVG	2.23	2.28	2.33	2.28	2.30	2.33	2.31	2.31	2.32	2.33	2.32	2.29	2.31	2.45
SD	0.02	0.03	0.02	0.05	0.04	0.05	0.01	0.05	0.02	0.02	0.02	0.05	0.02	0.05

Table 15 Disintegration time (s) of MCC tablets with or without poly(MAA-co-EGDMA).

No.	No DTs	SSG	Poly(MAA-co-EGDMA) resin											
			H form				Na form				K form			
			0.25%	2%	8%	16%	0.25%	2%	8%	16%	0.25%	2%	8%	16%
1	1069	57	78	117	796	644	133	26	48	34	38	44	30	45
2	1092	66	79	118	828	1012	134	27	48	35	40	44	30	46
3	1237	66	80	119	937	1015	135	27	49	36	41	45	31	47
4	1405	71	80	119	946	1038	135	27	50	36	41	45	31	47
5	1857	81	82	120	961	1067	137	28	50	37	42	45	32	47
6	1934	82	83	121	1052	1099	138	28	51	38	43	46	33	48
AVG	1432.33	70.50	80.33	119.00	920.00	979.17	135.33	27.17	49.33	36.00	40.83	44.83	31.17	46.67
SD	379.14	9.65	1.86	1.41	93.71	167.47	1.86	0.75	1.21	1.41	1.72	0.75	1.17	1.03

Factors affecting the disintegrant properties

1. Effect of concentration and tableting force

Table 16 Hardness (kg_F) of MCC tablets containing poly(MAA-co-DVB) with 16 % DVB in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	22.83	19.67	17.43	17.74	21.61	19.47	23.65	22.02	24.87	26.61	21.92	21.51
2	22.73	20.49	17.33	18.76	22.32	21.30	22.73	21.30	24.06	24.77	22.53	22.43
3	20.08	19.88	17.13	17.74	21.81	19.37	23.04	21.30	25.28	25.59	23.75	22.43
4	20.29	20.29	16.92	19.06	20.49	20.59	24.16	21.00	25.08	25.89	23.24	22.43
5	23.75	19.57	18.14	19.78	21.92	21.00	23.14	22.12	25.59	24.77	23.45	22.53
6	21.20	22.73	17.53	19.06	23.65	20.59	24.77	21.00	25.99	25.38	22.32	21.00
7	22.32	17.94	18.96	19.16	22.43	20.69	24.77	22.31	24.57	26.40	23.34	22.73
8	20.80	22.32	18.65	18.96	22.73	20.39	23.96	21.61	25.38	24.97	22.32	22.73
9	19.27	20.47	18.14	18.14	21.20	21.00	24.46	20.18	24.87	25.38	23.24	21.41
10	21.00	21.00	16.21	19.98	22.43	19.88	22.96	21.00	24.77	25.18	22.43	23.04
AVG	21.43	20.44	17.64	18.84	22.06	20.43	23.76	21.38	25.05	25.49	22.85	22.22
SD	1.42	1.38	0.83	0.77	0.87	0.66	0.77	0.65	0.55	0.64	0.62	0.67

Table 17 Diameter (mm) of MCC tablets containing poly(MAA-co-DVB) with 16 % DVB in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	6.47	6.49	6.51	6.50	6.52	6.51	6.52	6.52	6.51	6.51	6.52	6.49
2	6.48	6.48	6.51	6.50	6.52	6.49	6.51	6.52	6.51	6.48	6.50	6.49
3	6.48	6.49	6.50	6.49	6.52	6.49	6.49	6.49	6.50	6.50	6.50	6.50
4	6.47	6.48	6.51	6.49	6.52	6.50	6.52	6.51	6.49	6.48	6.50	6.49
5	6.47	6.48	6.51	6.49	6.52	6.49	6.52	6.49	6.48	6.51	6.52	6.48
6	6.47	6.49	6.52	6.50	6.52	6.49	6.52	6.52	6.50	6.51	6.50	6.49
7	6.48	6.50	6.50	6.40	6.51	6.50	6.52	6.49	6.49	6.50	6.51	6.50
8	6.48	6.48	6.52	6.40	6.52	6.50	6.48	6.49	6.50	6.48	6.50	6.49
9	6.47	6.49	6.50	6.50	6.51	6.49	6.51	6.52	6.50	6.50	6.53	6.49
10	6.48	6.48	6.50	6.50	6.52	6.50	6.52	6.52	6.48	6.50	6.53	6.49
AVG	6.48	6.49	6.51	6.48	6.52	6.50	6.51	6.51	6.50	6.50	6.51	6.49
SD	0.01	0.01	0.01	0.04	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Table 18 Thickness (mm) of MCC tablets containing poly(MAA-co-DVB) with 16 % DVB in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	2.37	2.35	2.33	2.31	2.37	2.33	2.24	2.34	2.32	2.31	2.35	2.34
2	2.36	2.38	2.34	2.33	2.33	2.32	2.34	2.34	2.30	2.34	2.26	2.38
3	2.33	2.36	2.32	2.34	2.38	2.28	2.21	2.34	2.34	2.37	2.28	2.33
4	2.31	2.31	2.32	2.38	2.36	2.28	2.33	2.29	2.31	2.36	2.34	2.38
5	2.37	2.36	2.32	2.34	2.29	2.34	2.24	2.28	2.33	2.30	2.29	2.39
6	2.33	2.35	2.32	2.33	2.26	2.35	2.26	2.35	2.33	2.31	2.38	2.39
7	2.36	2.33	2.33	2.36	2.33	2.36	2.21	2.28	2.32	2.36	2.28	2.33
8	2.33	2.37	2.33	2.37	2.35	2.31	2.22	2.34	2.30	2.29	2.37	2.38
9	2.33	2.36	2.36	2.31	2.24	2.36	2.27	2.25	2.34	2.38	2.28	2.40
10	2.32	2.36	2.34	2.34	2.38	2.31	2.26	2.27	2.30	2.26	2.29	2.38
AVG	2.34	2.35	2.33	2.34	2.33	2.32	2.26	2.31	2.32	2.33	2.31	2.37
SD	0.02	0.02	0.01	0.02	0.05	0.03	0.05	0.04	0.02	0.04	0.04	0.03

Table 19 Disintegration time (s) of MCC tablets containing poly(MAA-co-DVB) with 16 % DVB in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	166	42	20	12	94	40	28	27	334	94	41	26
2	169	46	21	12	97	45	29	28	341	99	43	27
3	175	48	21	13	102	46	30	28	353	102	45	28
4	180	50	22	13	103	49	32	29	364	106	46	28
5	191	51	24	13	106	50	33	29	372	110	47	29
6	191	52	25	14	107	51	34	30	408	114	47	30
AVG	178.67	48.17	22.17	12.83	101.50	46.83	31.00	28.50	362.00	104.17	44.83	28.00
SD	10.71	3.71	1.94	0.75	5.09	4.07	2.37	1.05	26.56	7.33	2.40	1.41

Table 20 Hardness (kg_F) of MCC tablets containing poly(MAA-co-EGDMA) with 16 % EGDMA in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	20.49	18.86	19.57	15.29	21.30	18.25	22.02	19.88	24.87	22.22	23.85	22.32
2	22.12	20.69	20.39	18.04	20.59	18.04	22.12	21.20	26.61	23.65	23.75	22.02
3	17.29	19.37	19.47	18.45	20.80	18.55	22.73	18.45	25.99	24.06	24.26	22.12
4	21.04	21.00	19.57	14.78	21.51	18.86	22.43	20.29	25.59	25.48	23.14	22.32
5	22.12	21.10	19.88	18.96	20.49	19.16	22.53	18.25	26.61	24.16	23.04	21.61
6	21.92	21.00	19.16	16.11	22.22	18.86	22.02	19.67	26.50	23.45	23.45	21.30
7	19.57	19.57	18.45	14.78	23.04	18.96	22.22	19.47	27.83	23.75	23.24	20.59
8	22.32	19.57	17.74	16.31	21.71	18.14	22.02	21.10	27.22	25.28	24.77	20.69
9	20.49	21.71	19.98	16.31	22.02	18.76	21.61	18.76	28.13	24.06	22.53	21.92
10	21.30	19.06	20.18	16.00	23.24	19.47	22.94	21.10	25.99	24.77	21.51	20.18
AVG	20.87	20.19	19.44	16.50	21.69	18.71	22.26	19.82	26.53	24.09	23.35	21.51
SD	1.54	1.01	0.81	1.49	0.96	0.46	0.39	1.11	1.00	0.94	0.91	0.78

Table 21 Diameter (mm) of MCC tablets containing poly(MAA-co-EGDMA) with 16 % EGDMA in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	6.50	6.50	6.50	6.50	6.50	6.49	6.52	6.51	6.52	6.51	6.50	6.50
2	6.48	6.51	6.50	6.49	6.49	6.48	6.52	6.51	6.52	6.52	6.51	6.50
3	6.48	6.51	6.52	6.49	6.49	6.49	6.47	6.51	6.52	6.50	6.51	6.50
4	6.47	6.58	6.52	6.48	6.48	6.50	6.51	6.52	6.49	6.48	6.50	6.49
5	6.48	6.58	6.52	6.49	6.49	6.49	6.51	6.52	6.51	6.50	6.51	6.50
6	6.50	6.58	6.48	6.50	6.49	6.50	6.51	6.51	6.49	6.51	6.50	6.50
7	6.47	6.58	6.52	6.50	6.50	6.50	6.52	6.51	6.49	6.48	6.50	6.50
8	6.47	6.51	6.52	6.50	6.49	6.49	6.49	6.51	6.51	6.48	6.50	6.49
9	6.51	6.50	6.46	6.50	6.48	6.50	6.52	6.50	6.52	6.48	6.48	6.49
10	6.51	6.51	6.47	6.50	6.50	6.48	6.51	6.49	6.51	6.50	6.50	6.50
AVG	6.49	6.54	6.50	6.50	6.49	6.49	6.51	6.51	6.51	6.50	6.50	6.50
SD	0.02	0.04	0.02	0.01	0.01	0.01	0.02	0.01	0.01	0.02	0.01	0.00

Table 22 Thickness (mm) of MCC tablets containing poly(MAA-co-EGDMA) with 16 % EGDMA in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	2.35	2.39	2.43	2.41	2.33	2.38	2.32	2.33	2.35	2.25	2.38	2.52
2	2.38	2.38	2.41	2.50	2.35	2.35	2.41	2.31	2.32	2.26	2.37	2.45
3	2.40	2.37	2.42	2.50	2.32	2.42	2.39	2.34	2.33	2.38	2.27	2.47
4	2.40	2.40	2.38	2.46	2.38	2.37	2.40	2.30	2.26	2.39	2.34	2.49
5	2.37	2.43	2.44	2.47	2.30	2.44	2.34	2.33	2.25	2.32	2.30	2.46
6	2.36	2.35	2.38	2.43	2.33	2.47	2.42	2.31	2.36	2.21	2.40	2.51
7	2.33	2.40	2.36	2.44	2.33	2.35	2.30	2.33	2.33	2.32	2.47	2.50
8	2.38	2.32	2.36	2.45	2.29	2.37	2.33	2.29	2.31	2.24	2.36	2.42
9	2.30	2.40	2.40	2.42	2.31	2.35	2.33	2.32	2.36	2.27	2.31	2.50
10	2.34	2.37	2.44	2.49	2.34	2.34	2.33	2.34	2.24	2.38	2.29	2.48
AVG	2.36	2.38	2.40	2.46	2.33	2.38	2.36	2.32	2.31	2.30	2.35	2.48
SD	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.02	0.05	0.07	0.06	0.03

Table 23 Disintegration time (s) of MCC tablets containing poly(MAA-co-EGDMA) with 16 % EGDMA in Na form.

No.	0.5 Ton				1 ton				2 ton			
	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
1	192	147	52	28	217	61	45	34	234	48	36	21
2	196	151	55	30	219	65	46	35	237	50	36	21
3	199	161	60	31	224	67	47	36	242	53	37	22
4	202	162	61	33	231	68	48	36	258	56	38	23
5	207	166	63	34	232	70	49	37	261	59	40	24
6	212	172	66	35	238	74	51	38	270	60	41	26
AVG	201.33	159.83	59.50	31.83	226.83	67.50	47.67	36.00	250.33	54.33	38.00	22.83
SD	7.31	9.33	5.17	2.64	8.18	4.42	2.16	1.41	0.15	4.84	2.10	1.94

2. Effect of tablet weight (size)

Table 24 Physical properties of MCC tablets containing poly(MAA-co-DVB) with 16 % DVB in Na form.

Weight (mg)	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
100	Hardness (kg_F)	22.02	21.30	21.30	21.00	22.12	21.00	22.31	21.61	20.18	21.00	21.38	0.65
	Diameter (mm)	6.52	6.52	6.49	6.51	6.49	6.52	6.49	6.49	6.52	6.52	6.51	0.01
	Thickness (mm)	2.34	2.34	2.34	2.29	2.28	2.35	2.28	2.34	2.25	2.27	2.31	0.04
	Disintegration time (s)	27	28	28	29	29	30	-	-	-	-	28.50	1.05
250	Hardness (kg_F)	30.38	29.77	30.58	31.80	30.38	29.05	28.13	30.78	28.95	28.85	29.87	1.11
	Diameter (mm)	9.54	9.56	9.56	9.55	9.56	9.53	9.53	9.55	9.56	9.56	9.55	0.01
	Thickness (mm)	2.66	2.68	2.68	2.71	2.72	2.68	2.68	2.67	2.72	2.68	2.69	0.02
	Disintegration time (s)	14	14	15	16	17	17	-	-	-	-	15.50	1.38
500	Hardness (kg_F)	28.85	29.05	27.83	27.32	29.56	29.15	28.64	27.73	29.15	29.36	28.66	0.77
	Diameter (mm)	12.75	12.75	12.75	12.76	12.75	12.76	12.76	12.76	12.75	12.75	12.75	0.01
	Thickness (mm)	3.19	3.20	3.22	3.20	3.19	3.24	3.19	3.20	3.20	3.20	3.20	0.02
	Disintegration time (s)	9	11	11	12	12	13	-	-	-	-	11.33	1.37

Table 25 Physical properties of MCC tablets containing poly(MAA-co-EGDMA) with 16 % EGDMA in Na form.

Weight (mg)	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
100	Hardness (kg_F)	19.88	21.20	18.45	20.29	18.25	19.67	19.47	21.10	18.76	21.10	19.82	1.11
	Diameter (mm)	6.51	6.51	6.51	6.52	6.52	6.51	6.51	6.51	6.50	6.49	6.51	0.01
	Thickness (mm)	2.33	2.31	2.34	2.30	2.33	2.31	2.33	2.29	2.32	2.34	2.32	0.02
	Disintegration time (s)	34	35	36	36	37	38	-	-	-	-	36.00	1.41
250	Hardness (kg_F)	25.69	26.10	27.52	27.22	27.12	27.93	26.50	27.62	27.83	27.62	27.12	0.77
	Diameter (mm)	9.56	9.55	9.54	9.56	9.54	9.54	9.55	9.56	9.56	9.56	9.55	0.01
	Thickness (mm)	2.77	2.77	2.76	2.78	2.78	2.76	2.76	2.79	2.78	2.77	2.77	0.01
	Disintegration time (s)	34	34	35	36	37	38	-	-	-	-	35.67	1.63
500	Hardness (kg_F)	23.65	24.87	26.30	24.97	25.59	27.93	25.18	24.57	26.91	25.59	25.56	1.23
	Diameter (mm)	12.76	12.76	12.76	12.75	12.75	12.74	12.75	12.76	12.75	12.75	12.75	0.01
	Thickness (mm)	3.33	3.32	3.27	3.31	3.30	3.27	3.30	3.31	3.26	3.27	3.29	0.02
	Disintegration time (s)	33	35	36	41	42	44	-	-	-	-	38.50	4.42

3. Type of tablet filler

Table 26 Physical properties of tablets without disintegrant.

Filler	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
MCC	Hardness (kg_F)	24.77	27.12	27.10	27.73	27.42	28.13	24.85	25.99	25.71	27.23	26.61	1.19
	Diameter (mm)	6.51	6.49	6.48	6.48	6.47	6.47	6.48	6.49	6.48	6.48	6.48	0.01
	Thickness (mm)	2.24	2.21	2.22	2.23	2.19	2.25	2.20	2.26	2.24	2.23	2.23	0.02
	Disintegration time (s)	1069	1092	1237	1405	1857	1934	-	-	-	-	1432.33	379.14
DCP	Hardness (kg_F)	3.98	6.83	2.34	3.98	7.44	4.49	2.09	1.83	6.42	1.22	4.06	2.23
	Diameter (mm)	6.53	6.53	6.53	6.54	6.53	6.53	6.54	6.54	6.54	6.54	6.54	0.01
	Thickness (mm)	1.64	1.67	1.64	1.67	1.67	1.64	1.68	1.64	1.64	1.64	1.65	0.02
	Disintegration time (s)	11400	12600	13380	14400	14400	14880	-	-	-	-	13510.00	1323.50
Lactose	Hardness (kg_F)	6.22	6.22	5.28	6.28	6.52	5.46	5.22	6.10	6.22	6.25	5.98	0.47
	Diameter (mm)	6.53	6.53	6.53	6.54	6.54	6.54	6.53	6.54	6.53	6.53	6.53	0.01
	Thickness (mm)	2.18	2.20	2.18	2.18	2.20	2.18	2.19	2.18	2.18	2.18	2.19	0.01
	Disintegration time (s)	14	15	15	17	17	17	-	-	-	-	15.83	1.33

Table 27 Physical properties of tablets containing poly(MAA-co-DVB) with 16 % DVB in Na form.

Filler	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
MCC	Hardness (kg_F)	22.02	21.30	21.30	21.00	22.12	21.00	22.31	21.61	20.18	21.00	21.38	0.65
	Diameter (mm)	6.52	6.52	6.49	6.51	6.49	6.52	6.49	6.49	6.52	6.52	6.51	0.01
	Thickness (mm)	2.34	2.34	2.34	2.29	2.28	2.35	2.28	2.34	2.25	2.27	2.31	0.04
	Disintegration time (s)	27	28	28	29	29	30	-	-	-	-	28.50	1.05
DCP	Hardness (kg_F)	5.30	4.38	4.49	3.98	4.49	4.28	5.10	3.98	4.08	4.89	4.50	0.46
	Diameter (mm)	6.55	6.55	6.53	6.55	6.56	6.56	6.56	6.51	6.55	6.53	6.55	0.02
	Thickness (mm)	1.74	1.83	1.75	1.77	1.75	1.75	1.79	1.78	1.78	1.76	1.77	0.03
	Disintegration time (s)	1	1	2	2	2	2	-	-	-	-	1.67	0.52
Lactose	Hardness (kg_F)	2.85	2.75	2.85	3.16	3.06	2.55	3.06	3.06	3.26	3.06	2.97	0.21
	Diameter (mm)	6.54	6.54	6.54	6.54	6.55	6.55	6.54	6.55	6.54	6.52	6.54	0.01
	Thickness (mm)	2.22	2.27	2.26	2.25	2.24	2.25	2.26	2.23	2.25	2.26	2.25	0.02
	Disintegration time (s)	5	6	6	7	7	7	-	-	-	-	6.33	0.82

Table 28 Physical properties of tablets containing poly(MAA-co-EGDMA) with 16 % EGDMA in Na form.

Filler	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
MCC	Hardness (kg_F)	19.88	21.20	18.45	20.29	18.25	19.67	19.47	21.10	18.76	21.10	19.82	1.11
	Diameter (mm)	6.51	6.51	6.51	6.52	6.52	6.51	6.51	6.51	6.50	6.49	6.51	0.01
	Thickness (mm)	2.33	2.31	2.34	2.30	2.33	2.31	2.33	2.29	2.32	2.34	2.32	0.02
	Disintegration time (s)	34	35	36	36	37	38	-	-	-	-	36.00	1.41
DCP	Hardness (kg_F)	2.85	2.96	3.26	3.26	2.85	2.75	3.67	2.75	3.26	3.77	3.14	0.37
	Diameter (mm)	6.52	6.52	6.52	6.54	6.54	6.54	6.52	6.52	6.54	6.48	6.52	0.02
	Thickness (mm)	1.83	1.85	1.85	1.85	1.85	1.88	1.85	1.86	1.86	1.86	1.85	0.01
	Disintegration time (s)	1	1	2	2	2	2	-	-	-	-	1.67	0.52
Lactose	Hardness (kg_F)	1.63	1.83	2.14	1.83	1.73	2.04	1.83	1.73	1.83	1.83	1.84	0.15
	Diameter (mm)	6.58	6.55	6.52	6.57	6.59	6.56	6.52	6.57	6.56	6.53	6.56	0.02
	Thickness (mm)	2.39	2.40	2.38	2.40	2.42	2.40	2.39	2.41	2.41	2.40	2.40	0.01
	Disintegration time (s)	5	5	6	6	7	8	-	-	-	-	6.17	1.17

4. The presence of magnesium stearate

Table 29 Physical properties of MCC tablets containing poly(MAA-co-DVB) with 16 % DVB in Na form.

Mg stearate (%)	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
0	Hardness (kg_F)	22.02	21.30	21.30	21.00	22.12	21.00	22.31	21.61	20.18	21.00	21.38	0.65
	Diameter (mm)	6.52	6.52	6.49	6.51	6.49	6.52	6.49	6.49	6.52	6.52	6.51	0.01
	Thickness (mm)	2.34	2.34	2.34	2.29	2.28	2.35	2.28	2.34	2.25	2.27	2.31	0.04
	Disintegration time (s)	27	28	28	29	29	30	-	-	-	-	28.50	1.05
0.5	Hardness (kg_F)	19.88	20.59	19.67	19.16	19.57	20.39	19.88	18.76	20.69	19.98	19.86	0.61
	Diameter (mm)	6.50	6.50	6.50	6.47	6.49	6.50	6.50	6.50	6.48	6.50	6.49	0.01
	Thickness (mm)	2.41	2.37	2.37	2.35	2.36	2.35	2.39	2.37	2.37	2.42	2.38	0.02
	Disintegration time (s)	25	26	26	26	28	31	-	-	-	-	27.00	2.19
1	Hardness (kg_F)	18.25	18.65	17.74	18.14	17.94	17.53	18.35	18.45	17.64	18.35	18.10	0.38
	Diameter (mm)	6.50	6.50	6.47	6.50	6.48	6.50	6.50	6.50	6.50	6.48	6.49	0.01
	Thickness (mm)	2.42	2.42	2.43	2.42	2.42	2.41	2.41	2.40	2.37	2.43	2.41	0.02
	Disintegration time (s)	20	20	20	21	22	23	-	-	-	-	21.00	1.26

Table 30 Physical properties of tablets containing poly(MAA-co-EGDMA) with 16 % EGDMA in Na form.

Mg stearate (%)	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
0	**Hardness (kg_F)**	19.88	21.20	18.45	20.29	18.25	19.67	19.47	21.10	18.76	21.10	19.82	1.11
	Diameter (mm)	6.51	6.51	6.51	6.52	6.52	6.51	6.51	6.51	6.50	6.49	6.51	0.01
	Thickness (mm)	2.33	2.31	2.34	2.30	2.33	2.31	2.33	2.29	2.32	2.34	2.32	0.02
	Disintegration time (s)	34	35	36	36	37	38	-	-	-	-	36.00	1.41
0.5	**Hardness (kg_F)**	17.43	17.84	16.41	15.60	16.92	15.80	17.23	15.49	17.33	16.92	16.70	0.83
	Diameter (mm)	6.50	5.47	6.46	6.50	6.50	6.50	6.50	6.48	6.47	6.50	6.39	0.32
	Thickness (mm)	2.45	2.47	2.46	2.42	2.42	2.44	2.43	2.47	2.45	2.44	2.45	0.02
	Disintegration time (s)	16	17	17	18	19	21	-	-	-	-	18.00	1.79
1	**Hardness (kg_F)**	16.21	16.31	16.62	16.41	15.49	16.41	15.49	16.72	16.21	16.31	16.22	0.42
	Diameter (mm)	6.52	6.49	6.49	6.50	6.52	6.52	6.52	6.52	6.52	6.52	6.51	0.01
	Thickness (mm)	2.47	2.48	2.47	2.50	2.47	2.48	2.48	2.48	2.47	2.50	2.48	0.01
	Disintegration time (s)	22	22	23	23	24	26	-	-	-	-	23.33	1.51

Ion-exchange effect on drug release

1. Physical properties of propranolol HCl tablets

Table 31 Physical properties of propranolol HCl tablets containing 2.5% disintegrant.

Type of DTs	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
No DTs	Hardness (kg_F)	16.82	16.72	16.51	16.92	16.72	16.72	17.33	16.92	16.51	17.64	16.88	0.36
	Diameter (mm)	6.51	6.49	6.49	6.49	6.49	6.49	6.49	6.51	6.51	6.51	6.50	0.01
	Thickness (mm)	2.36	2.36	2.36	2.36	2.37	2.36	2.36	2.37	2.36	2.38	2.36	0.01
	Disintegration time (s)	5132	5294	5312	5341	5363	5384	-	-	-	-	5304.33	90.55
SSG	Hardness (kg_F)	15.49	16.00	16.72	16.62	15.90	16.21	15.90	16.82	16.41	16.62	16.27	0.44
	Diameter (mm)	6.53	6.53	6.52	6.50	6.53	6.52	6.53	6.53	6.53	6.53	6.53	0.01
	Thickness (mm)	2.35	2.34	2.38	2.36	2.34	2.36	2.37	2.37	2.36	2.36	2.36	0.01
	Disintegration time (s)	730	733	737	743	746	751	-	-	-	-	740.00	8.05
poly(MAA-co-DVB)	Hardness (kg_F)	16.82	16.11	16.62	15.80	16.21	16.31	15.80	15.39	16.00	16.72	16.18	0.45
	Diameter (mm)	6.52	6.52	6.49	6.51	6.52	6.52	6.52	6.52	6.52	6.51	6.52	0.01
	Thickness (mm)	2.37	2.38	2.39	2.38	2.38	2.37	2.36	2.35	2.37	2.40	2.38	0.01
	Disintegration time (s)	573	582	583	590	593	596	-	-	-	-	586.17	8.47
poly(MAA-co-EGDMA)	Hardness (kg_F)	16.62	15.90	16.21	15.90	16.00	16.41	16.82	16.11	17.23	16.11	16.33	0.44
	Diameter (mm)	6.52	6.52	6.52	6.52	6.50	6.52	6.52	6.52	6.52	6.52	6.52	0.01
	Thickness (mm)	2.36	2.40	2.38	2.38	2.37	2.38	2.36	2.38	2.35	2.34	2.37	0.02
	Disintegration time (s)	469	474	474	474	478	479	-	-	-	-	474.67	3.56

Table 32 Physical properties of propranolol HCl tablets containing 10% disintegrant.

Type of DTs	Physical properties	1	2	3	4	5	6	7	8	9	10	AVG	SD
No DTs	Hardness (kg_F)	16.82	16.72	16.51	16.92	16.72	16.72	17.33	16.92	16.51	17.64	16.88	0.36
	Diameter (mm)	6.51	6.49	6.49	6.49	6.49	6.49	6.49	6.51	6.51	6.51	6.50	0.01
	Thickness (mm)	2.36	2.36	2.36	2.36	2.37	2.36	2.36	2.37	2.36	2.38	2.36	0.01
	Disintegration time (s)	5132	5294	5312	5341	5363	5384	-	-	-	-	5304.33	90.55
SSG	Hardness (kg_F)	15.70	15.49	15.19	15.70	16.21	15.60	15.19	15.70	15.80	15.47	15.61	0.30
	Diameter (mm)	6.54	6.54	6.51	6.50	6.54	6.53	6.50	6.54	6.54	6.54	6.53	0.02
	Thickness (mm)	2.36	2.36	2.37	2.41	2.40	2.35	2.37	2.36	2.36	2.37	2.37	0.02
	Disintegration time (s)	88	91	91	92	92	92	-	-	-	-	91.00	1.55
poly(MAA-co-DVB)	Hardness (kg_F)	11.62	12.64	12.84	12.23	12.54	12.74	13.35	12.33	12.64	12.64	12.56	0.45
	Diameter (mm)	6.55	6.54	6.55	6.56	6.55	6.55	6.54	6.52	6.55	6.52	6.54	0.01
	Thickness (mm)	2.42	2.43	2.43	2.42	2.44	2.41	2.41	2.43	2.43	2.42	2.42	0.01
	Disintegration time (s)	62	63	63	63	63	63	-	-	-	-	62.83	0.41
poly(MAA-co-EGDMA)	Hardness (kg_F)	12.23	11.21	11.31	11.62	11.72	11.82	12.03	12.33	11.21	10.91	11.64	0.47
	Diameter (mm)	6.57	6.51	6.54	6.54	6.54	6.54	6.54	6.50	6.53	6.52	6.53	0.02
	Thickness (mm)	2.46	2.47	2.47	2.43	2.48	2.47	2.48	2.46	2.46	2.49	2.47	0.02
	Disintegration time (s)	18	18	18	18	19	19	-	-	-	-	18.33	0.52

2. Dissolution of propranolol HCl

2.1 Standard curve of propranolol HCl

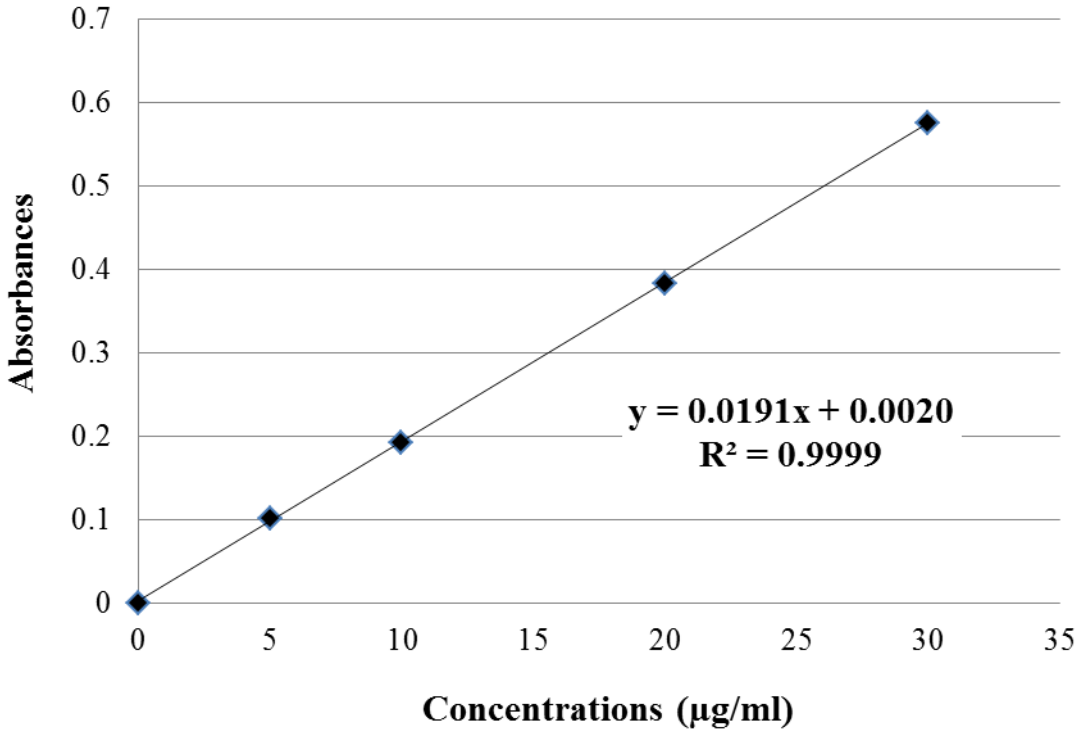


Figure 1 Standard curve of propranolol HCl.

Table 33 Drug content (%) in propranolol hydrochloride tablets (2.5 % disintegrant).

Type of DTs	Absorbance			Conc.(µg/ml)			%Drug content			AVG	SD
	1	2	3	1	2	3	1	2	3		
No DTs	0.383	0.379	0.388	19.948	19.738	20.209	99.738	98.691	101.047	99.825	1.180
SSG	0.361	0.369	0.366	18.796	19.215	19.058	93.979	96.073	95.288	95.113	1.058
DVB	0.391	0.392	0.396	20.366	20.419	20.628	101.832	102.094	103.141	102.356	0.693
EGDMA	0.371	0.363	0.379	19.319	18.901	19.738	96.597	94.503	98.691	96.597	2.094

Table 34 Drug content (%) in propranolol hydrochloride tablets (10% disintegrant).

Type of DTs	Absorbance			Conc.(µg/ml)			%Drug content			AVG	SD
	1	2	3	1	2	3	1	2	3		
No DTs	0.383	0.379	0.388	19.948	19.738	20.209	99.738	98.691	101.047	99.825	1.180
SSG	0.390	0.387	0.392	20.314	20.157	20.419	101.571	100.785	102.094	101.483	0.659
DVB	0.386	0.386	0.388	20.105	20.105	20.209	100.524	100.524	101.047	100.698	0.302
EGDMA	0.367	0.387	0.389	19.110	20.157	20.262	95.550	100.785	101.309	99.215	3.185

2.2 % Cumulative released of propranolol HCl

Table 35 % Cumulative released of propranolol HCl from tablets containing no disintegrant.

Time (min)	% Cumulative released of propranolol HCl						AVG	SD
	1	2	3	4	5	6		
5	10.70	10.77	11.78	10.41	11.26	9.80	10.79	0.68
10	15.69	14.28	15.03	14.09	14.99	14.28	14.73	0.62
15	20.71	19.20	19.63	19.30	19.63	19.75	19.70	0.54
30	40.29	38.74	40.15	41.82	38.97	38.55	39.75	1.25
45	52.40	51.63	53.13	56.83	51.91	51.08	52.83	2.08
60	61.07	61.85	62.89	61.07	61.85	62.16	61.82	0.69

Table 36 % Cumulative released of propranolol HCl from tablets containing 2.5 % SSG.

Time (min)	% Cumulative released of propranolol HCl						AVG	SD
	1	2	3	4	5	6		
5	11.26	11.73	18.00	12.63	10.58	14.61	13.14	2.76
10	12.23	18.10	22.93	22.76	22.41	20.57	19.83	4.15
15	29.74	34.19	35.58	36.71	35.98	30.73	33.82	2.92
30	49.67	59.38	63.34	69.09	64.23	55.80	60.25	6.87
45	76.08	75.92	80.51	87.63	82.73	77.64	80.09	4.55
60	81.90	86.12	90.93	90.65	90.08	86.47	87.69	3.53

Table 37 % Cumulative released of propranolol HCl from tablets containing 2.5 % poly(MAA-co-DVB) resin.

Time (min)	% Cumulative released of propranolol HCl						AVG	SD
	1	2	3	4	5	6		
5	17.62	22.60	19.93	22.22	25.59	19.11	21.18	2.86
10	43.00	46.72	43.17	46.18	49.01	42.08	45.03	2.69
15	58.13	61.05	58.15	59.28	62.04	55.00	58.94	2.49
30	82.99	81.50	81.57	83.95	83.06	79.59	82.11	1.55
45	93.85	97.03	90.41	93.28	92.29	90.27	92.86	2.51
60	97.48	97.15	95.00	97.05	96.58	94.51	96.30	1.24

Table 38 % Cumulative released of propranolol HCl from tablets containing 2.5 % poly(MAA-co-EGDMA) resin.

Time (min)	% Cumulative released of propranolol HCl						AVG	SD
	1	2	3	4	5	6		
5	46.98	54.64	51.48	61.31	44.91	42.25	50.26	7.02
10	69.18	75.05	70.52	77.12	63.50	57.54	68.82	7.30
15	78.23	82.94	80.37	85.39	74.06	67.86	78.14	6.37
30	92.13	95.19	95.64	95.48	89.51	83.95	91.98	4.61
45	97.50	99.72	98.21	97.12	95.05	89.66	96.21	3.55
60	98.30	99.55	98.82	97.48	97.74	95.52	97.90	1.39

Table 39 % Cumulative released of propranolol HCl from tablets containing 10 % SSG.

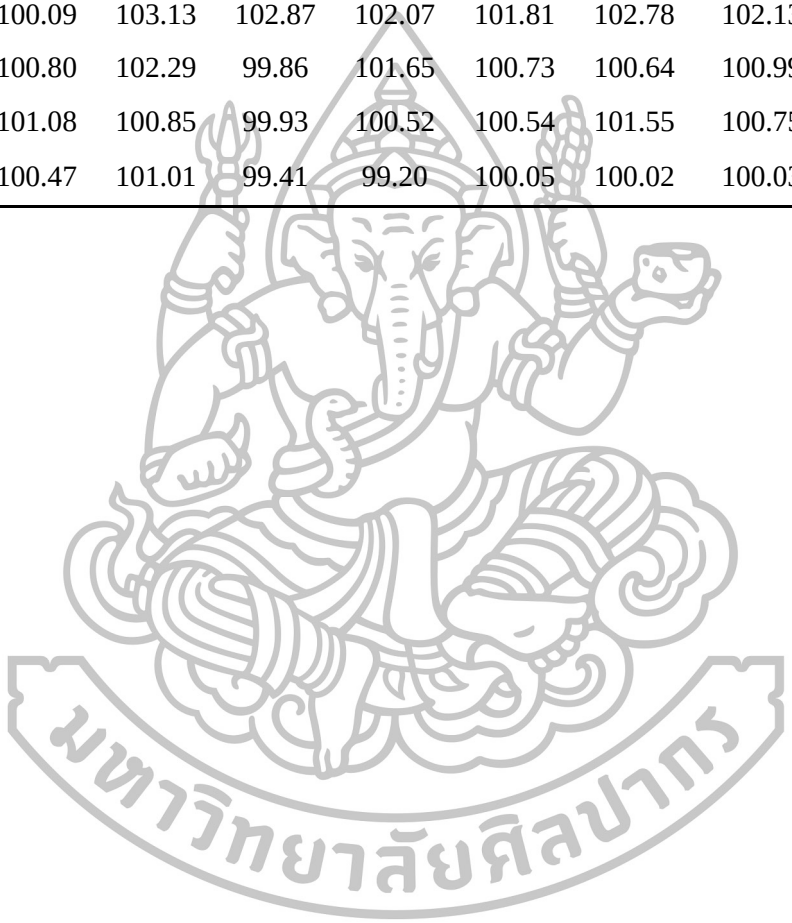
Time (min)	% Cumulative released of propranolol HCl						AVG	SD
	1	2	3	4	5	6		
5	102.29	96.49	98.23	99.34	99.69	92.81	98.14	3.23
10	100.35	97.88	97.60	98.92	98.87	98.28	98.65	0.99
15	100.87	99.03	98.44	98.92	98.70	100.24	99.37	0.96
30	100.31	99.46	102.90	100.19	98.80	102.33	100.66	1.62
45	101.88	99.69	99.67	99.25	98.87	101.86	100.20	1.33
60	103.91	101.93	102.24	102.57	101.60	102.71	102.49	0.80

Table 40 % Cumulative released of propranolol HCl from tablets containing 10 % poly(MAA-co-DVB) resin.

Time (min)	% Cumulative released of propranolol HCl						AVG	SD
	1	2	3	4	5	6		
5	103.04	98.61	102.43	102.36	100.35	105.02	101.97	2.22
10	106.53	99.43	98.21	98.49	96.89	101.46	100.17	3.47
15	101.15	99.03	98.16	98.02	96.44	100.75	98.93	1.78
30	100.75	99.10	98.42	98.84	97.10	100.64	99.14	1.39
45	101.08	98.77	97.53	98.21	99.41	101.18	99.36	1.50
60	101.81	98.28	97.29	97.90	96.80	100.68	98.79	2.00

Table 41 % Cumulative released of propranolol HCl from tablets containing 10 % poly(MAA-co-EGDMA) resin.

Time (min)	% Cumulative released of propranolol HCl						AVG	SD
	1	2	3	4	5	6		
5	101.81	102.21	103.02	103.53	101.48	104.81	102.81	1.24
10	102.52	103.49	103.86	104.69	102.21	104.41	103.53	1.00
15	100.09	103.13	102.87	102.07	101.81	102.78	102.13	1.12
30	100.80	102.29	99.86	101.65	100.73	100.64	100.99	0.85
45	101.08	100.85	99.93	100.52	100.54	101.55	100.75	0.55
60	100.47	101.01	99.41	99.20	100.05	100.02	100.03	0.67



BIOGRAPHY

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Poster presentation

Siraprapa Chansatidkosol, Praneet Opanasopit and Prasert Akkaramongkolporn. "Tablet Disintegrant Derived from Crosslinked Methacrylic Acid and Divinylbenzene Copolymers". PharmaTech 2014, 1-2 December 2014, Queen Sirikit National Convention centre, Bangkok, Thailand.

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Working profile

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