Original Article

HPMC Matrix Granule Formation: Selection of Suitable Granulating Fluid

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ABSTRACT

Objective: The purpose of this study was to investigate and select the suitable granulating fluid for the matrix granules consisting of hydroxypropyl methylcellulose (HPMC). **Method:** Viscosity of the granulating fluids containing HPMC in different solvents was determined. The matrix granules obtained from mixing the granulating fluid with propranolol HCl, HPMC and lactose were assessed for bulk density, particle size distribution, flowability and friability. SEM, DSC, powder x-ray diffraction and drug dissolution studies were conducted to characterize the physical properties of the granules. **Results**: Type of granulating liquid affected the granule properties. The utilization of isopropyl alcohol as a granulating liquid and subsequently adding with water was a suitable system for agglomeration of powders. Good physical properties were obtained for the granule prepared by using this granulating fluid. **Conclusion:** Type of solvent and amount of water played an important role for physical properties of HPMC in the formation of the matrix granule due to the hydrophilicity and gel formation of this polymer. The use of isopropyl alcohol as granulating liquid and subsequently adding with water was a suitable process in producing the matrix granules consisting of HPMC.

Keywords: hydroxypropyl methylcellulose, matrix granule, granulating fluid

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Introduction

Oral matrix system is the most popular form among sustainable release dosage forms in terms of effectiveness in controlling drug release and economics in manufacturing process. The matrix device consists of drug particles dispersed homogenously at molecular or particular level throughout a polymer matrix.[1] Oral controlled-release dosage forms are able to improve the patient compliance due to a reduced dosing frequency. Furthermore, these systems might provide a decrease of incidence or intensity of the side effect, prolonged therapeutic effect, as well as an increase of cost effectiveness. Solid oral controlled-release dosage forms are available either as single-unit or multiple-unit. The gastro-intestinal tract dispersion of multiple-unit dosage forms also reduces the risk of local irritation of gastric mucosa and also promotes the drug absorption.[2]

Multiple-unit dosage forms could be prepared in form of pellet, granule, multi-particulate and mini-tablet. Granule could be produced by wet and dry granulation techniques. Addition of hydrophilic polymer as matrix component might prolong the drug release from the granule. Hydrophilic matrix has become extremely popular in controlling rate of drug release from solid dosage forms. Hydroxypropyl methylcellulose (HPMC)

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has been employed extensively as a hydrophilic matrix former in the oral controlled-release dosage forms for various drugs including propranolol HCl. Its popularity can be attributable to its non-toxic nature, small influence of processing variables on drug release, ease of compression, and capability to accommodate a high level of drug loading.[3,4]

The use of water as the granulating liquid for hydrophilic matrix compositions could give the lump formation[5], but some research claimed that water could be employed for this purpose. Steam granulation was attempted as an alternative granulation technique to improve the dissolution of poorly soluble drug.[6,7] When the HPMC particles are exposed to the water during the granulation, a highly viscous gel layer forms around them. The granule produced from low molecular weight HPMC using water as granulating liquid was less compact with poor flowability and lower bulk density. This is because this polymer had lower viscosity and thinner gel layer, which consequently promoted the lower adhesion between particles.[8] The poor water uptake owing to the gel-forming property of HPMC retarding the water penetration affected the wettability of the powder mixture and granule formation.[9] The water uptake, gelling rate and viscosity were the important factors affecting the granule formation.[10] Because of high hydration and gel forming properties of HPMC after contact with water, the sticky mass was formed and it was difficult to pass through the screen to form the granule. Therefore, this study wished to select the suitable solvent system for producing the granule consisting of HPMC with diminishment of lump formation.

Propranolol hydrochloride is a β-adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at β-adrenergic receptor sites. It is widely used in therapeutics for the antihypertensive, anti-angorous and antiarrhythmic properties. Furthermore, with its short elimination half-life of 3 hours[11], it is a suitable model drug to be developed into prolonged release dosage form.

In this study, the assessment of the different solvent systems was performed to select the suitable granulating fluid for producing the propranolol HCl granule containing HPMC as matrix component. The characterization of granule prepared from different solvents was carried out.

Material and Methods

Materials

Propranolol hydrochloride (lot no. 941002, China National Chemical Imp. Exp., China), hydroxypropyl methylcellulose K 15M (Methocel® K 15M) (lot no. NH 16012N11, Colorcon Asia Pacific Pte. Ltd.) and Emcompress® (Mendell, Bodenheim, Germany) were used as received. Dichloromethane (lot no. 02110176, Reagent Chemical Industry Ltd., Thailand), ethanol (lot no. 0501252, VWR International Ltd., England), isopropyl alcohol (lot no. K33157272, VWR International Ltd., England) were used as granulating fluid. HCl solution (lot no. A01025, Baker Analyzed® A.C.S. Reagent, USA), monobasic potassium phosphate (lot no. 45-2, P.C. Drug Center Co. Ltd., Thailand), sodium hydroxide pellet (lot no. 03/07/157A) and sodium chloride (lot no. 1149, P.C. Drug Center Co. Ltd., Thailand) were purchased from P.C. Drug Center Co. Ltd., Thailand. HPMC capsule no. 1 (Capsugel, Thailand) and NP™ capsule no. 1 (Capsugel, Thailand) were used as received.

Determination Solubility Property of HPMC

Solubility of HPMC in various solvents was determined. The solubility data were utilized to select the granulating liquids for producing the granules. The solvents used in this determination were considered based on solubility and viscosity of HPMC. The employed liquids were water, 95% ethanol, dichloromethane, isopropyl alcohol (IPA), mixtures of ethanol (E) and dichloromethane (D), and mixtures of IPA and water. HPMC powder (3 g) was dispersed in 150 ml of various liquid and stirred with magnetic stirrer for 24 hours in the closed container. The appearance of

mixture was observed and then the viscosity was measured using Brookfield viscometer (Brookfield Engineering Laboratories Inc., USA.) (n = 3).

Preparation of Matrix Granules

13.34-g propranolol HCl, 21.67-mg HPMC (25% of diluent) and 64.99-mg lactose (75% of diluent) were mixed for 5 minutes using mortar and pestle. Matrix granules were prepared by wet granulation method. All materials were mixed in a porcelain mortar by geometric dilution and then wetted with granulating liquid in sufficient quantity to achieve the funicular state of agglomeration. The liquids employed in wet granulation were water, 95% ethanol, dichloromethane, isopropyl alcohol (IPA), mixtures of ethanol and dichloromethane, and mixtures of isopropyl alcohol and water. The wet mass was passed through a sieve No. 20 mesh and dried in a hot air oven at 50 $^{\circ}$C for 5 hours, then left to cool down to room temperature. The dried granules were rescreened through the sieve No. 20 mesh. The prepared granule was filled into capsule No. 1 using capsule filling machine No. 1 (S.T.P. No.1 B.M., Thailand) which one capsule contained 40-mg propranolol HCl and 25% HPMC, and lactose 75% were used as diluent. To decrease the adhesion of the granules during dissolution test, 10% polyplasdone XL was mixed with the granules and added into the capsule. HPMC capsule and NP™ capsule were used in this study.

Evaluation of Physical Properties of Matrix Granules

Bulk Density of Granules

The bulk density of granules was determined by pouring 10 g of the granules into a 50 mL cylinder and measuring the volume of granules. Tapped density was determined after tapping the cylinder until no further decrease in the granule volume. The Carr's (compressibility) index was calculated from the following equation:

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \quad \text{(eq. 1)}$$

This index is interpreted in the following way: the higher the compressibility index, the poorer the flowability.

Particle Size Distribution

Particle size distribution was determined by sieve analysis. The set of standard sieve consisted of sieves No. 20, 40, 60, 80, 100, 200 mesh and collection pan respectively. Approximately 20 g of granules were put on the top sieve series. The sieve series was placed on the sieve shaker and shaken for 5 minutes. The granules retained on each sieve size were weighed and calculated in percentage of total weight. These values were plotted against particle size.

Flowability

The angle of repose was used to determine the flowability of powder and granules. The angle of repose was measured from pouring the granules into a teflon pipe (3-inch height and 4.3-cm diameter) which was placed on a graph paper. Then the teflon pipe was raised up. The angle of repose (θ) was then calculated as $\tan \theta = h/r$; where h and r equaled height and radius of the cone respectively.

Friability

The friability of granules was determined by a friabilator (Yieheng Engineering, Bangkok, Thailand). One gram of granules with average particle size of 850 μm was accurately weighed by an analytical balance. This weight was designated as W_0. The granules were filled into a spherical container and rotated at 25 rpm for 4 minutes with friabilator. These granules were

rescreened through sieve No. 40 mesh and reweighed "W". The percent of friability was calculated based on the following equation. The result was obtained from the average of three determinations.

$$\% \text{ Friability} = \{(W_0 - W)/ W_0\} \times 100 \qquad \text{(eq. 2)}$$

Determination of Shape and Surface Topography of Granules

The shape and surface topography of prepared granules were analyzed with scanning electron microscopy (SEM) (Maxim 200 Camscan, Cambridge, England). The samples were stuck on a metal stub using carbon double adhesive tape and sputter-coated with gold before test. Micrographs were taken with a scanning electron microscope operated at an accelerating voltage of 20 KeV.

The Differential Scanning Calorimetry (DSC)

The DSC curves of drug, HPMC, prepared granules and physical mixture of these substances as the same ratio in the granule were obtained using a differential scanning calorimeter (DSC) (Pyris Sapphire DSC, Standard 115V, Perkin-Elmer Instruments, Japan). Samples of approximately 5 mg were weighed into non-hermetically sealed aluminium pans. The experiment was done between 25 °C and 250 °C with a heating rate of 10 °C/min and using nitrogen as a purge gas (20 mL/min).

The Powder X-ray Diffraction

The powder X-ray diffractometer (Diffractometer DS, Bruker, AXS, Germany) was used to determine the crystalline transformation and interaction between each component after mixing and wet granulating processes. The X-ray diffraction patterns were recorded from 5 °2θ - 50 °2θ.

Study of Drug Release

The dissolution of propranolol hydrochloride was performed with the basket method using a dissolution apparatus (type 1) (Prolabo, France). The dissolution fluid used was 900 mL HCl buffer pH 1.2. The speed of basket rotation was 100 rpm maintained at 37 °C. The amount of propranolol hydrochloride was 40 mg per capsule for all formulations. The samples were withdrawn at predetermined time intervals. The amount of drug released was measured using UV spectrophotometer (Perkin-Elmer, Germany) at 320 nm. The cumulative percentage of propranolol hydrochloride released was calculated and plotted against time.

Results

Solubility of HPMC

The physical appearances of systems containing HPMC in various solvents are shown in Figure 1. HPMC could form a viscous colloidal solution in water and mixtures of ethanol and dichloromethane (E:D) in ratios of 50:50, 40:60 and 30:70 (Figure 1A, 1B). There was a precipitation of HPMC powder in ethanol and isopropyl alcohol (Figure 1A, 1C). The viscosity values of systems containing HPMC are shown in Table 1. The viscosity of HPMC solution in different types of liquid were ranked as water > E:D (40:60) > E:D (30:70) > E:D (50:50) > E:D (60:40) > IPA-water (10%) mixture > E:D (70:30) > IPA > dichloromethane > ethanol, respectively. HPMC could be soluble in water and in mixtures of ethanol and dichloromethane in ratios of 50:50, 40:60 and 30:70 (Figure 1A). Moreover, by visual inspection it was partially soluble in dichloromethane, mixtures of ethanol and dichloromethane in ratios of 70:30 and 40:60, and mixture of isopropyl alcohol and water (10%) (Figure 1) but it was insoluble in ethanol and isopropyl alcohol.

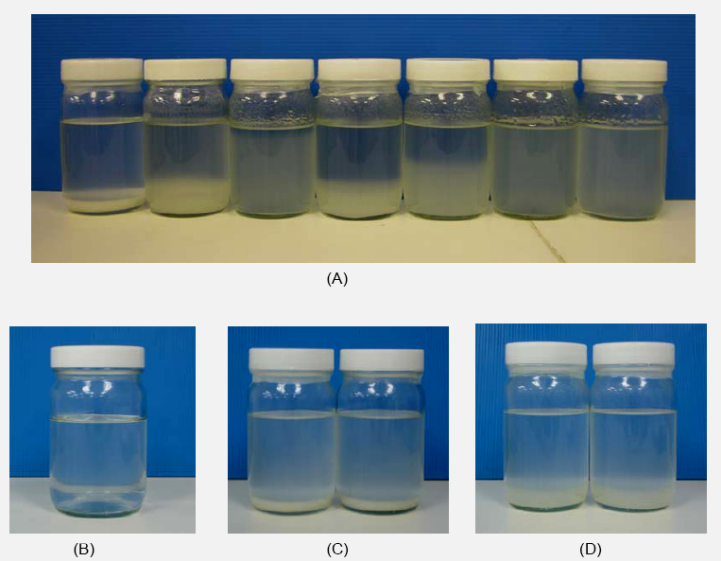


Figure 1 Appearance of systems containing 2% w/v Methocel K 15M in various liquids; (A) ethanol, dichloromethane, mixtures of ethanol and dichloromethane in ratios of 50:50, 70:30, 60:40, 30:70 and 40:60 respectively (left to right); (B) water; (C) isopropyl alcohol and (D) mixtures of isopropyl alcohol and water (10%).

Table 1 Viscosity of the systems containing HPMC in various solvents.

Solvent	Viscosity (mPa·s) (mean ± S.D.) (n = 3)
Ethanol 95% (E)	6.53 ± 0.31
Dichloromethane (D)	7.47 ± 0.12
E:D (50:50)	263.73 ± 16.48
E:D (70:30)	12.60 ± 0.35
E:D (60:40)	32.20 ± 1.20
E:D (30:70)	1092.00 ± 26.00
E:D (40:60)	1210.67 ± 18.90
Water	2686.67 ± 18.90
Isopropyl alcohol (IPA)	10.13 ± 0.46
IPA + water (10%)	13.60 ± 0.20

Characterization of Granules

Initially, the preparation of granules containing propranolol HCl, lactose and HPMC was attempted using water as granulating liquid. A large amount of lump appeared during the preparation of the wet mass and it was difficult to pass through a sieve to form the granules (Figure 2A, 2B). Therefore, an organic solvent was used as a solvent for granulating fluid. The first organic solvent used was 95% ethanol but a large volume of ethanol was needed. The solid mixture was rather difficult to be wet and a large amount of fine powder was evident. An addition of the water into the system using 95% ethanol as granulating fluid resulted in the lump formation similar to the system using water (Figure 2D). Hence, the addition of water in wet granulation process containing HPMC generated the problem mentioned above. The systems containing HPMC in the mixtures of ethanol and dichloromethane in ratios of 50:50, 40:60 and 30:70 exhibited viscous solution similar to the system containing HPMC dispersed in water. The solvent systems were further utilized as a granulating fluid since they could promote the good granule formation without losing wet mass owing to the lump formation. Therefore, the mixtures of ethanol and dichloromethane could be applied as granulating fluid. Especially, the E:D mixtures in the ratios of 50:50 and 40:60 provided the granules

with good appearance but the mixture of E:D in a ratio of 30:70 notably provided a lot of fine particles in the granulation process (Figure 3A, 3B, 3C).

The utilization of isopropyl alcohol as granulating liquid to produce tablets comprising HPMC K4M by wet granulation method has been previously reported.[12] Isopropyl alcohol was demonstrated to be used as granulating fluid in this experiment. Apparently, an amount of isopropyl alcohol used for agglomeration of powder mixture to obtain the wet mass was less than that of ethanol. Moreover, it exhibited a good wetting, i.e. slower evaporation, than ethanol, thereby HPMC powder could not swell. After screening, the system contained large amount of somewhat fine particles (Figure 3D). Therefore, water in an amount of 10% (v/v) was added to the solid mixture. By visual inspection, there was a less swelling of solid mixture, but the agglomeration of solid mixture could be formed. The lump formation disappeared from the obtained wet mass.

Figure 2 Appearance of propranolol HCl granules prepared using two different granulating liquids; 1) water: in form of (A) granules, (B) wet mass and 2) mixtures of ethanol and water: in form of (C) granules and (D) wet mass.

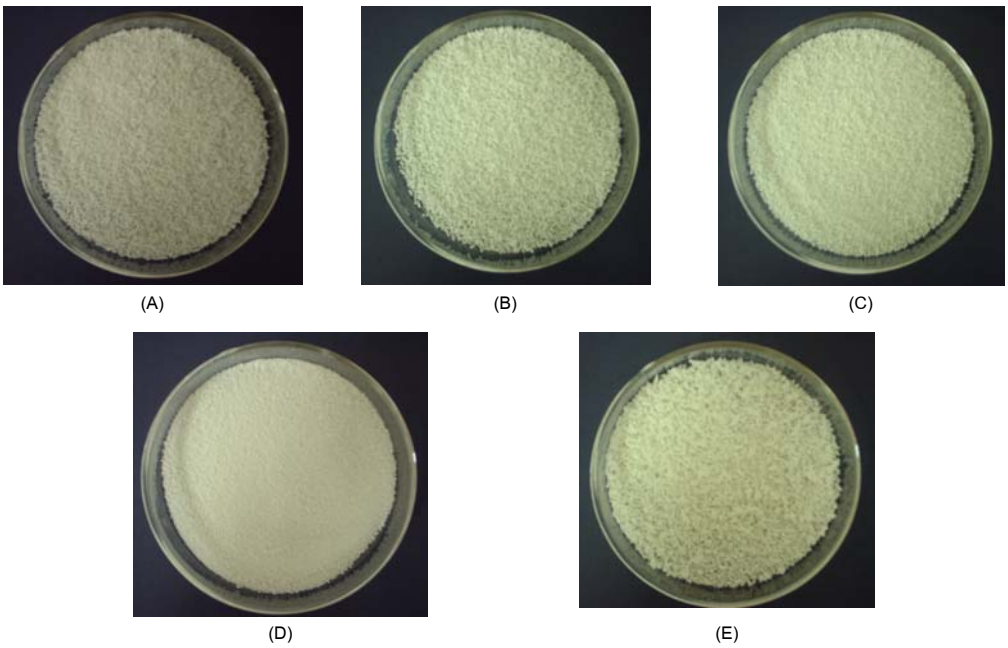


Figure 3 Appearance of propranolol HCl granules prepared using different granulating liquids; mixtures of ethanol and dichloromethane in ratios of 50:50 (A), 40:60 (B) and 30:70 (C), isopropyl alcohol (D), and isopropyl alcohol subsequently added with water (10% v/v) (E).

Particle Size Distribution and Granule Friability

The particle size distribution of the granules made from different granulating liquids, i.e. mixtures of ethanol (E) and dichloromethane (D) in the ratios of 50:50, 40:60, 30:70 and isopropyl alcohol subsequently added with water in the amount of 10% v/v, is shown in Figure 4. The particle size distributions of most granules that were rescreened through sieve No. 20 mesh were 425 - 850 µm. The utilization of E:D (50:50) as granulating liquid provided granules with obviously larger particle size (850 µm) than isopropyl alcohol with water subsequently added in the amount of 10%v/v did with the particle size of 425 µm. The particle size of Emcompress was not determined in this investigation; however the typical Emcompress has the median particle size of 130 - 150 µm. The % friability of the granules made from different granulating liquids were ranked as E:D (30:70) > E:D (60:40) > E:D (50:50) > IPA + water (10% v/v), respectively (Table 2). This result signified that the granules produced by using isopropyl alcohol with water subsequently added in an amount of 10% v/v as granulating liquid were harder than those produced by other solvents.

Table 2 Friability of propranolol HCl granules produced using different granulating liquids.

Granulating liquid	% Friability (n = 3)	
	Mean	S.D.
E:D (50:50)	10.14	1.01
E:D (40:60)	10.48	0.58
E:D (30:70)	16.49	2.09
IPA + water (10% v/v)	7.14	1.01

Note: E = ethanol, D = dichloromethane, IPA = isopropyl alcohol.

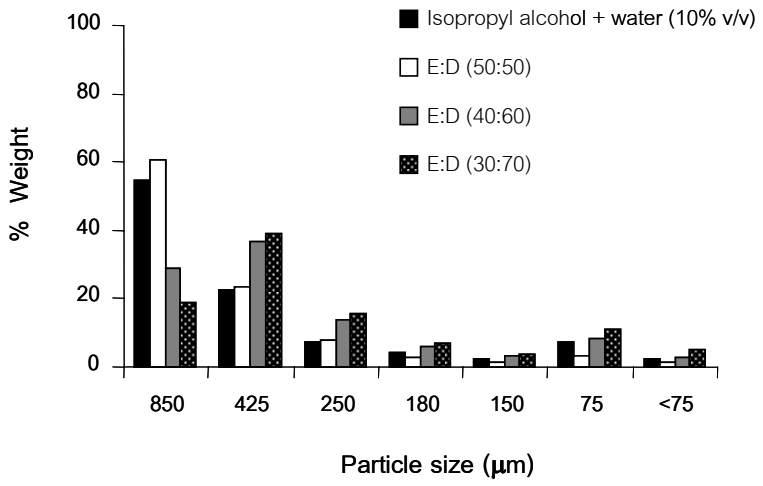


Figure 4 Particle size distribution of propranolol HCl granules made from different granulating liquids.

Note: E = ethanol, D = dichloromethane

Bulk density, tapped density, compressibility index and angle of repose

Emcompress granules were used as a reference for testing the physical properties of granules in this experiment. The bulk and tapped densities of the granules made from different granulating liquids are presented in Table 3. The bulk and tapped densities of granules which were screened through sieve No. 40 mesh were higher than the granules that were screened through sieve No. 20 mesh. The Carr's indexes of powders were higher than that of all prepared granules and Emcompress granules. This result indicated that the prepared granules had better flow properties than the powders. The Carr's index of the granules produced from the granulating fluid containing mixtures of ethanol and dichloromethane in the ratios of 50:50 and 40:60 and isopropyl alcohol and water subsequently added in the amount of 10% v/v after rescreening through sieve No. 20 mesh were 6.47, 8.33 and 3.92%, respectively. Therefore, these granules exhibited the fairly good flow properties as classified by another researcher.[13] Because of the smaller granules size, the Carr's index of Emcompress granules was higher than that of the prepared granules. There was a high value of Carr's index of the granules made from mixtures of ethanol and dichloromethane in a ratio of 30:70 and the granules screened through sieve No. 40 mesh before test. This might be due to the formation of the large amount of fine particles during granulation. The angle of repose of powders and the granules made from different granulating liquids are reported in Table 2. The angle of repose of the granules (29° - 34°) exhibited lower value than the powder (37° - 40°), indicating better flow properties for all prepared granules.

Table 3 Flow properties of propranolol HCl granules prepared from different granulating liquids.

Granulating liquid	Bulk density (g/mL) (n = 3)	Tapped density (g/mL) (n = 3)	Carr's index (%) (n = 3)	Angle of repose (θ) (n = 3)
Propranolol HCl powder	0.30 ± 0.01	0.42 ± 0.00	28.90 ± 0.89	37.31 ± 2.34
HPMC powder	0.30 ± 0.01	0.46 ± 0.01	34.48 ± 1.98	38.22 ± 3.15
Lactose powder	0.45 ± 0.01	0.67 ± 0.00	32.81 ± 1.71	40.36 ± 0.00
Emcompress granules	0.91 ± 0.00	1.00 ± 0.00	9.06 ± 0.05	26.26 ± 0.53
E:D (50:50), 20# passed*	0.35 ± 0.01	0.38 ± 0.01	6.47 ± 0.97	31.90 ± 2.37
E:D (50:50), 40# passed*	0.41 ± 0.01	0.48 ± 0.01	15.50 ± 2.78	27.77 ± 0.52
E:D (40:60), 20# passed*	0.36 ± 0.00	0.39 ± 0.00	8.33 ± 1.03	31.23 ± 1.27
E:D (30:70), 20# passed*	0.38 ± 0.02	0.43 ± 0.01	10.88 ± 0.79	29.25 ± 0.00
IPA, 20# passed*	0.40 ± 0.01	0.50 ± 0.01	18.79 ± 1.07	33.02 ± 0.70
IPA + water (10%), 20# passed*	0.39 ± 0.01	0.41 ± 0.01	3.92 ± 1.89	29.80 ± 1.94
IPA + water (10%), 40# passed*	0.43 ± 0.01	0.50 ± 0.00	14.25 ± 2.09	30.11 ± 0.00

Note: E = ethanol, D = dichloromethane

* The number indicates the mesh number of the sieve the granules passed.

Granule Morphology

Scanning electron micrographs of the granules produced from the mixtures of ethanol and dichloromethane in the ratios of 50:50 and 40:60 are presented in Figure 5A-D. All granules obtained from the agglomeration of particles exhibiting porous surface. After rescreening, the granules were smaller and more spherical characteristics. The surface of the granules produced by using isopropyl alcohol as granulating liquid and subsequently added with water in the amount of 10% v/v showed the dense agglomerated particles and exhibited the less porous surface than the granules that were produced by using mixtures of ethanol and dichloromethane in the ratios of 50:50 and 40:60 (Figure 5G-H, 6A-C). On the other hand, scanning electron micrographs of the granules made from isopropyl alcohol exhibited fine particles and wide size distribution (Figure 5E-F).

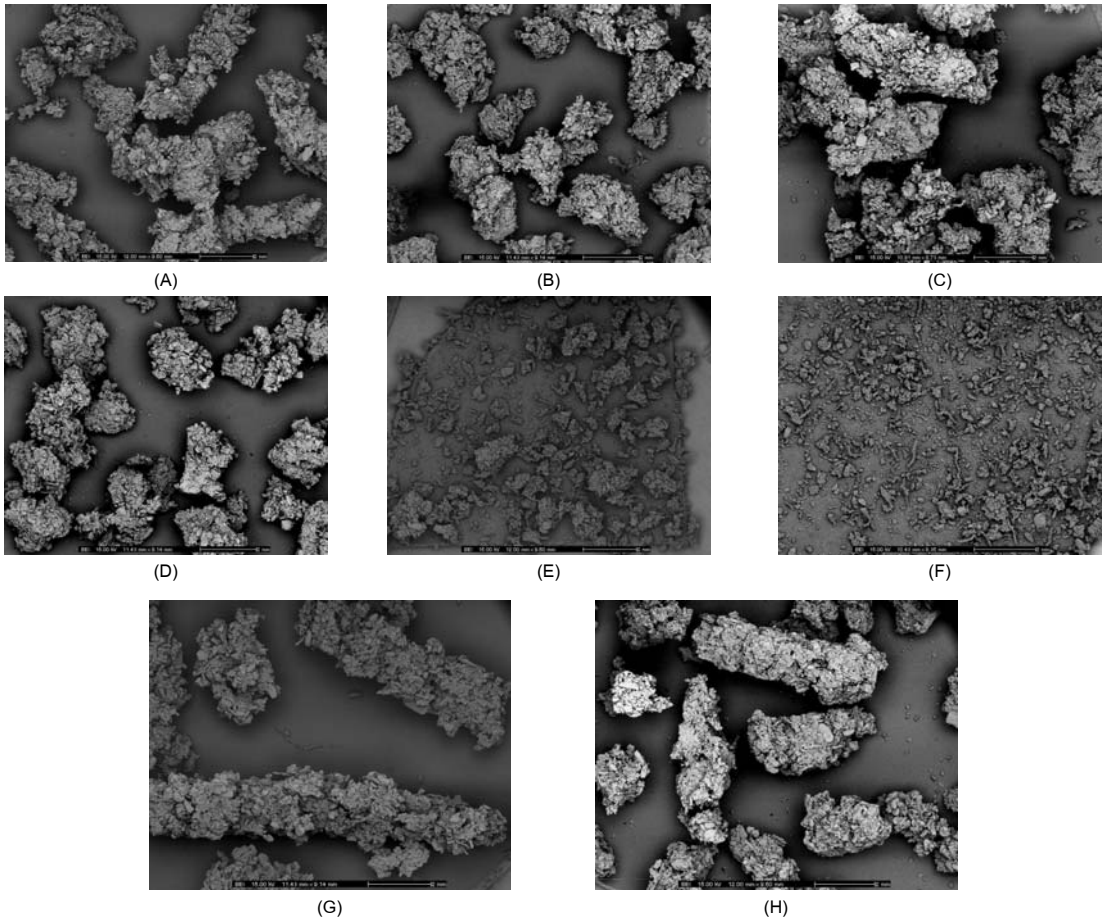
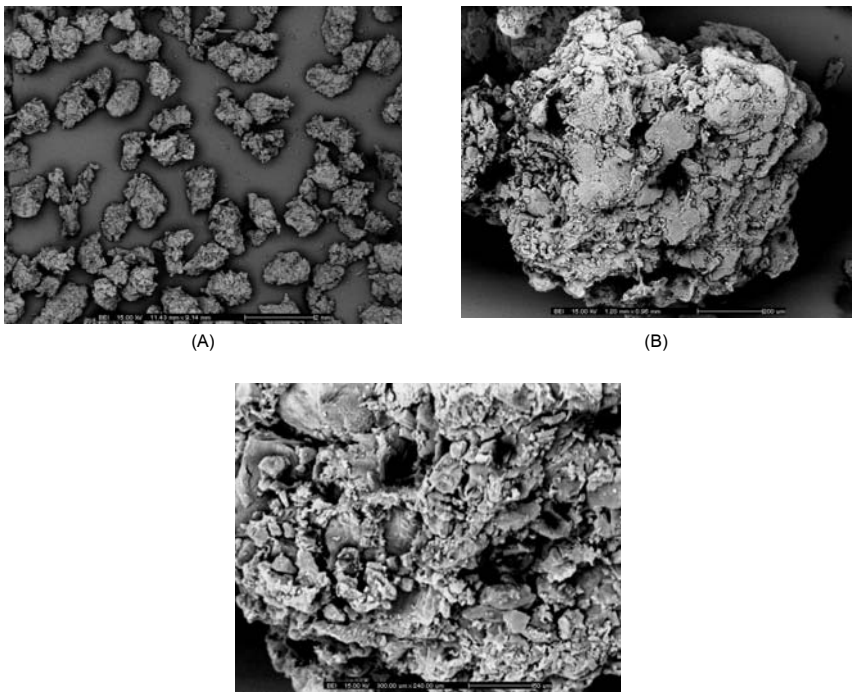


Figure 5 Scanning electron micrographs of propranolol HCl granules produced from 4 granulating liquids (10X): 1) mixtures of ethanol and dichloromethane in a ratio of 50:50: (A) after drying, and (B) rescreened through sieve No. 20 mesh; 2) mixtures of ethanol and dichloromethane in a ratio of 40:60: (C) after drying, and (D) rescreened through sieve No. 20 mesh; 3) isopropyl alcohol: (E) after drying, and (F) rescreened through sieve No. 20 mesh; 4) isopropyl alcohol with water subsequently added in an amount of 10% v/v as granulating liquid: (G) after drying, and (H) rescreened through sieve No. 20 mesh.



(A) (B)

(C)

Figure 6 Scanning electron micrographs of propranolol HCl granules produced using isopropyl alcohol with water subsequently added in an amount of 10% v/v as granulating liquid and rescreened through sieve No. 40 mesh with different magnifications: (A) 10X, (B) 100X, and (C) 400X.

Differential Scanning Calorimetry (DSC)

The DSC curves of propranolol HCl, HPMC, lactose, physical mixture and granules produced by using isopropyl alcohol with water subsequently added in an amount of 10% v/v as granulating liquid are shown in Figure 7. Propranolol HCl and HPMC exhibited the endothermic peak at 163.6 $^{\circ}$C and 49.8 $^{\circ}$C, respectively. The DSC curve of lactose showed two dominant endothermic peaks at 149.5 $^{\circ}$C and 217.9 $^{\circ}$C. From the DSC curves of physical mixture between drug and excipients, all major peaks of each component could still be detected. Propranolol HCl granule showed the characteristic peaks of each component in the formulation in DSC curves. This phenomena were also found in DSC curve of the prepared granules but the intensity of drug melting point in granules prepared by using a mixture of ethanol and dichloromethane (50:50) (data not shown) and isopropyl alcohol with water was less than that of physical mixture.

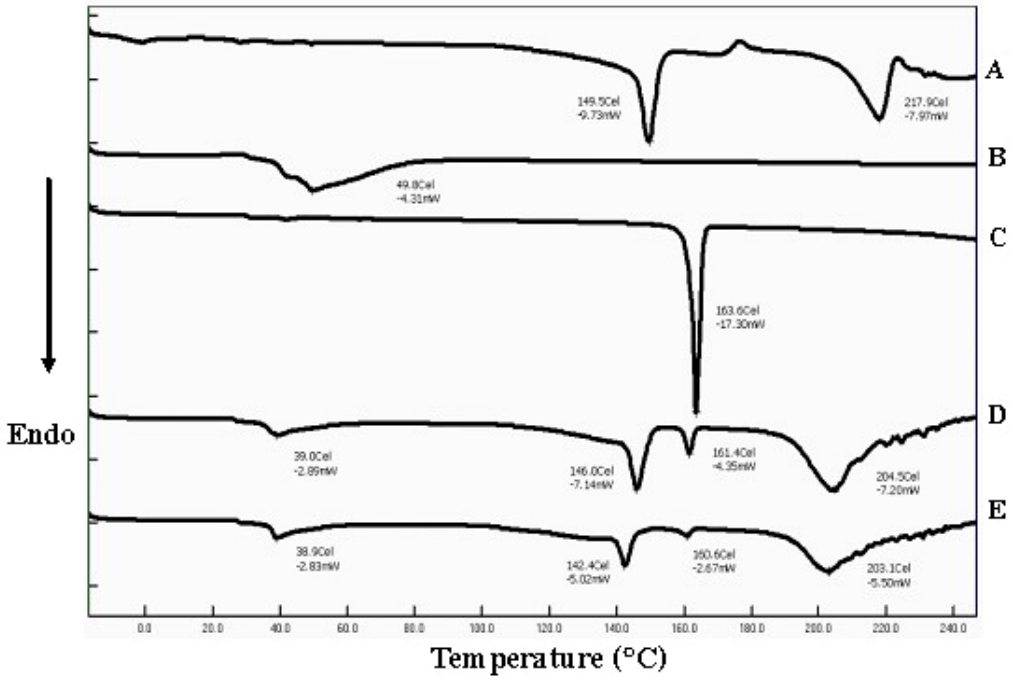


Figure 7 Differential scanning calorimetry thermograms of (A) lactose; (B) HPMC K15M; (C) propranolol HCl; (D) physical mixture; and (E) granule produced using isopropyl alcohol with water subsequently added in an amount of 10% v/v as granulating liquid.

Powder X-ray Diffraction

The powder X-ray diffraction patterns of propranolol HCl, HPMC K15M, lactose and physical mixture are presented in Figure 8. The X-ray diffraction patterns of propranolol HCl matrix granules prepared with different granulating liquids are shown in Figure 9. The X-ray diffraction pattern of propranolol HCl displayed peak at diffraction angle between 10°2θ and 30°2θ. The X-ray diffraction pattern of lactose showed sharp peak at diffraction angle between 18°2θ and 22°2θ. However, the characteristic peaks of physical mixture did not present a different peak from pure propranolol HCl, lactose or HPMC peak. The X-ray diffraction pattern of propranolol HCl matrix granule was not different from physical mixture but the peak intensity at diffraction angle about 38°2θ was decreased. This might be due to partial solubilization of this substance in these granulating liquids.

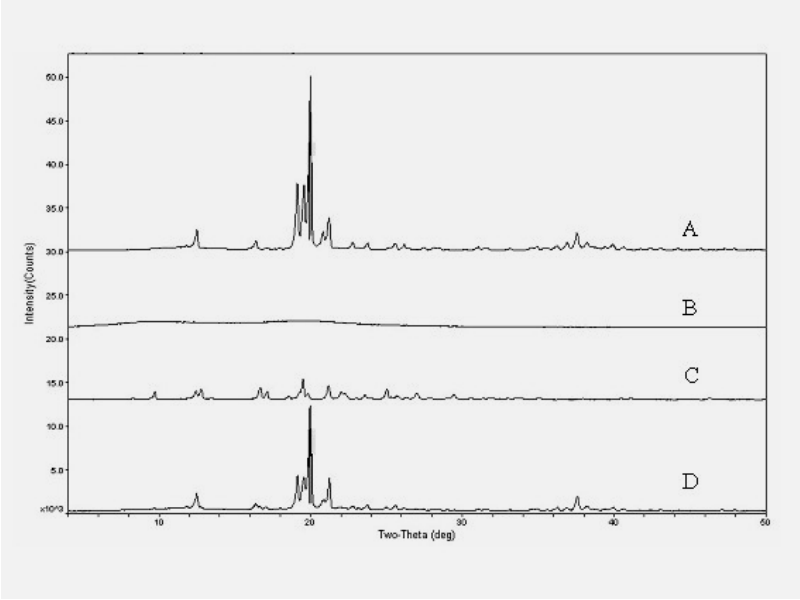


Figure 8 X-ray diffraction spectra of (A) lactose, (B) HPMC K15M, (C) propranolol HCl, and (D) physical mixture**.**

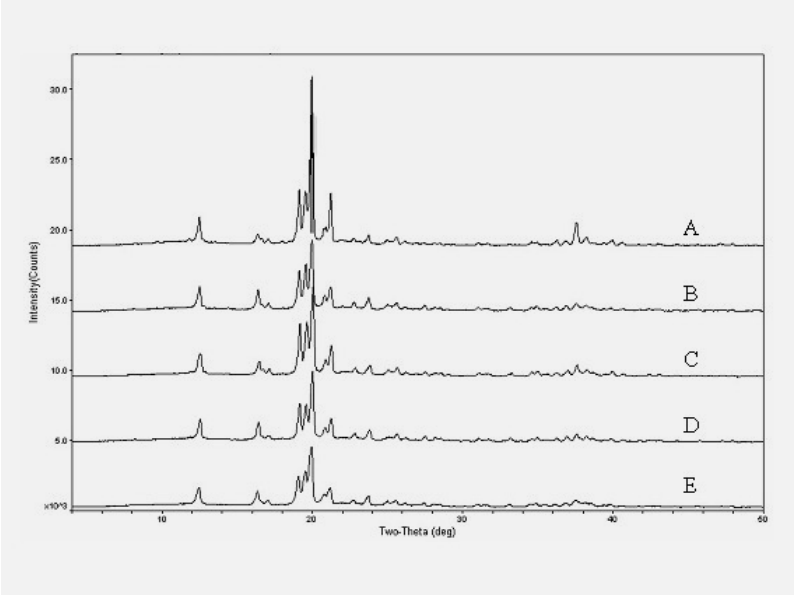


Figure 9 X-ray diffraction spectra of propranolol HCl matrix granule made with different granulating liquids; (A) physical mixture, (B) water, (C) IPA, (D) IPA-water, and (E) ethanol with dichloromethane (50:50)**.**

Drug Release

The release of propranolol HCl from granules filled into NP caps™ was faster than that of the granules filled into HPMC capsule (Figure 10). The granules filled into HPMC capsule exhibited a tendency to adhere to one another, because HPMC capsule hydrated more slowly than NP caps™. On the other hand, the NP caps™ could disintegrate quickly when it contacted the dissolution medium. Therefore, the NP caps™ capsule

was chosen for development of the multiple-unit preparations. The polyplasdone XL which is a superdisintegrant was used to add into multiple-unit formulation to decrease the adhesion of the granules.

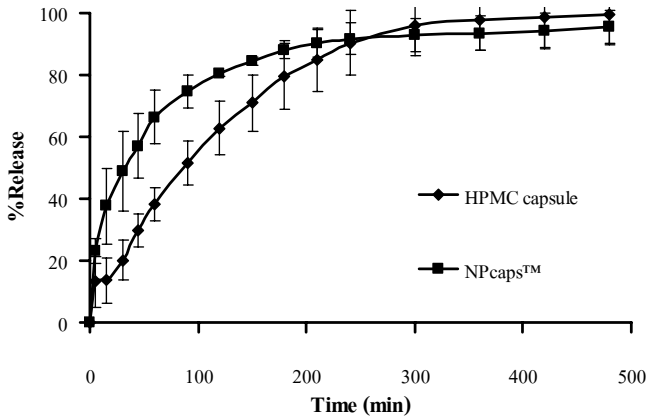


Figure 10 Dissolution profiles of propranolol HCl released from HPMC matrix granules containing 75% lactose in HCl buffer pH 1.2 using basket method.

Discussion

Effect of Granulating Liquid on Granule Formation

The propranolol HCl powder component containing 25% HPMC and 75% lactose was used as the matrix granule. Utilization of water as granulating liquid in wet granulation method led to the large amount of lump formation in wet mass. This wet mass was difficult to pass through sieve to form the granules due to hydrophilicity and gel formation of HPMC in the formulation. HPMC could be soluble in the mixtures of ethanol and dichloromethane in ratios of 50:50, 40:60 and 30:70, as well as in the water. However, viscosity of HPMC solution using these liquids was lower than that in the water. This result indicated that the degree of swelling of HPMC in mixtures of ethanol and dichloro-methane was less than that in the water. Ethanol and dichloromethane were rapidly evaporated. Thus, the utilization of mixtures between ethanol and dichloro-methane in the ratios of 50:50, 40:60 and 30:70 as granulating liquid provided the granules with a good characteristic thereby the lump formation did not occur.

In addition, isopropyl alcohol could be used for agglomeration of powder mixture since it exhibited a good wetting and slower evaporation than ethanol. The lump formation disappeared but the large amount of fine particle occurred when isopropyl alcohol was utilized as granulating liquid. In order to increase a binding property, the water was added about 10% (v/v). HPMC could act as its own binder by forming a gel layer when contacting with water.[14] Therefore the water was an important factor in the HPMC matrix granule preparation.

Effect of Granulating Liquid on Granule Properties

During the wet mass granulation and the stages of drying, the drug and any soluble excipients will dissolve, recrystalize, and then form solid interparticulate bridges after the binder vehicle is evaporated. The strength of the crystalline bridges depends on the amount of solid

deposition and rate of crystallization. Both properties are dependent on the solubility of the drug and other excipients in the granulating solvent.[15] The granules produced by using the mixtures of ethanol and dichloromethane in the ratios of 50:50 and 40:60 had an obviously porous surface because lactose in the formulation was not soluble in the mixture of ethanol and dichloromethane in the ratio of 50:50 while HPMC and propranolol HCl could dissolve in this liquid (Figure 11 - 12).

Lactose or propranolol HCl powders (3 g) were dispersed in 150 mL of solvent and stirred with magnetic stirrer for 24 hours before this visual observation. Therefore, solid interparticulate bridges of the granules might be less compact and this resulted in a more porous surface of the granules. Moreover, the percentage of friability of these granules was higher than that of the granule matrix producing by using isopropyl alcohol subsequently added with water (10% v/v). The surface of the granules produced by using isopropyl alcohol with water (10% v/v) showed the dense agglomerated particles and exhibited the less porous surface than the granules produced with mixtures of ethanol and dichloromethane in the ratios of 50:50 and 40:60. Basically, lactose and propranolol HCl could be soluble in the former solvent (Figure 11 - 12) and HPMC in formulation also acted as binder after exposure to the water. This resulted in the stronger bonding according to adhesion and cohesion forces between particles promoting the lower percentage of friability of granules.

Wells and Walker (1983)[16] has previously reported the effect of wet-massing acetylsalicylic acid with aqueous and hydroalcoholic solutions of PVP which the greater drug solubility produced the granules of larger size, low particle size distribution and reduced the friability. Therefore, using isopropyl alcohol with water subsequently added (10% v/v) as granulating liquid was the appropriate system in wet granulation method in this experiment. This granulating liquid was selected for development of the propranolol HCl matrix granules.

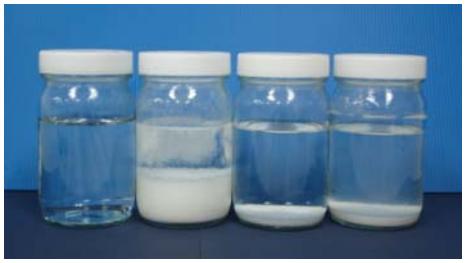


Figure 11 Appearance of systems containing lactose in water, 50:50 ethanol and dichloromethane, 90:10 isopropyl alcohol and water, and IPA, respectively (left to right).

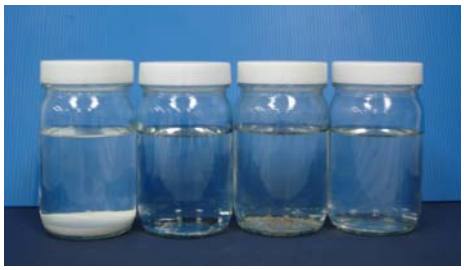


Figure 12 Appearance of systems containing propranolol HCl in IPA, 90:10 isopropyl alcohol and water, water, and 50:50 ethanol and dichloro-methane, respectively (left to right).

The DSC curve of physical mixture (propranolol HCl, HPMC and lactose) and the matrix granule exhibited all major peaks of each component indicating the substance in the mixtures to be compatible. The DSC curve of lactose exhibited two endothermic peaks. The first and second endothermic curves corresponded to the loss of crystalline water and the melting of lactose followed by its decomposition, respectively.[17] From X-ray powder diffractograms, propranolol HCl and lactose showed a crystalline characteristic. The intensity of diffraction peaks of propranolol HCl in matrix granule at diffraction angle about 38°2θ was decreased. This might be due to partial solubilization of this substance in the granulating liquids. The decrease of crystallinity of soluble substance has been previously reported in case of increasing the temperature during mixing the granule containing HPMC with high-shear granulator.[18]

The propranolol HCl matrix granule containing HPMC was developed as multiple-unit dosage form. The prepared granules were filled into NP cap™ capsule since this capsule could disintegrate quickly after contacting the dissolution medium. The polyplasdone XL was used to add into multiple-unit formulation as superdisintegrant to decrease the adhesion of the granules during dissolution test. The initial drug release from the granule containing 75% lactose and 25% HPMC was rather fast because of high surface area and the presence of water-soluble filler. Therefore, more amount of polymer in matrix component or surface coating may be needed for prolongation of drug release from this granule. The diminishment of surface area by tabletting the obtained granule should prolong the drug release. However, our on-going research will concentrate on the incorporation of hydrophobic wax into this HPMC matrix granule to modulate the drug release.

Conclusion

Type of granulating liquid influenced the granule properties. The system containing isopropyl alcohol and water was a suitable granulating liquid for agglomeration of powders in which water was the important factor in preparing the propranolol HCl matrix granule containing HPMC.

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