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Studies on the novel dosage form of fenofibric acid using various pharmaceutical excipients

조선대학교 대학원

식품의약학과

장 재 상

다양한 부형제를 활용한 fenofibric acid 의 새로운 제형 개발에 관한 연구

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이 논문을 약학 박사학위신청 논문으로 제출함

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Contents

LIST OF TABLES

LIST OF FIGURES

국문초록

Studies on the novel dosage form of fenofibric acid using various pharmaceutical excipients

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지도 교수 : 최 후 균

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초록: Fenofibric acid는 fibrate계열의 약물인 Fenofibrate의 활성 대사체로써 고지혈증 치료에 선택적으로 사용되는 약물이다. 고지혈증 치료제 제 1선택 약물인 statin계열의 의약품에 비해 낮은 시장점유율을 가지고 있으나 Total cholesterol, triglycerides 그리고 LDL 을 낮추는 효과로 인해 최근 다시 각광을 받는 의약품이다.

Fenofibrate를 주성분으로 하는 대표 의약품은 Lipidil Supra®로써 160mg 제형이다. 또한 나노크리스탈 기술을 적용한 Abbot社의 Tricor® 의 경우 48mg과 145mg 2가지가 있다. 국내의 경우 나노기술과 고체분산체 기술을 적용하여 110mg 까지 주성분을 절감시킨 제형까지 허가를 받았다.

Fenofibrate 의 가용화를 통한 개량신약의 개발은 물리적인 한계에 도달한 것으로 예상되는 가운데 2 가지의 새로운 제형이 시장에 선보였다. 첫째로 Fenofibrate에 Choline 염을 붙여 물에 freely soluble한 Abbot社의 Tilipix®

135mg 제형이다. 두 번째로 Fenofibrate의 활성 대사체인 Fenofibric acid를 주성분으로 한 한미社의 페노시드® 135mg 제형이다. 우리가 타겟으로 삼은 제형은 이 한미社의 페노시드® 제형이다.

한미社의 페노시드®은 활성 대사체로 의약품 허가를 받은 최초의 제형이며 산성약물인 Fenofibric acid에 Alkali agent를 사용하여 용해도를 향상시키고 Ethyl Cellulose 를 이용하여 서방화시킨 과립을 캡슐에 넣은 제품이다. 한미社의 특허 청구항 1번에선 Fenofibric acid를 중화시킬 수 있는 Alkali agent 의 양을 0.22~1 중량부로 한정하고 있으며, 청구항 4 번에서 다양한 Alkali agent를 특허로 걸어두고 있다. 따라서 본 연구의 목표는 한미의 특허를 회피하며 주성분의 함량을 감소시켜 개량신약으로써의 가능성을 높인 정제의 개발이다.

Fenofibric acid의 가용화에 최적인 알칼리화제의 선정을 위하여 여러 종류의 알칼리화제 수용액을 이용한 용해도 실험을 실시하였다. 한미社의 특허 내용을 회피하기 위해서는 알칼리화제의 종류와 그 중량비율이 매우 중요하다. 선행 특허를 회피하기 위하여 우선적으로 알칼리화제로써 Neusilin S1 과 S2 를 선택하였지만 이들에 의한 Fenofibric acid의 용해도는 상당히 낮은 편이었다. 즉 Neusilin S1 만 사용해서는 증류수에서 충분한 FA 의 용해도를 보이지 못하였기 때문에 용해도 시험에서 Fenofibric acid의 용해도 증진 효과가 가장 뛰어 났던 MgO를 추가 하였다. 따라서 MgO는 0.15 중량부를 사용하고 Neusilin S1은 1 중량부에 해당하는 양을 알칼리화제로 선택하였다.

Fenofibric acid를 포함한 속방정을 제조하기 위하여 습식 과립법을 사용하여 정제를 제조하였다. 정제를 제조하여 용출률을 확인하면서 formulation 을

변경하여 부형제 비율을 최적화 하였다. 정제의 가장 많은 비율을 차지하는 주약과 Neusilin S1의 비 친수성 때문에 정제가 잘 습윤 되지 않는 모습을 보였기 때문에 습윤을 도와주기 위해 계면활성제를 스크리닝하여 Soluplus®을 적용시켰다. 또한 정제가 초반에는 잘 붕해되나 내부 코어가 잘 붕해되지 않는 모습을 보여 선첨 과정에 붕해제를 충분히 넣어주도록 하였다. 또한 과립의 성상을 좋게 하기위해 Lactose monohydrate의 양을 늘려주었다. Formulation 3로 제조된 정제는 정제의 강도에 따라 붕해시간이 변동되는 결과를 보였는데 이는 추후 붕해제의 양을 좀 더 늘리는 방안을 생각해 볼 수 있다. 실제로 Lipidil Supra®에선 붕해제가 약 15% 근처로 사용되는데 이는 붕해시간을 일정하게 맞추기 위해 선택한 것으로 예상된다.

제조된 정제내의 알칼리화제가 위액내에서 중화 되는 것을 방지하기위하여 장용코팅을 진행하였다. 장용코팅을 한 fenofibric acid 정제는 대한약전 붕해시험법의 시험액 제 1 액에서 충분한 내산성을 보여주었고 이는 소장 상부에서부터 약물이 붕해되며 알칼리화제의 소실 없기 때문에 충분히 모든 FA를 용해시킬 것으로 예상된다. 붕해시간은 제 2액 조건에서 약 20분 내외로 측정되었다. 용출실험결과 1액에서는 약물의 용출이 거의 일어나지 않았고, 2 액 조건으로 변경 후 30 분 지점에서 80%의 용출률을 보였다. 약 한시간 후에는 95% 수준의 용출율을 보였다.

본 연구에서 Fenofibric acid 와 알칼리화제를 함유하고 습식과립법을 이용하여 제조된 정제는 난용성 약물인 Fenoficric acid의 투여에 있어 개선된 생체이용률을 나타내는 효과적인 경구용 의약품이 될 수 있을 것이다.

Keywords: Fenofibric acid, Fenofibrate, Alkali agent, bioavailability

1. Introduction

Fenofibrate, marketed as Tricor® is a drug in the fibrate family and its chemical structure is shown fig. 1. It is white or almost white crystalline powder, insoluble in water (<0.3 μg/ml), and slightly soluble in alcohol. It is stable under ordinary conditions with melting point of 79–82° and its partition coefficient (log P) is 4.6 between n-octanol/pH 6.8 buffer [1]. It is mainly used in hypertriglyceridaemia to reduce very low-density lipoprotein(VLDL), low-density lipoprotein(LDL) and total triglycerides as well as increasing high-density lipoprotein(HDL) levels in people at risk of cardiovascular disease [2].

Fenofibrate is essentially insoluble in aqueous solvents and can be considered as a prodrug. After ingestion, fenofibrate is rapidly and completely metabolized, essentially to its major active metabolite, fenofibric acid (FETA) by plasma and tissue esterases [3].

Fenofibrate, in its original commercialized form, is insoluble and is recommended to be ingested with food. To improve bioavailability, a micronized fenofibrate with reduced food effect was subsequently developed but still required that the drug be administrated with food [4]. New nanocrystal formulation of fenofibrate have been developed that further increase bioavailability and reduce the food effect [2]. As a result, the currently marketed formulation of fenofibrate, based on nanocrystal technology, can be taken with or without food for reducing elevated levels of VLDL, LDL and total triglycerides and increasing HDL in adult patients. Abbott laboratories continued filing NDA′s by changing the dose in order to obtain market exclusivity [5]. Interestingly, FETA , an active metabolite of fenofibrate, was found to be responsible for the therapeutic activity of fenofibrate formulations [6]. This fact was well explored by Abbott and developed choline-fenofibrate, a soluble and light-stable salt of FETA [7]. The salt form of fenofibrate was developed into a delayed release capsule and was approved by the FDA.

In the recent time, this delayed release formulation has become one of blockbuster product. [8].

Recently, FETA, a major active metabolite of fenofibrate, was developed as an alternative to fenofibrate for oral administration [9]. FETA is a white to almost white crystalline powder that is stable under ordinary conditions, and has a melting point of 179 – 183°C. Its empirical formula is $C_{17}H_{15}ClO_4$ and molecular weight 318.75. It is insoluble in water; its solubility increases with pH in buffered media (Table 2) [10]. Like other fibrates, it reduces both LDL and VLDL levels, as well as increasing HDL levels and reducing triglyceride levels and it is mainly absorbed in the gastrointestinal tract [11].

In this study, to develop a novel pharmaceutical formulation using FETA with improved solubility and dissolution rate, Alkalizers were screened for the selection of solubilizer of FETA.

We prepared FETA tablets using a wet granulation method and enteric coating. Prepared FETA tablets were compared with the marketed product Fenocid® that was prepared with a capsule formulations of FETA containing enteric coated granules.

The tablets were characterized for hardness, friability, dissolution profile and storage stability. In addition, a comparative dissolution study between Fenocid®, and FETA tablet was performed.

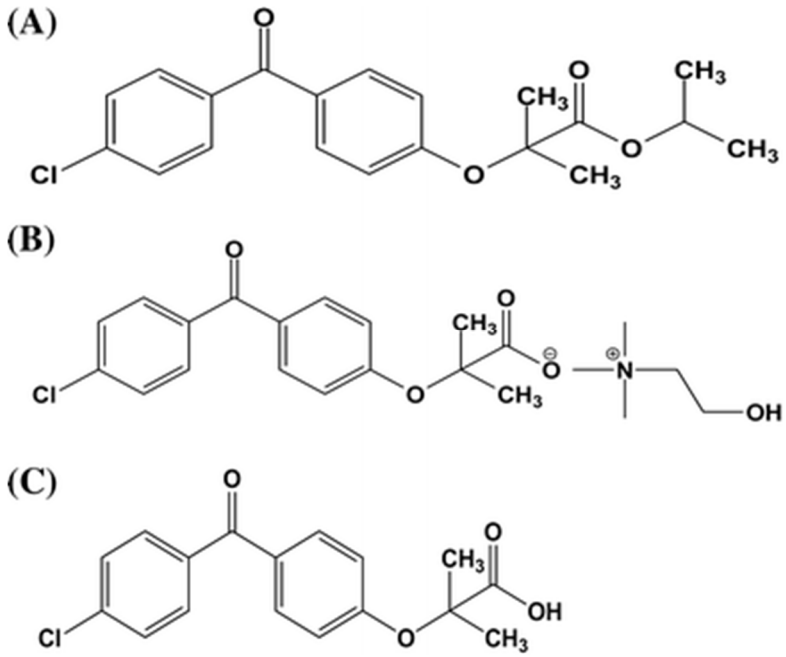

Figure 1 Chemical structure: a fenofibrate; b choline fenofibrate; c fenofibric acid

Classification	Contents
Micronized Fenofibrate	- micronization of crystalline form of Fenofibrate - Solubility : Less than 1 μg/mL - Representative Product : Lipidil Supra® (160mg)–Mylan N.V. / Tricor® (145mg)-Abbott
Fenofibric Acid	- Primary active metabolite of Fenofibrate - Solubility : Less than 165 μg/mL - Representative Product : Fenocid® (135mg)-Hanmi Pharm. Co. Ltd.
Choline Fenofibrate	- Water-soluble salt form of Fenofibric acid - Solubility : more than 1500 μg/mL (freely soluble) - Representative Product : Trilipix® (135mg)-Abbott

Table 1 Classification of Marketed Fibrate family

Molecular Weight	318.76
Solubility	0.165 mg/ml in water
	5 mg/ml in ethanol
Log P	4.86 ~ 5.28
Melting Point	179 ~ 183°C
pKa	2.9

Table 2 Physicochemical property of FETA

2. Materials and methods

2.1. Materials

Fenofibric acid was purchased from Alembic Pharmaceuticals Ltd (Gujarat, India). Neusilin was purchased from Fuji chemical industries co. ltd (Toyama, Japan). Magnesium Oxide (MgO) and other alkalizers were purchased from Sigma-Aldrich Co. (St. Louis, MO). Soluplus® (polyethylene glycol, polyvinyl acetate and polyvinylcaprolactame-based graft copolymer) was obtained from BASF (Ludwigshafen, Germany). All other chemicals were of reagent grade and used without further purification.

2.2. Methods

2.2.1. Determination of pH value

The FETA and Neusilin S1, S2 were added in 100 ml volumetric flasks containing 100 ml of water, separately. The volumetric flasks were vortexed for 1 min and shaken in a 25°C waterbath for 3 hours. The pH value was measured using SevenEasy S20-KS pH meter (Mettler Toledo, USA) and Inlab®SciencePro pH electrode (Mettler Toledo, USA).

2.2.2. Alkalizer ratio screening test

Predetermined amount of FETA and the mixture of FETA and various alkalizers were added in 100 ml volumetric flasks containing 100 ml of water. The mixture of FETA and alkalizer was prepared by simply mixing the compounds at a predetermined ratio (Table3, 4). The volumetric flasks were vortexed for 1 min and shaken in a 37°C waterbath for 2.5 hours. The samples were filtered through syringe filter with 0.45 um pore size (Whatman™, UK) and diluted with ethanol at 1:1 ratio. The solubility of FETA in various alkalizer solutions were measured by HPLC.

	Fenofibric acid (mg)	Alkalizing Agent			
		CaCO3	MgCO3	Meglumine	MgO
Y4-1	200	30			
Y4-2	200	40			
Y5-1	200		30		
Y5-2	200		40		
Y6-1	200			30	
Y6-2	200			40	
Y7-1	200				30
Y7-2	200				40

Table 3 Ratio of FETA and alkalizers for screening of alkalizers

	Fenofibric acid (mg)	Alkalizing Agent		
		Neusilin S1	Neusilin S2	MgO
Y1-1	200	10		
Y1-2	200	20		
Y1-3	200	30		
Y1-4	200	40		
Y1-5	200	80		
Y1-6	200	200		
Y2-1	200		10	
Y2-2	200		20	
Y2-3	200		30	
Y2-4	200		40	
Y2-5	200		80	
Y2-6	200		200	
Y3-1	200			10
Y3-2	200			20
Y3-3	200			30
Y3-4	200			40
Y3-5	200			80
Y3-6	200			200

Table 4 Ratio of FETA and alkalizers for screening of alkalizers

2.2.3. Surfactant screening study

50mg of FETA and surfactant were added in 50 ml volumetric flasks containing 50 ml of water. The volumetric flasks were vortexed for 1 min and shaken in a 25°C waterbath for 3 days. The samples were filtered through syringe filter with 0.45 um pore size (Whatman™, UK) and diluted with ethanol at 1:1 ratio. The solubility of FETA in various surfactant solutions was measured by HPLC.

2.2.4. Milling and determination of particle size distribution

The raw material of FETA was size reduced by Jet milling and hand milling. The jet milling was carried out using a jet mill (AFG 100, Hosokawa, Augsburg, Germany). FETA was jet milled at the pressures of Inlet 6bar, Outlet 4bar for 30 minutes.3 and 5 bars.

The particle size distribution of FETA was measured by laser diffraction method using HELOS™ (Sympatec, Germany).

2.2.5. Preparation of FETA tablet by wet granulation method

FETA tablets were prepared by wet granulation method (Fig. 2) and content of formulation is summarized in Table 5. The morphology of the FETA tablet was white and cylindrical shaped. MgO and Soluplus® were used as solubilizing agents, and PVP and croscarmellose sodium (ac-di-sol®) were used as the binder and disintegrant, respectively. After Soluplus® and PVP were dissolved in 95%, the resultant liquid was mixed with API and excipients and kneaded manually. Then, it was passed through a 20-mesh sieve to prepare the granules and dried at 40°C until loss on drying (LOD) reached less than 2%. After the dried granules were screened with a 25-mesh sieve, they were mixed with croscarmellose sodium and magnesium stearate and formed into tablets using a rotary tableting machine. The hardness of FETA tablet was adjusted to 6~7 kgf/cm^2

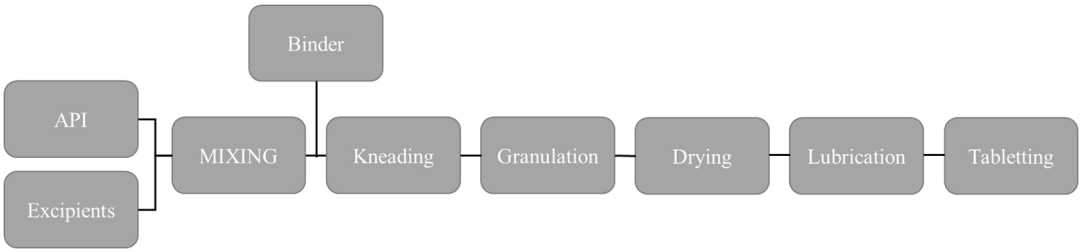

Figure 2 Stages of wet granulation process

Component	Function	F1	F2	F3
Fenofibric acid	API	135	135	135
Neusilin S1	Filler	135	135	135
MgO	Alkalizing agent	20.3	20.3	20.3
Lactose monohydrate	Filler	20.3	20.3	40.5
PVP K30	Binder	33.3	33.3	33.3
Soluplus®	Solubilizer	0	3.4	3.4
Ac-di-sol®	Disintegrant	7.1	7.1	40.5
Magnesium stearate	Lubricant	2	2	3.4
Total tablet weight		353.0	356.4	411.4

Table 5 Formulation of Fenofibric acid tablet (mg per tablet)

2.2.6. Hardness

Tablet hardness was defined as the compression force immediately before the crushing the tablet in the diagonal axis with a compressive force and was measured using an Erweka TBH28 (Heusenstamm, Germany) (n = 5).

2.2.7. Friability test

The total weight of 20 tablets were measured before and after friability test in the drum of a tablet friability test apparatus using PHARMA TEST type PTFR-A (Hainburg, Germany)

2.2.8. Enteric coating of FETA tablets

Eudragit® L100-55 (Evonik, Germany) was added in water and Stirred for 5 min. Then slowly 1N NaOH was added to the above solution under constant stirring for 30min. Finally, this solution was filtered through 100 mesh sieve.

Compressed tablets were coated with inlet temperature 45 °C and exhaust temperature 30 °C. Pan speed was kept 2.3 rpm. Drying of the tablets was done for 15 min.

2.2.9. In vitro dissolution test

To investigate the release rate of FETA tablets, in vitro drug dissolution study was conducted, employing USP-II paddle method and 900 ml of deionized water (DIW) for 60 min.

In-vitro dissolution studies of enteric coated tablets were performed using dissolution test apparatus USP II paddle type. The dissolution media was consisted of 900 ml of 0.1 N HCl for first 2 hours followed by pH 6.8 phosphate buffer for 6 h. They were kept stirring at 75 rpm in 37 ºC. At predetermined time interval, 5 mL of samples were withdrawn and refilled with fresh media. Samples were filtered through 0.45 um nylon membrane syringe filter and analyzed by HPLC.

2.2.10. HPLC analysis

Chromatographic analysis were performed, Hitachi HPLC system consisting of a pump (Model L-2130), an auto-sampler (Model L-2130), and a UV-VIS spectro-photometric detector (Model L-2400). The C18 reverse phase column 4.6 x 250mm (Phenomenex®, USA) was used at 35ºC, and the mobile phase consisted of a 75:25 (% v/v) mixture of acetonitrile and aqueous solution of phosphoric acid (pH 2). The flow rate was 1.0 mL/min, and the signal was detected at 286 nm.

2.2.11. Stability studies

Accelerated stability study and Long-term stability study of the FETA tablets were carried out for 6 month period. FETA tablets were stored protected from light at 40±2 / 75±5% relative humidity for accelerated stability study and 25±2 / 60±5% relative humidity for long-term stability study. At the predetermined time interval, 3 and 6 month period, FETA tablets were evaluated by HPLC.

3. Results and conclusion

3.1. Milling and determination of particle size distribution of FETA

Raw FETA supplied as a raw material had very nonuniform particle size, and there was a necessity to ensure particle uniformity. Fig. 3 is a particle distribution diagram of Raw FETA. The average particle diameter was 46.46 um, but large particles larger than 100 um were present. It seems that the dissolution rate decreases due to such large particles.

Jet-milled FETA and Hand-milled FETA confirmed that the value of D90 became very small and large particles disappeared (fig. 4). In addition, the dissolution results in fig. 5 also showed higher dissolution rate than Raw FETA. When compared with Jet-milled FA, the hand-milled FA did not differ greatly between its particle size distribution and dissolution profile, so in subsequent experiments, all hand-milled FETA was used (Table 6).

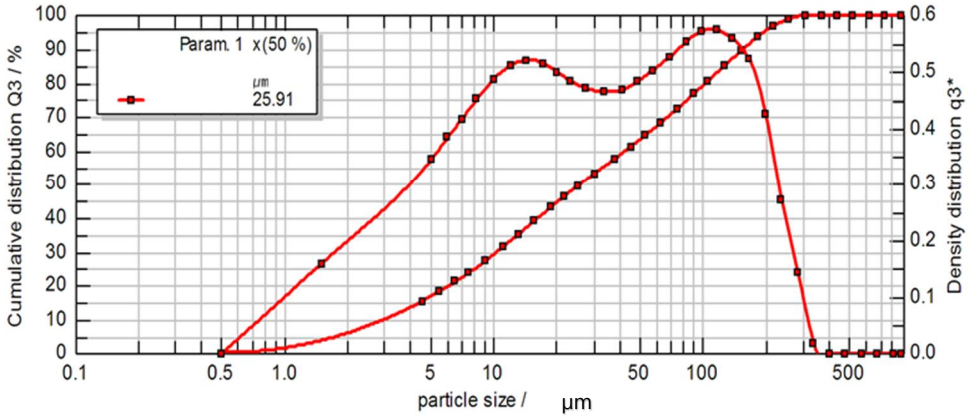

Figure 3 Particle size distribution of raw FETA

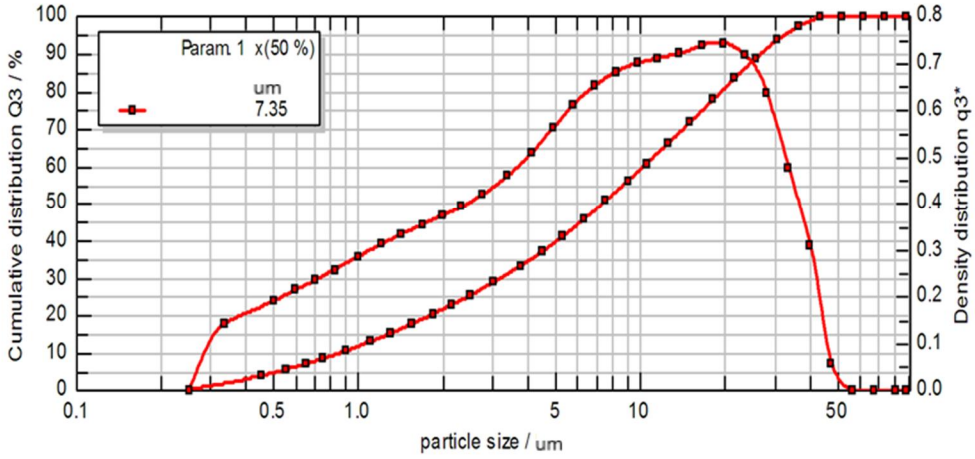

Figure 4 Particle size distribution of jet-milled FETA

	D_{10}	D_{50}	D_{90}	VMD*
Raw FETA	3.05 ± 0.23 μm	22.88 ± 3.80 μm	128.04 ± 25.33 μm	46.46 μm
Jet-milled FETA	0.81 ± 0.11 μm	6.49 ± 1.52 μm	24.04 ± 4.03 μm	9.71 μm
Hand-milled FETA	1.20 ± 0.13 μm	8.92 ± 0.89 μm	29.29 ± 0.93 μm	12.38 μm

Table 6 Particle size distribution parameter of raw, jet-milled and hand-milled FETA

(VMD* = Volume mean diameter)

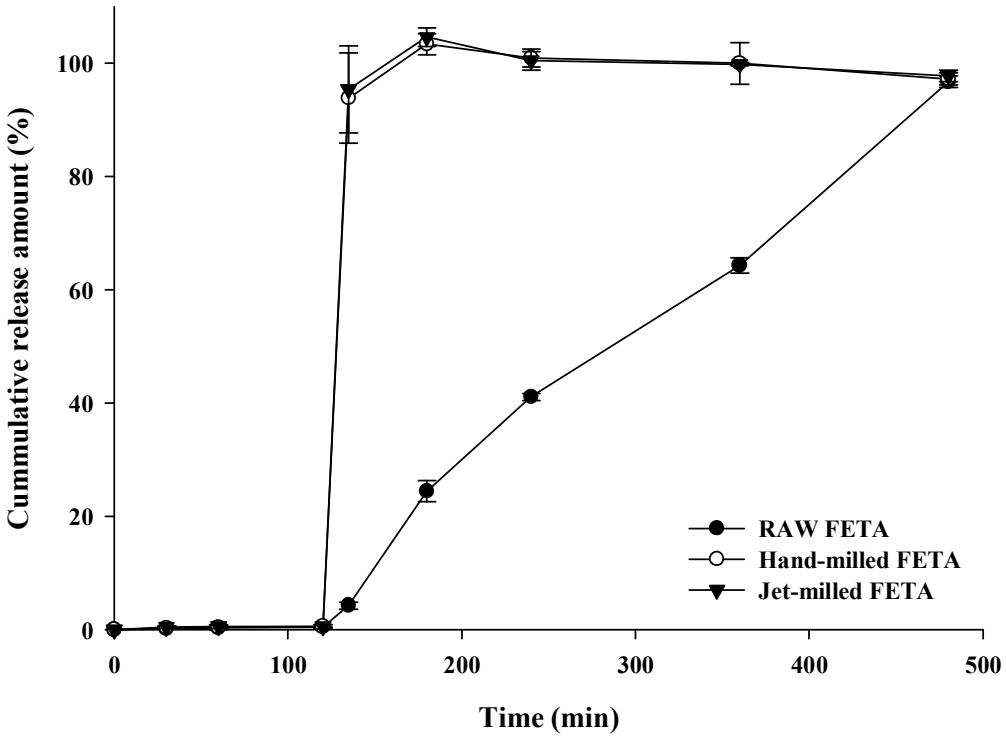

Figure 5 Dissolution profiles of raw, jet-milled and hand-milled FETA

3.2. Determination of pH value

According to the results of pH tests, FETA was weakly acidic and the pH difference between Neusilin S1 and S2 was not insignificant, but Neusilin S1 with a higher pH value was selected as a filler for FETA tablets (Table 7).

	FETA	Neusilin S1	Neusilin S2
pH value	4.32±0.16	8.85±0.24	8.45±0.15

Table 7 pH of FETA and Neusilin solution

3.3. Alkali agent ratio screening test

According to solubility study result, it was evident that FETA was insoluble in DIW (29.75 ± 2.23 ug/ml) and Neusilin S1 and S2 increased the solubility of FETA by about 5 to 6 times, but it was insufficient to solubilize all amount of added FETA (fig. 7).

Since Neusilin S1 and S2 did not significantly improve the solubility of FETA, it was necessary to add akalizer to FETA tablet. Four alkalizers which are $CaCO_3$, $MgCO_3$, Meglumine, and MgO, were screened to evaluate their effects on the FETA solubility in DIW as shown in fig. 7. Among four alkalizers, MgO exhibited a good solubility enhancement of FETA in DIW (fig. 8).

MgO was further investigated to optimize the alkalizer content of FETA tablet. At the ratio of FETA and MgO was 0.15 or more, it was possible to solubilize added amount of FETA (fig. 9).

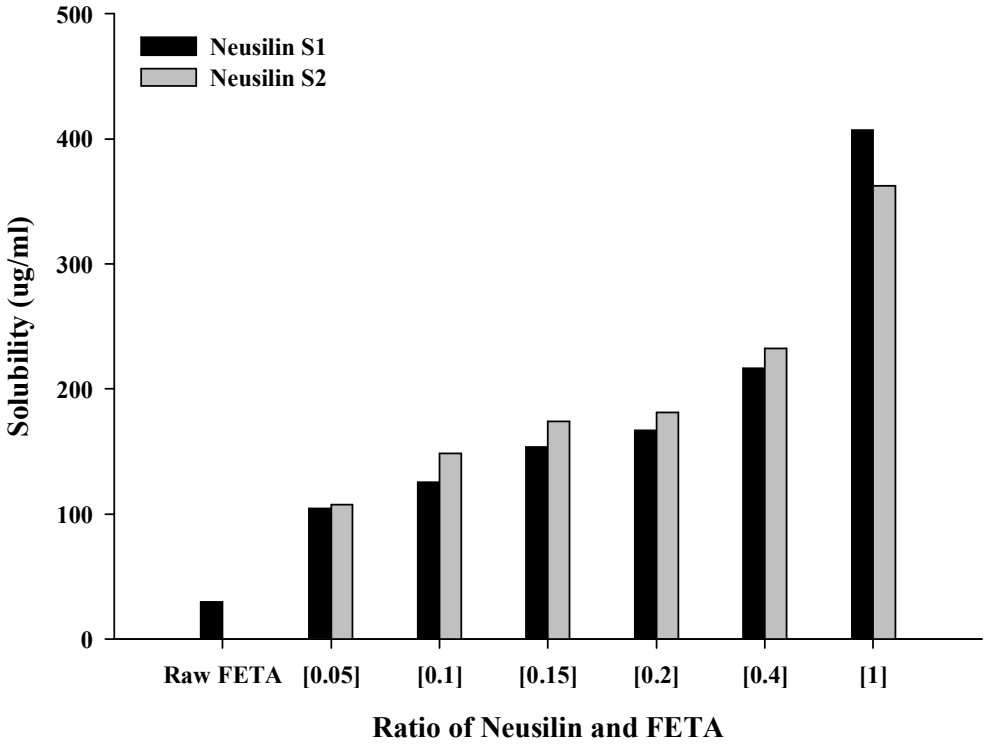

Figure 6 Solubility of FETA by increasing ratio of Neusilin S1 and S2

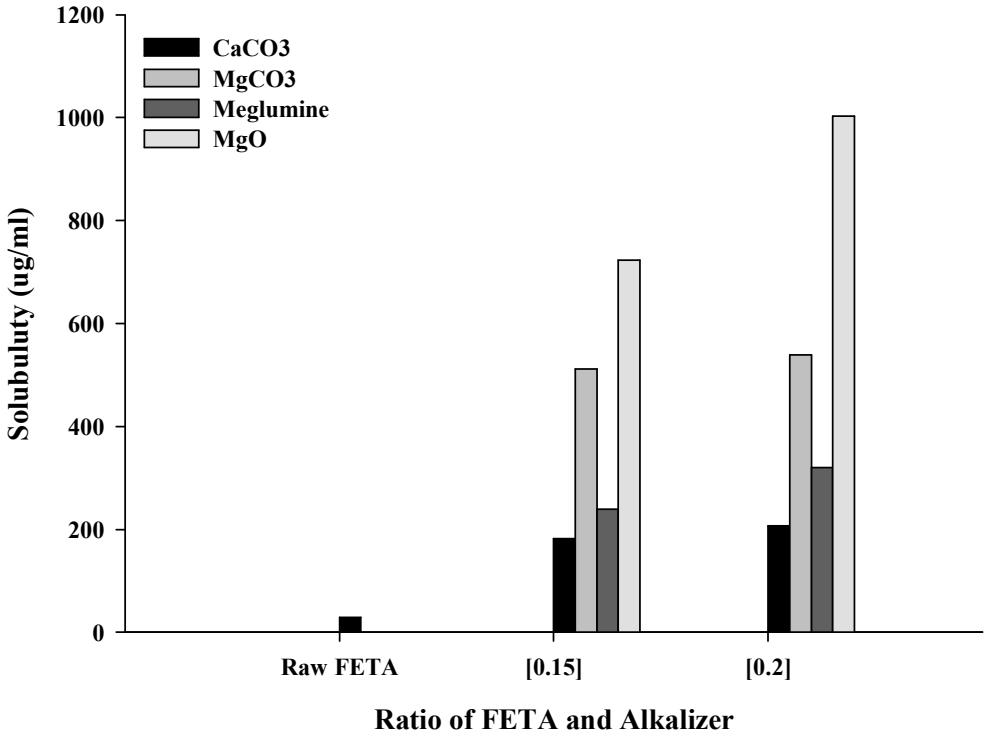

Figure 7 Solubility of FETA in various alkalizer

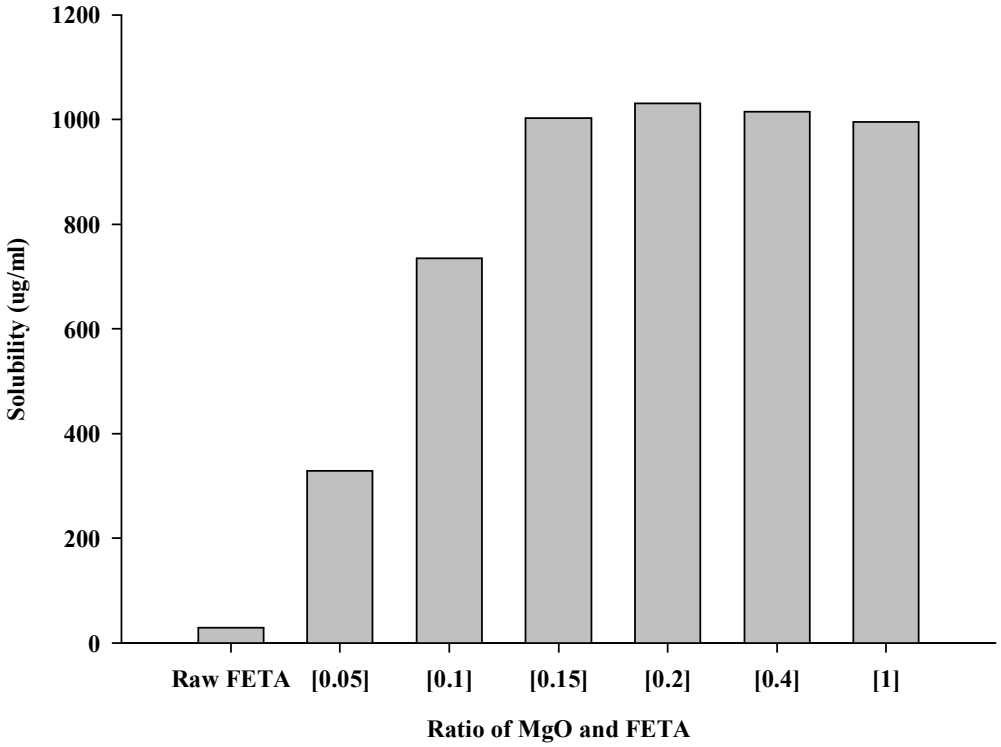

Figure 8 Solubility of FETA by increasing ratio of MgO

3.4. Surfactant screening study

To improve a wettability of FETA and Neusilin S1, hydrophobic components, surfactant screening was carried out. As a result, Soluplus® was most effective on improvement of FETA solubility (fig. 10).

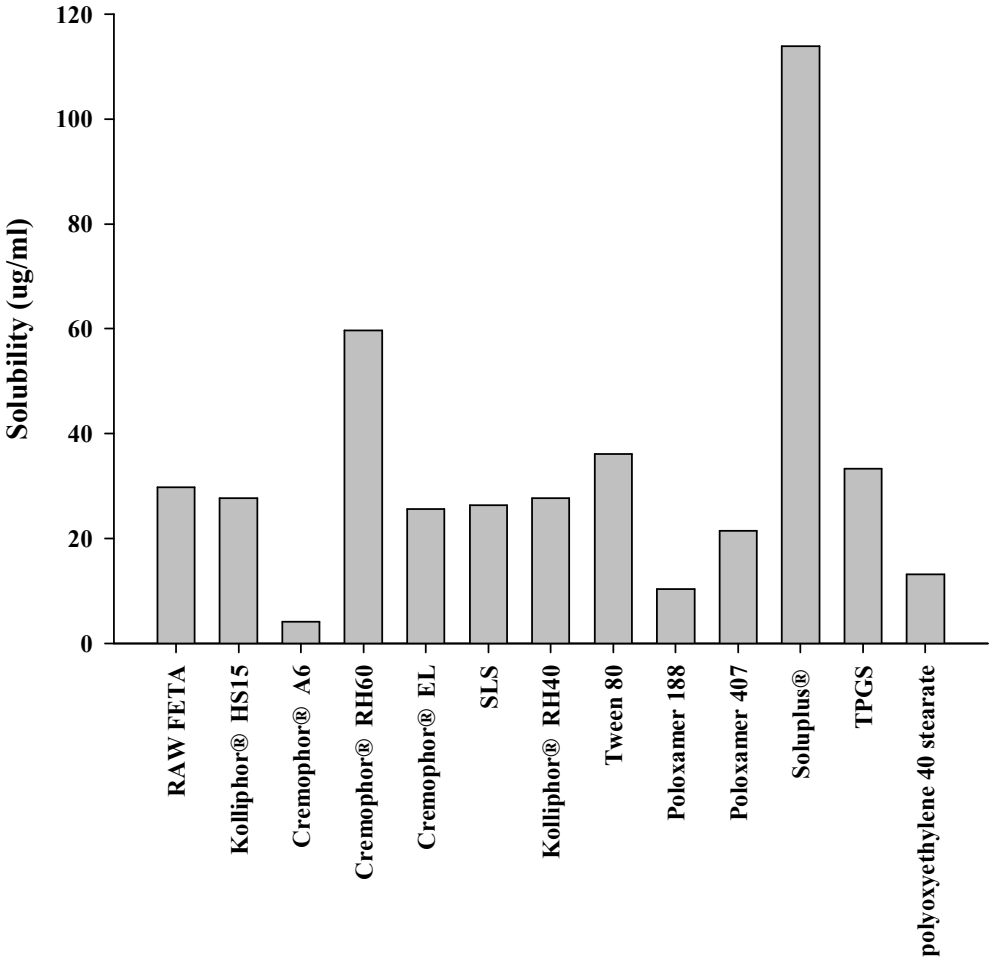

Figure 9 Surfactant screening study

3.5. Evaluation of uncoated FETA tablets

FETA tablets were prepared by wet granulation method by formulation of Table 5. The morphology of the FETA tablet was white and cylindrical shaped. The hardness and friability of the FETA tablets are summarized in Table 8. The FETA tablet was sufficiently hard and friability was less than 0.1%.

	F1	F2	F3
Weight(mg)	**356.8±12.3**	**358.9±8.8**	**410.7±15.7**
Thickness (mm)	**5.6**	**5.61**	**6.31**
Hardness (kg/cm^2)	**6.11**	**5.32**	**7.18**
Disintegration Time (min)	**More than 20**	**More than 20**	**15**
Friability	**less than 0.1%**	**less than 0.1%**	**less than 0.1%**

Table 8 Evaluation of FETA tablet

Figure 10 Morphology of FETA tablet

3.6. In vitro dissolution profile study

3.6.1. In vitro dissolution profile study of uncoated FETA tablets

The in vitro drug dissolution profiles of uncoated FETA tablets were investigated using USP dissolution test apparatus type-II (Paddle type) in 900 ml of pH 6.8 phosphate buffer as the dissolution medium for 60 min at 37 ± 0.5 °C temperature and rotated at 75 rpm. As shown in fig. 12, there was a significant difference among F1, F2, and F3. In case of F1 tablet, disintegration was proceeded in the early stage of the dissolution test, but disintegration was uncompleted due to lack of wettability of F1 tablet. Dissolution rate of F2 tablet which manufactured by adding Soluplus® to the binding solution to improve wettability of F1 tablet was slightly increased compared to F1 tablet. But, disintegration was also uncompleted until dissolution test was terminated. F3 tablet was prepared to decrease the disintegration time of F2 tablet by adding 10% of disintegrant. F3 tablet showed about 98.65 % of release amount at 60 minutes after dissolution test. It showed highest release rate when compared to other batches as in the batch F1, F2.

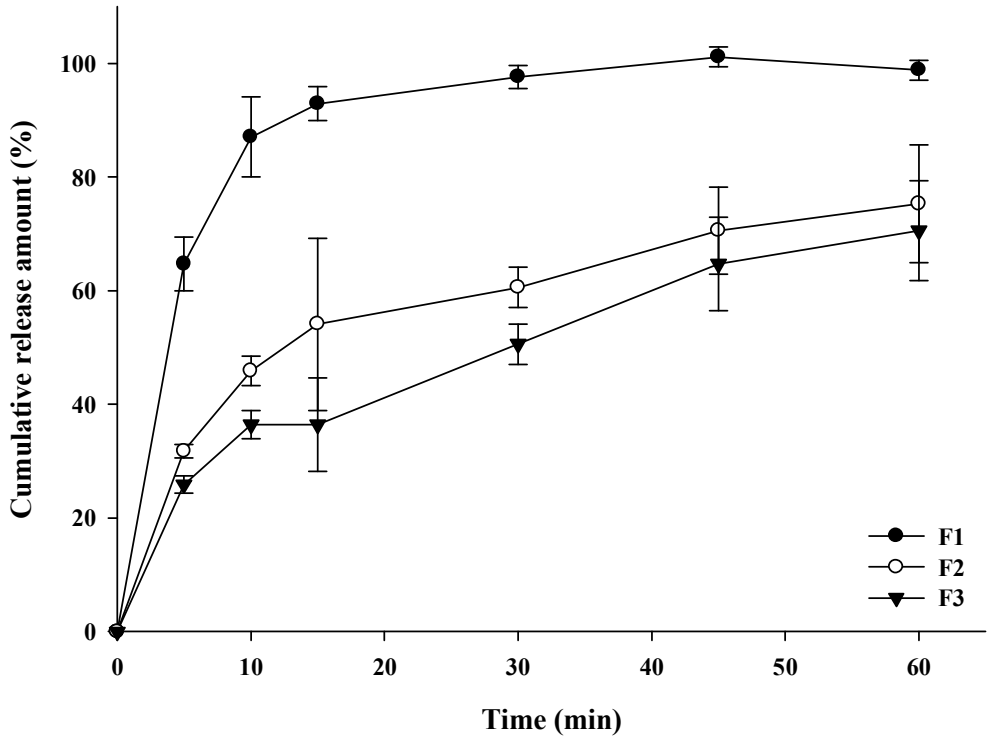

Figure 11 Dissolution profiles of F1, F2, and F3 in pH 6.8 phosphate buffer at 75 rpm, 37°C

3.6.2. In vitro dissolution test of pre marketed enteric coated granule with capsule (Fenocid®, Hanmi Pharm.Co., Ltd.)

In former patented literature, Fenocid® capsule, a delayed release dosage form with insoluble ethylcellulose coated granules, showed low variability of dissolution profile for 6 hours of dissolution test. But, actual test results exhibited high variable dissolution profile in pH 1.2 and pH 6.8 buffer. It seemed to be due to withdrawal of the alkalizer which was withdrawn from the granule without sufficient coating thickness to resist the penetration of buffer (fig. 13, 14, 15). It seemed to be due to coating thickness of the granule is insufficient to prevent alkalizer withdrawing caused by buffer penetration.

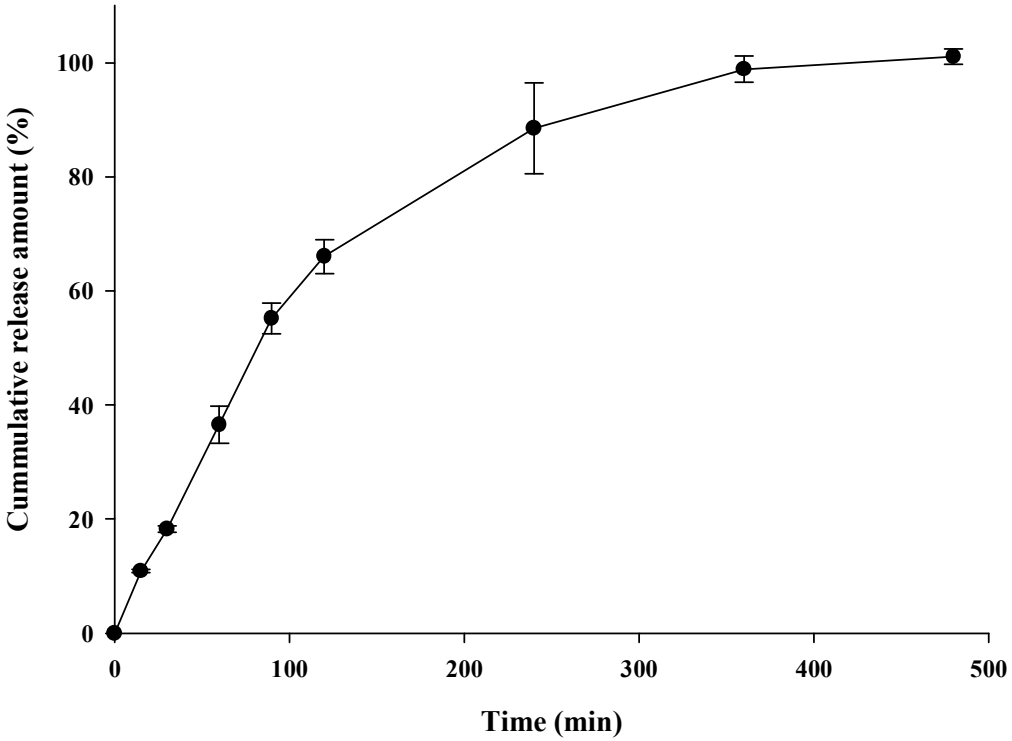

Figure 12 Dissolution profile of Fenocid® in DIW at 75 rpm, 37°C

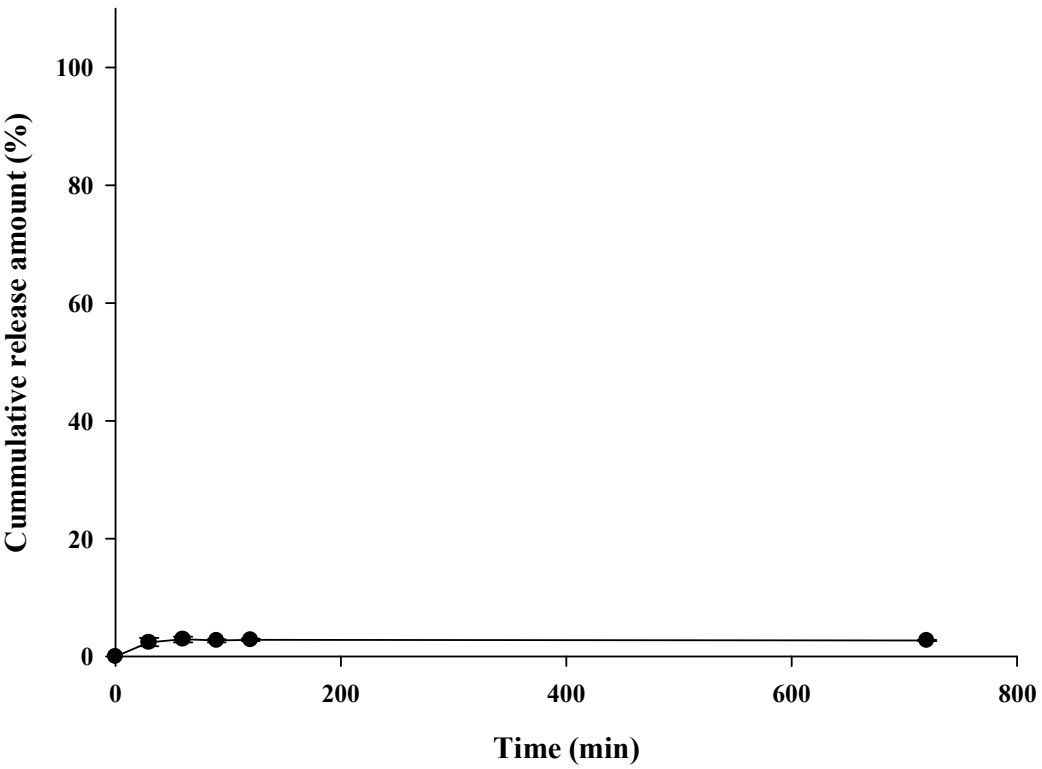

Figure 13 Dissolution profile of Fenocid® in pH 1.2 buffer at 75 rpm, 37°C

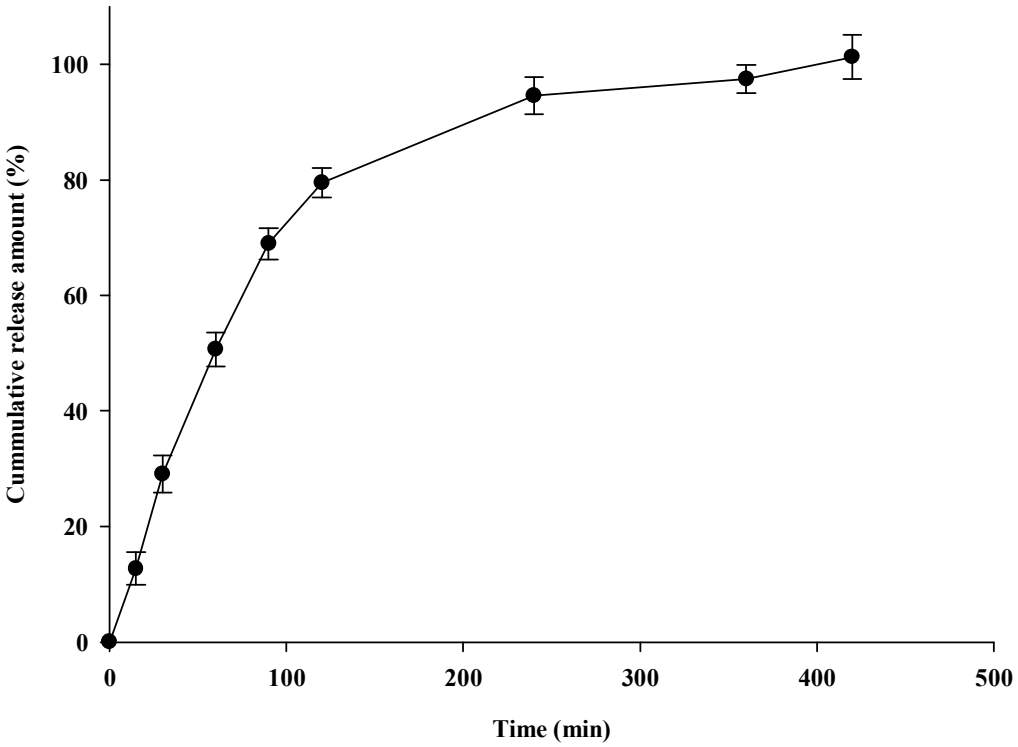

Figure 14 Dissolution profile of Fenocid® in pH 6.8 buffer at 75 rpm, 37°C

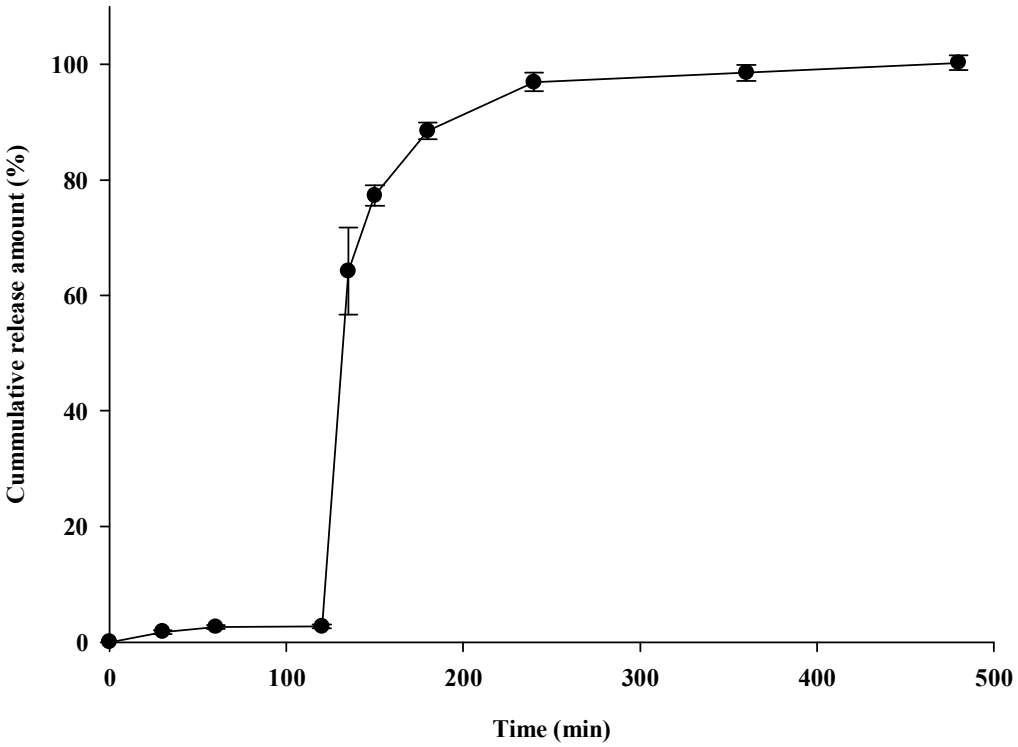

Figure 15 Dissolution profile of Fenocid® in pH 1.2 and 6.8 buffer

3.6.3. Dissolution of enteric coated FETA tablet

F3 tablet was coated with 20 mg, 30 mg and 40 mg of Eugragit L100-55. As a result, Tablets coated with 20 mg and 30 mg of Eugragit L100-55 were collapsed under pH 1.2 condition due to its insufficient acid tolerance (fig. 17).

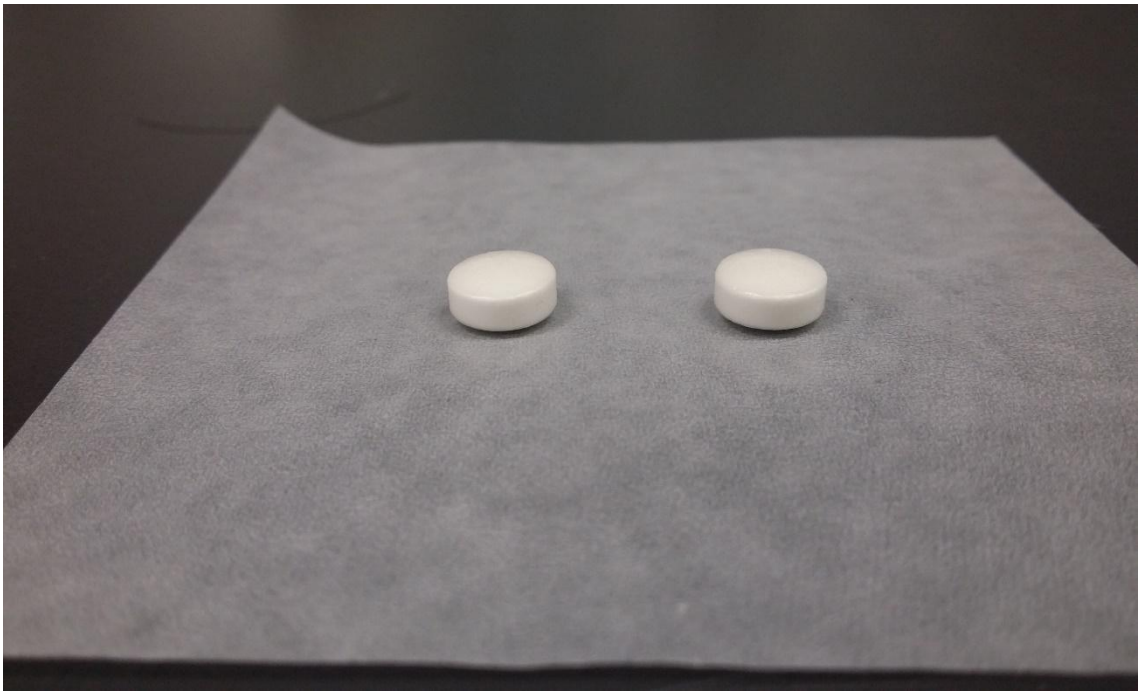

Figure 16 Morphology of FETA tablet enteric coated with 40mg of Eudragit L100-55

Enteric coated FETA tablets were showed sufficient acid tolerance since it did not collapsed during disintegration test in pH 1.2 buffer for 2 hours. Therefore it is expected that disappearance of akalizer due to collapse of enteric coating film can be prevented and it could be have effect on enhanced dissolution of FETA in the upper part of the small intestine.

Disintegration time was measured about 20 minutes in pH 6.8 phosphate buffer (table 9). As a result of the dissolution test, no significant change in tablet appearance at pH 1.2 buffer was observed, and after changing the dissolution medium to pH 6.8 buffer, at 30 minutes sampling point, the percentage of cumulative release amount of FETA was about 80% and about 95% at 60 minutes (fig. 18).

	No.1	No.2	No.3	No.4	Average
Disintegration Time (min)	22	25	18	19	21

Table 9 Disintegration time of FETA tablets in pH 6.8 phosphate buffer

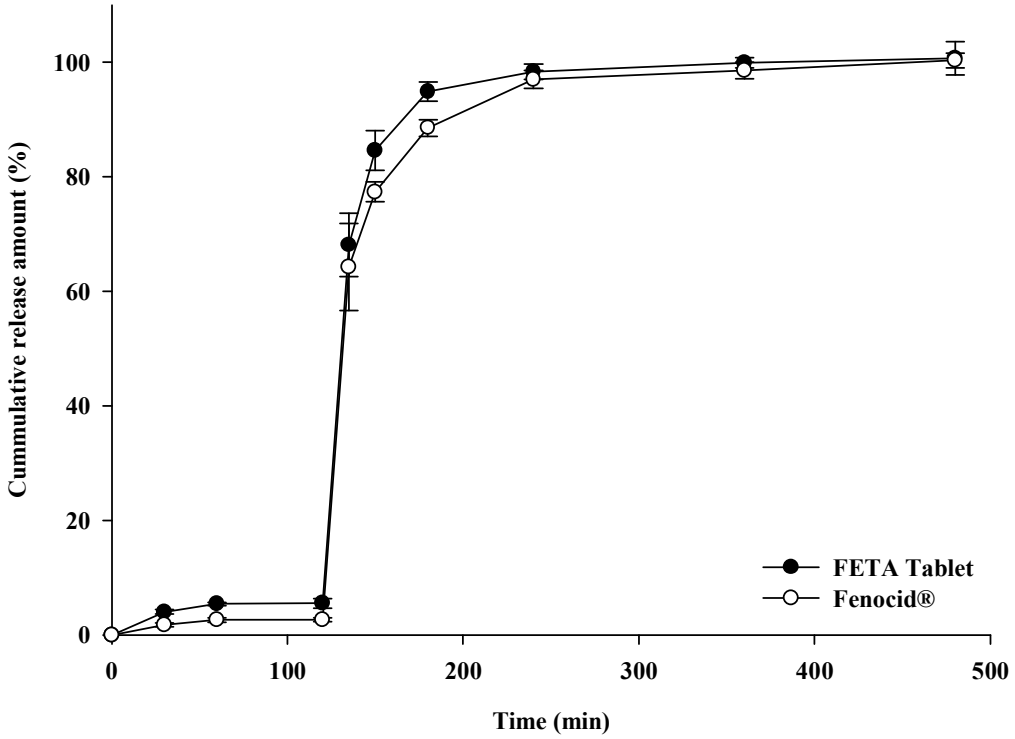

Figure 17 Comparative dissolution study between Enteric coated FETA tablet and Fenocid®

3.6.4. Stability studies

Accelerated stability study and Long-term stability study of the FETA tablets were carried out for 6 month period. FETA tablets were stored protected from light at 40±2 / 75±5 for accelerated stability study and 25±2 / 60±5% relative humidity for long-term stability study. At the predetermined time intervals of 3 and 6 months, period, dissolution, drug content and related substances of the FETA tablets were evaluated.

There were no significant changes were observed in related substances, drug content, and in vitro drug release in optimized formulation after storage at Long-term stability and at accelerated conditions, for 6 months (Table 10).

				Accelerated (month)		Long-term(month)	
		Acceptance criteria	Initial	3	6	3	6
Related substances	Impurity	NMT*0.2%	0.01	0.01	0.01	0.01	0.01
	Impurity	NMT 0.2%	0.03	0.03	0.03	0.03	0.04
	Unknown impurity	NMT 0.2%	0.00	0.00	0.00	0.00	0.00
	Total impurities	NMT 1.0%	0.04	0.04	0.04	0.04	0.05
Dissolution		NMT 10% acidic condition at 120min	0.00	0.00	0.00	0.00	0.00
		NLT** 75% basic condition at 30min	81.98	91.51	78.73	77.68	85.05
Drug content		95.0~ 105.5% of labeled content	98.59	97.87	98.76	99.23	98.38

Table 10 Stability of FETA tablet at accelerated and long-term stability test condition

4. Conclusion

To prepare immediate release tablets containing Fenofibric acid by wet granulation method, the formulation was refined and optimized while confirming the dissolution profile of FETA tablet. Because FETA tablet was not disintegrated due to the hydrophobic nature if Neusilin S1 and FETA, we screened the surfactant and Soluplus® was added to formulation to increase the wettability of FETA tablet. Also, Since FETA tablet did not disintegrated during the dissolution test, 10% of disintegrant was added.

Tablet manufactured by F3 showed the result that the disintegration time was fluctuated by the strength of tablet. Therefore, it seems necessary to study to reduce this variation of disintegration time in further study.

Fenocid® capsule which has ethyl cellulose coated sustained release granule, disintegration has started in pH 1.2 buffer. Therefore it seems that the alkalizer will dissolve out during gastric retention time and lose its function due to strong acid condition of gastric juice. The amount of the alkalizer dissolving out in pH 1.2 buffer is estimated to be about 20%. Of course we cannot see that the In vivo behavior of Fenocid® is the same as the in vitro dissolution profile, but it can be anticipated that the disappearance of the alkalizer in dosage form will affect bioavailability obviously. On the other hand, FETA tablet has conventional manufacturing process, uses less alkalizer compared with Fenocid® and enteric coating of that could be prevent losing of alkalizer in stomach. Therefore FETA tablet will be a dosage form that can maximize bioavailability of fenofibric acid.

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