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EFFECT OF COMBINED CARRIERS OF COLLOIDAL SILICON DIOXIDE AND WATER-SOLUBLE POLYMER ON DISSOLUTION AND DENSITY OF FENOFIBRATE FORMULATIONS PREPARED BY MELTING METHOD

Buncha Limpiviriyachit[1], Supapit Wiangperm[1], Poj Kulvanich[2], and Vasinee Limwong[2]*

[1]College of Pharmacy, Rangsit University, Pathumthani, Thailand.
[2] Department of Manufacturing Pharmacy, College of Pharmacy, Rangsit University, Thailand.

*Corresponding author: E-mail: vasinee.m@rsu.ac.th
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Abstract: Fenofibrate (FN), colloidal silicon dioxide (CSD) and water-soluble carriers (PEG4000 or PEG6000) at the ratio of 1:1:1 was prepared by melting method. Dissolution profiles of different types of PEG were similar. PEG4000 was selected to prepare the formulations and order of mixing during melting process on drug release was investigated. Melting FN and CSD before adding PEG4000 gave higher drug dissolution than other type of order of mixing. Poloxamer188 (P188) was also used in comparison with PEG4000. Formulations of PEG4000 (1:1:0.1, 1:1:0.5, 1:1:1) and that of P188 (1:1:0.5, 1:1:0.75, 1:1:1) were prepared to investigate the effect of type and quantity of combined carriers on drug dissolution and granule density. Increasing of combined carriers ratio would markedly increase granule density while decreasing of drug dissolution. Formulation of FN:CSD:P188 at the ratio of 1:1:0.5 produced high drug release and increased in granule density, therefore, it was selected to prepare the capsules product with and without superdisintegrant (croscarmellose sodium). It was found that capsules containing croscarmellose sodium gave faster disintegration time and higher drug release than that of without disintegrant. The formulation of FN and CSD could be prepared by melting method with P188 as combined carrier for increasing dissolution and granule density.

Keywords: Fenofibrate, Combined carriers, Dissolution, Density, Melting method

INTRODUCTION

Fenofibrate (FN) is a typical BCS class II drug (low solubility and high permeability), its solubility is a rate-limiting step of drug absorption. Therefore, increasing of drug dissolution would improve drug bioavailability. Various methods were used to increase drug dissolution such as solid dispersion (Sheu et al., 1994 and Srinarong et al., 2009), micronization, spray drying (Vogt et al., 2008), and adsorption on mesoporous silica. (Ahern et al., 2013 and Uejo et al., 2013)

From previous study (Piyatassie et al., 2015), FN was melted and adsorbed on the surface of colloidal silicon dioxides (CSD). Various ratios of drug:CSD were prepared and investigated their effect on drug dissolution compared to FN powder. It was found that an increasing of CSD in the formulation would increase drug release and FN:CSD at 1:1 which gave highest drug release was chosen for filling in capsule. Force was used to compress the powder during filling process due to high bulk density of powder mixture. Therefore, drug dissolve from capsule was decreased resulting from powder compaction in capsule.

The objectives of this study were to increase drug dissolution and density of powder mixture by adding water-soluble carrier in a formulation FN:CSD at the ratio of 1:1. Three hydrophilic polymers which have low melting point property i.e. PEG4000, PEG6000 and Poloxamer188 were used as a combined carrier with CSD. The formulation was prepared by melting method. Influencing factors: type of order of mixing during melting method, type and quantity of combined carriers on drug dissolution and granule density were investigated. The selected formulation was formulated into capsules and the effect of adding superdisintegrant on drug dissolution was also studied.

MATERIALS AND METHODS

Materials

Fenofibrate (Batch No. 10019716) was obtained as a kind gift sample from Siam Pharmaceutical Co., Ltd., Thailand. Colloidal silicon dioxide (Aerosil®, Lot No. 154042814, Evonik Industries AG, Germany) was also obtained as a gift sample from Jebsen & Jessen Ingredients (T) Ltd., Thailand. The following materials were purchased from commercial sources. Polyethylene glycol 4000 (Lot No. 1207483) and polyethylene glycol 6000 (Lot No. 0904102) were obtained from Ajax Finechem Pty., Ltd., New Zealand. Poloxamer 188 (Pluracare® F 68 G, Lot No. 99670636W0) was purchased from O-BASF The Chemical Company, Germany. Croscarmellose sodium (Ac-Di-Sol®, Lot No.TN11822911) was purchased from Onimax Co., Ltd., Thailand. Sodium lauryl sulfate (Lot No. 39577) was supplied by PT.Kao Indonesia Chemical, Indonesia.

Preparation

Preparation of different types of PEG formulations

Accurate amount of FN:CSD:PEG4000 or PEG6000 at the ratio of 1:1:1 were weighed and mixed for 10 minutes in a mortar and pestle. The obtained mixture was added into evaporating dish and immersed in water bath at around 80^{o}C. The mixture was melted and stirred for 10 minutes. After cooling at room temperature, the solidified mixture which was like granules were screened though a 40 mesh sieve and collected in amber plastic bag which kept in desiccator for dissolution testing.

Order of mixing of PEG in formulations

PEG4000 was selected to study the order of mixing at ratio of 1:1:1. Three formulations were prepared as follows: (I) (FN+PEG)+CSD formulation: FN and PEG4000 were firstly mixed in a mortar and pestle for 10 minutes. The obtained mixture was melted in evaporating dish which was kept in a water bath at around 80^{o}C until molten mass was obtained. Finally, CSD was added into molten mass and mixed with stirring for 5 minutes until adsorption was completed. After cooling at room temperature, the solidified mixture was sieved though a 40 mesh sieve. (II) (FN+CSD)+PEG: FN and CSD were prepared by mixing in mortar and pestle for 10 minutes. The mixture was added into evaporating dish and kept in a water bath for 10 minutes. Finally, PEG4000 was added, melted and stirred for another 5 minutes. After cooling at room temperature, the solidified mixture was sieved though a 40 mesh sieve. (III) FN+CSD+PEG: FN, CSD and PEG4000 were mixed in a mortar and pestle for 10 minutes and added into evaporating dish and melted in a water bath for 15 minutes. After cooling at room temperature, the solidified mixture was sieved though a 40 mesh sieve. The obtained granules were collected in amber plastic bag which kept in desiccator for dissolution testing.

Type and quantity of combined carrier in formulations

Formulations of (FN+CSD)+PEG at ratio of 1:1:0.1, 1:1:0.5, 1:1:1 and (FN+CSD)+P188 at ratio of 1:1:0.5, 1:1:0.75, 1:1:1 were prepared as described in order of mixing (II). The obtained granules were collected in amber plastic bag which kept in desiccator for testing of granule properties such as bulked density, tapped density, % compressibility, Hausner ratio and drug dissolution.

Preparation of capsule formulation

Granules of (FN+CSD)+P188 which gave high drug dissolved were selected to fill into capsules. 2%w/w of croscarmellose sodium was used as disintegrant in the capsule formulation compared with granule formulation which filling into capsules without adding a disintegrant. For 2%w/w of croscarmellose sodium formulation, granules and disintegrant were weighed and mixed by geometric dilution for 3 minutes. Accurate amount of granules (equivalent to 100 mg of fenofibrate) was weighed and filled into capsule size no. 1 by individual weighing. Capsules were tested for assay, disintegration time, and dissolution.

Evaluation

Bulk and tapped density studies

Granules were weighed and poured into graduated cylinder. The initial volume was noted, tapping was performed at a lift height of 2.5 cm until the constant volume was obtained and recorded. Bulk and tapped density were calculated in triplicate. The static powder flow was determined based on the Carr's index (Compressibility index, CI) and Hausner ratio, according to the following equation:

$$\% \text{ Compressibility Index, CI} = \left(\frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}}\right) \text{x } 100$$

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Dissolution studies, disintegration time and drug content

Dissolution

Drug dissolution was performed (an amount equivalent to 100 mg of FN was used, n=3 for granules, n=6 for capsules) using Type 2 (paddle method) dissolution apparatus (Distek®, Model No.2100B, USA) at 75 rpm. The dissolution medium was 900 mL water containing of 0.05 M SLS at 37 ± 0.5°C. Samples of 5 mL were withdrawn at 5, 10, 15, 20, 30, 40, 50, and 60 minutes, followed by addition of an equal volume of fresh medium in order to keep the constant volume of dissolution medium. Then, the samples were filtered and analyzed using UV-VIS spectrophotometer (Evolution 201® UV-VIS spectrophotometer, Thermo Fisher Scientific, China) at the wavelength of 291 nm.

Disintegration time

Six capsules were evaluated for disintegration time by USP type disintegrator (K.S.L. engineering Co., Ltd., Thailand) using distilled water (37±2°C) as a medium. The disintegration time was tested with disc. Disintegration time of each capsules was recorded when capsules were completely disintegrated and passed through sieve mesh of the apparatus.

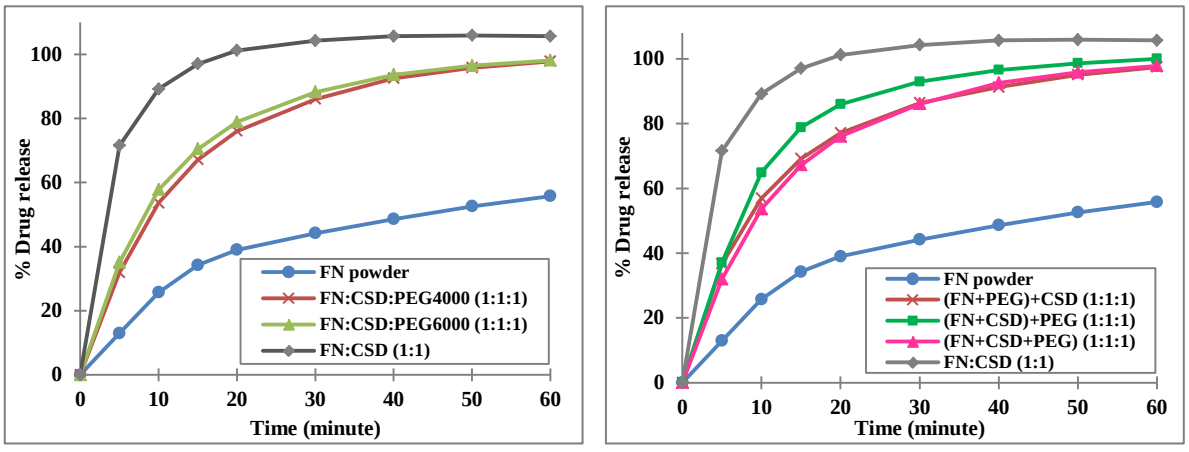
Drug content

Drug content of selected formulations were determined as follow. Accurately weight of granules equivalent to 100 mg FN was dissolved and swirled in methanol for 10 minutes. After adjustment of the volume with methanol, the obtained suspension was filtered (0.45 micron PVDF filter) and appropriately diluted in 0.05 M SLS aqueous solution. The final solution was analyzed by spectrophotometer at 291 nm using 0.05 M SLS aqueous solution as a blank and calculated as percent drug content. Drug content of granules was determined in triplicate.

RESULTS AND DISCUSSION

From previous study (Piyatassie et al., 2015), melting FN:CSD at 1:1 ratio could improve drug dissolution compared to FN powder. Due to high bulk density of powder mixture, PEG4000 or PEG6000 was used as combined carriers with drug and CSD at 1:1:1 ratio and prepared by melting method. It was found that an inclusion of PEG in the formulation would transform the bulk powder mixture to dense granules. Drug release from FN:CSD:PEG formulation was lower than FN:CSD powder at 1:1 ratio (Figure 1A) due to agglomeration of powder mixture which reduce surface area to contact with dissolution medium.

Due to PEG4000 and PEG 6000 provided similar result of dissolution profile, for ease of preparation only PEG4000 that had lower MW and melting point than PEG6000 was used to study the order of mixing during melting method (as described in MATERIALS AND METHODS) on drug release. It was found that (FN+CSD)+PEG order of mixing gave higher drug dissolution than the other two methods (Figure 1B). It might be due to drug molecule was adsorbed on CSD surface on the first stage of melting which reduced drug agglomeration. After adding PEG on the mixture, melted PEG might be coated or welded the adsorbed drug particles which were on CSD particles and produced granules of the mixture. When comparing to FN:CSD at 1:1 ratio which was in powder form, combined carrier formulation provided dense granules while lower drug dissolution.



(A) (B)

Figure 1. Dissolution profiles of FN powder**,** FN:CSD (1:1) and FN combined carrier formulations: (A) PEG type and (B) order of mixing during melting method.

PEG or P188 at various ratios were used as combined carriers with CSD to study the effect of type and amount of polymer on drug dissolution and granule density. Granule properties of various ratios of FN:CSD:PEG4000 or P188 were shown in Table 1. It was found that an increasing in the ratio of combined carrier would produce dense granules of agglomerated powder which improve granule density and flowability while drug dissolution was reduced. (Figure 2)

Table 1. Granule properties of FN:CSD, FN:CSD:PEG4000 and FN:CSD:P188.

Formulations	Ratio	Bulk Density (g/mL) Mean (SD)	Tapped Density (g/mL) Mean (SD)	Carr's Index Mean (SD)	Hausner Ratio Mean (SD)
FN:CSD	1:1	0.1920 (0.0049)	0.2213 (0.0079)	13.15 (4.70)	1.15 (0.06)
FN:CSD:PEG4000	1:1:0.1	0.3524 (0.0116)	0.4079 (0.0144)	13.54 (0.18)	1.16 (0.003)
	1:1:0.5	0.6338 (0.0025)	0.6338 (0.0025)	0.00 (0.00)	1.00 (0.00)
	1:1:1	0.5654 (0.0054)	0.6005 (0.0194)	4.93 (3.44)	1.06 (0.04)
FN:CSD:P188	1:1:0.5	0.5565 (0.0602)	0.5750 (0.0502)	1.78 (1.31)	1.04 (0.04)
	1:1:0.75	0.5296 (0.0283)	0.5647 (0.0457)	3.75 (3.30)	1.07 (0.07)
	1:1:1	0.5736 (0.0479)	0.5949 (0.0365)	3.10 (1.68)	1.04 (0.02)

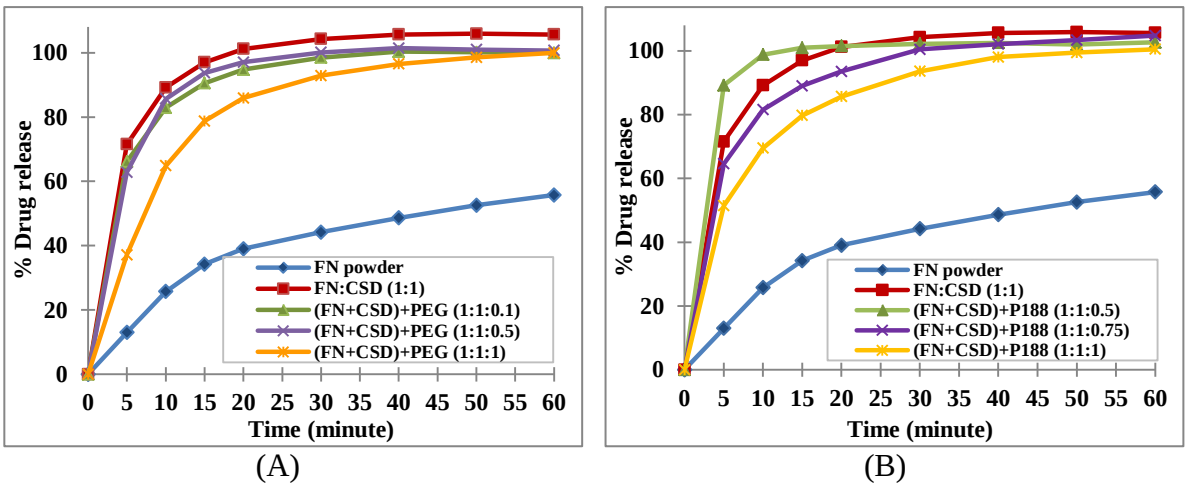
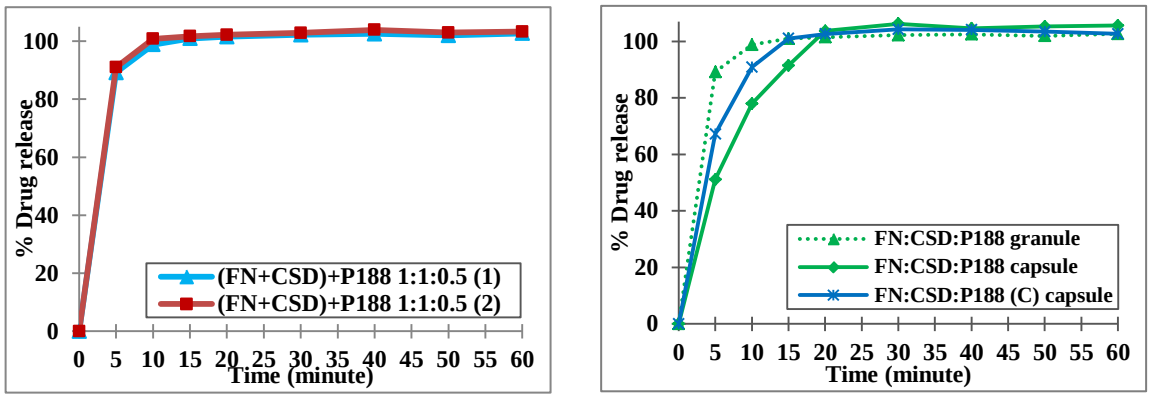


Figure 2. Dissolution profiles of FN powder, FN:CSD (1:1) and various ratio of combined carrier formulations: (A) PEG and (B) P188.

Formulation FN:CSD:P188 granules at 1:1:0.5 ratio provided the highest drug release at an initial stage (89% at 5 minutes and 99% at 10 minutes) compared to FN:CSD (1:1) powder and FN:CSD:PEG4000 granules (at the same ratio) therefore it was chosen for filling into capsules (Figure 2B). Formulation of FN:CSD:P188 at this ratio was prepared in

sufficient amount for capsule formulation and before subjection to filling into capsules products, granules was subjected for dissolution test as shown as line (2) with solid square symbol in Figure 3A (line (1) is the dissolution profile of previous smaller amount of preparation). It was found that this formulation could be reproducibly prepared because they provided similar drug dissolution profiles. Drug content of FN:CSD:P188 in capsules was 100.4% ± 0.55. Dissolution profiles of capsule product were performed in 0.05 M SLS aqueous solution in accordance with USP specification, it was found that FN:CSD:P188 capsule provided lower drug release than that of FN:CSD:P188 granule because of capsule shell disintegration effect. (2.48±0.15 minutes) Croscarmellose sodium at 2%w/w was included in the formulation (drug content was 99.6% ± 0.29) to reduce capsule disintegration time (1.69±0.05 minutes) therefore drug dissolution at first stage was increased as shown as FN:CSD:P188 (C) capsule in Figure 3B. According to USP35 NF30, FN capsules would pass dissolution requirement when drug dissolved of each capsules were not less than 85% in 30 minutes. From dissolution profiles, such formulations which composed of CSD and P188 gave more than 90% drug dissolved at 15 minutes and complied with the compendial requirement. (Table 2)



(A) (B)

Figure 3. Dissolution profiles of FN:CSD:P188 formulations: (A) granules and (B) capsules.

Table 2. % Drug release from granules and capsules.

Formulation	% Drug release	
	15 minutes	30 minutes
FN:CSD:P188 granules	100.9 (3.25)	102.2 (3.39)
FN:CSD:P188 capsules	91.4 (4.29)	106.3 (1.37)
FN:CSD:P188 (C) capsules	101.1 (2.74)	104.3 (1.76)

CONCLUSION

FN dissolution would be improved by surface deposition of drug on colloidal silicon dioxide using melting method. PEG4000 or P188 could be used as combined carrier to optimize drug dissolution and granule density. Increasing the ratio of combined carrier in the formulation increased granule density while decrease drug dissolution. At the same ratio, granules of P188 as a combined carrier provided higher drug dissolution and granule density than that of PEG4000. FN:CSD:P188 at 1:1:0.5 granules provided the highest drug release

and could be filled into capsule size no. 1 and with incorporation of croscarmellose sodium at 2%w/w in the formulation could reduce disintegration time and promote initial drug dissolution.

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