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The Effect of Surfactants on Dissolution Profile of Poorly Water Soluble Acidic Drugs

朝鮮大學校 大學院

藥 學 科

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난용성 산성약물의 용출에 미치는 계면활성제의 영향

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(국문 초록)

난용성 산성약물의 용출에 미치는 계면활성제의 영향

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정제로부터 약물의 용출시험은 정제의 품질관리 단계에서 새로운 제형의 개발의 단계에서 제품의 평가함에 있어서 매우 중요한 인자이다. 하지만 난용성 약물의 경우 약물의 용출시험을 시행하는데 있어서 많은 어려움이 존재한다. 용해도가 매우 낮기 때문에 용출시험을 시행하면 모두 낮은 정도의 용출률을 나타내어서 배치간의 제품간의 비교를 하기가 어렵다. 이런 문제를 해결하기 위해서 과량의 용출액을 사용하는 방법, 용출액에 유기용매를 첨가하여 약물의 용해도를 높이는 방법, 계면활성제를 넣는 방법 등 여러 가지 시도가 연구되고 있다. 최근 들어 위 장관 환경과 가장 유사한 계면활성제를 이용하여 난용성 약물의 용출 시험을 하는 방법에 연구가 집중이 되고 있다.

이번 실험에서는 난용성 약물 중에서 산성약물인 메페남산, 니메수리드, 이부프로펜을 선택하여 계면활성제의 종류가 약물의 용출률 및 용해도에 어떠한 영향을 미치는지 살펴보았다. 양이온성 계면활성제로 cetyltrimethylammonium bromide (CTAB), 음이온성 계면활성제로 sodium lauryl sulfate (SLS), 비이온성 계면활성제로 polysorbate80 (PSB80)을 사용하였다. 이 계면활성제를 pH 1.2 또는 6.8 용출액에 1% 농도로 용해시키고 이 용출액에 산성약물의 대조약을 사용하여 용출시험을 시행하였으며 용해도 시험을 하여서 용출시험과의

상관 관계를 연구하였다. Noyes-whitney 식과 같이 각 약물의 용해도에 비례하여 약물의 용출 양상이 나타남을 확인할 수 있었다. 그리고 난용성 산성약물의 용출률 및 용해도를 가장 효과적으로 향상시켜주는 계면활성제는 양이온성 계면활성제인 CTAB임을 확인하였다.

이런 현상은 산성약물이 해리되어서 음이온성을 띄게 되어 양이온성인 계면활성제와 상호작용을 하기 때문인 것으로 보인다. 계면활성제와 약물이 용해되어있는 용액의 UV-spectrum을 비교하여 흡수극대파장의 이동을 통하여 양이온성 계면활성제와 산성약물의 상호작용이 있음을 확인하였다. 그리고 계면활성제의 미셀 내부와 용액과의 분배계수를 측정하여 산성 약물은 음이온성 계면활성제 보다 양이온성 계면활성제에 잘 분배되는 것을 알아보았다. 산성 약물 중 메페남산을 선택하여 4가지 다른 제형의 정제를 계면활성제가 함유된 용출액에서 용출시험을 실행한 결과 제형간의 분리능이 양이온성 계면활성제를 사용하였을 때 가장 뛰어남을 확인하였다.

난용성 산성약물의 용출 양상에 계면활성제의 영향을 살펴본 결과 양이온성 계면활성제가 가장 용출률을 향상시켜 줌을 확인할 수 있었다. 그 다음으로 상대적으로 pKa 값이 높으면 음이온성 계면활성제가 pKa값이 낮으면 비이온성 계면활성제가 용출률을 높여 줌을 확인하였다.

Abstract

Slightly water soluble acidic drugs were studied to compare the effect of classes of surfactants on the solubilization in aqueous solution. For evaluating the effect of surfactants on solubilization, aqueous micellar solutions which were pH 6.8 phosphate buffer containing 1% surfactants were prepared. Cetyltrimethylammonium bromide (CTAB) as a cationic surfactant, sodium lauryl sulfate (SLS) as an anionic surfactant and polysorbate80 (PSB80) as a non-ionic surfactant were used in this study. The tested drugs were selected by the acidity of drugs. The solubility of each drug was measured at prepared micellar solution. The dissolution tests were carried out in 900ml of the micellar solution at 37°C using USP dissolution apparatus II (paddle method) with a rotating speed of 50 rpm. And the interactions between drugs and surfactants were confirmed by the UV spectrophotometer. Partition coefficients of drugs between micelle and aqueous media were measured. The solubility of slightly water soluble acidic drugs was the highest in the solution containing cationic surfactant, CTAB. Maximum wavelengths of acidic drug in the 1% CTAB solution was shifted. This indicated the interaction of drug between surfactant. When acidic drug dissolved in the aqueous solution, this dissociated to anionic form. This ionic forms interacted with counterpart surfactants. Similar results were obtained from the dissolution tests of those drugs. Partition coefficients of acidic drugs to cationic micelle was higher than other micelle. It was confirmed that acidic drugs solublized well into the media containing cationic surfactants, because of the interaction of the ionic form of drugs with surfactants.

I-1. Introduction

In the state of developing the new formulation and evaluating the quality of the tablet, dissolution profile is the most important factor to direct for making the formulation. Especially, absorption of drug is in close connection with dissolution amount of drug in the case of poorly water soluble drugs (BCS Class II) when drugs are administrated orally. Since BCS Class II drugs have high membrane permeability, the amount of drug dissolved is the most important element [1].

However, dissolution medium used generally in laboratory can not dissolve water insoluble drugs completely. It is a struggling to assess lot-to-lot evaluation for ensuring the product quality and assist development of new formulation, using an in-vitro dissolution test [2]. Recently many researchers focus on development of new composed dissolution media for poorly water soluble drugs to overcome these problems by improving the dissolution rate of drugs [3, 4, 5]. And several studies were conducted to enhance the in-vitro / in-vivo correlation (IVIVC) by using new dissolution media [6, add]. Some kinds of methods were used to conduct dissolution tests of poorly water soluble drugs. One is to use large amount of dissolution buffer [3, 7] and another is co-solvent method which was adding organic solvent to the medium to enhance the solubility or make a sink condition [8, 9]. The other is dissolving the surfactants to the media [3, 4, 5]. Among these, using the dissolution media containing surfactants were proposed to suitable method for poorly water soluble drugs, because bile salts, lecithin, cholesterol and its ester existed in the intestinal fluid such as natural surfactants [1].

We conducted dissolution test of poorly water soluble drugs such as

mefenamic acid (pKa=4.2), nimesulide (pKa=6.5), ibuprofen (pKa=4.4) in the buffer containing several kinds of surfactants [10, 11]. These drugs were selected on the basis of their lower solubility and acidic character. And then we investigated the effect of surfactants according to their species on the dissolution profile of poorly water soluble acidic drugs.

Cetyltrimethylammonium bromide (CTAB) as a cationic surfactant, sodium lauryl sulfate (SLS) as an anionic surfactant and polysorbate80 (PSB80) as a non-ionic surfactant were used in this study. The solubility of drugs was measured in various media and the partition coefficients of drug between micelles and aqueous solution were calculated to study the effect of micellar solubilization. To explain this phenomenon, the interaction between surfactants and acidic drug was confirmed by UV-Visible spectrum. Additionally locus of solubilization of drug in the micelles was examined.

I-2. Materials and methods

I-2-1. Material

Mefenamic acid (99.3%) and nimesulide (99.6%) were purchased from Sigma-aldrich Chem. Co. (St. Louis, MO) and ibuprofen (100.2%) was donated from Hana Pharm. Co.(Kyeonggi, Korea). Commercial brands of mefenamic acid (PontalTM, 500mg tablet), nimesulide (MesulideTM, 100mg tablet) and ibuprofen (BrufenTM, 400mg tablet) tablets were supplied by Yuhan Co. (Seoul, Korea), Choongwae Pharm. Co. (Seoul, Korea) and Samil Phram. Co. (Seoul, Korea). Sodium lauryl sulfate (SLS, >95% purity) and Cetyltrimethylammonium bromide (CTAB) were purchased from Sigma-aldrich Chem. Co. (St. Louis, MO). Polysorbate80 (PSB80) was purchased from Junsei Chem. Co. (Tokyo, Japan). Sodium chloride, Sodium hydroxide, Hydrochloric acid were purchased from Merck (Darmstadt, Germany). Methanol, acetonitrile and tetrahydrofuran used for mobile phase were also obtained from Merck (Darmstadt, Germany) as a HPLC grade. All other chemicals were of reagent grade and were used without further purification.

I-2-2. Preparation of dissolution medium

50mM pH 6.8 phosphate buffer which is an artificial intestinal fluid without pancreatin (SIF) and pH 1.2 hydrochloric acid buffer which is a simulated gastric fluid without pepsin (SGF) were used as dissolution media. To evaluate the effect of surfactants on the dissolution rate of drugs, PSB80, SLS and CTAB were dissolved in the media. Concentration of each surfactant used was 1.0 w/v %.

I-2-3. Dissolution rate study

Drug release tests were carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). Test product was placed in 900 ml of dissolution media at 37°C using the USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. An aliquot of release medium was withdrawn at predetermined time intervals and equivalent amount of fresh medium was added to the release medium. Withdrawn samples were centrifuged at 5000 rpm for 5 min or filtered with 0.45μm syringe filter. Those sample were diluted at appreciate ratio with each dissolution media.

I-2-4. Solubility measurement

Excess amount of a drug was added to each dissolution medium in a 20ml vial. The contents were stirred by magnetic bar at 37°C for 24 hours. The saturated solution was centrifuged at 5000 rpm for 5 min. or filtered with 0.45μm syringe filter. The concentration of the drug was measured by HPLC system (Shimadzu Scientific Instruments, MD) or UV spectrophotometer (UV-1601, Shimadzu, Japan). Each experiment was done in triplication and the average was used.

I-2-5. UV-Visible spectrum

UV spectra of the mefenamic acid in pH 6.8 dissolution medium with and without a surfactant were measured by UV spectrophotometer (UV-1601, Shimadzu, Japan). The concentration of sample is 10μg/ml.

I-2-6. Assay methods

A Shimadzu HPLC system composed of a pump LC-10AD and an auto sampler SIL-10ADvp and an UV detector SPD-10A was used for analysis of mefenamic acid and ibuprofen. The separation of mefenamic acid and ibuprofen were conducted with ODS column (Luna 5μm C18, 4.6*250mm, Phenomenex) and ODS column (Luna 5μ C8, 4.6*150mm, Phenomenex). The mobile phase of mefenamic acid was acetonitrile/ tetrahydrofuran/50mM ammonium phosphate buffer (pH 5.0) = 61/14/25 (v/v/v) and the mobile phase of ibuprofen was acetonitrile/10mg/ml chloracetic acid buffer (pH 3.0) = 65/35 (v/v). Flow rate of mefenamic acid and ibuprofen were 1.0ml/min and 1.6 ml/min. The wavelength and injection volume of mefenamic acid and ibuprofen were 254nm and 10μl.

The concentration of nimesulide was measured by UV spectrophotometer (UV-1601, Shimadzu, Japan) at 297nm.

I-3. Results and discussion

The approach for studying the effect of classes of surfactants was conducted with the dissolution test of poorly water soluble drugs. The release amount of mefenamic acid versus time profile indicated which surfactant is the most efficient among the tested surfactants as shown in figure 2. Dissolution rate of mefenamic acid in pH 6.8 buffer is no more than 10%, but dissolution rate was increased up to 90% within 120 minutes by addition 1% CTAB to pH 6.8 buffer. And the dissolution rates in the media containing PSB80 and SLS are 40% and 15%, respectively.

We suppose that when acidic drug is dissolved in buffer, it dissociates to anionic drug. It easily interacts with cationic surfactant, so dissolution rate of acidic drug in the buffer contained cationic surfactants will increase more than other buffer.

The UV-Visible spectrum of mefenamic acid was measured to confirm the interaction between drug and surfactants in the presence and absence of CTAB. As can be seen in figure 3, absorption maximum of mefenamic acid shifted from 285.5nm to 294.5nm, indicating that the microenvironment polarity of mefenamic acid had been changed. This change in microenvironment seemed to be due to the penetration of mefenamic acid into the micelles of CTAB [12]. PSB80 also showed similar red shift in UV-Visible spectrum, indicating that the drug was solubilized in the micelles of PSB80. No shift in UV-Visible spectrum was observed in a mefenamic acid solution containing SLS.

From the following Noyes-Whitney equation (Eq 1.), the solubility of a drug in dissolution media is a major driving force in detecting dissolution rate of the drug.

$$Rd = K \times A(Cs - C) \quad (1)$$

Rd is the dissolution rate, K is the dissolution rate constant, A represents the average surface area of undissolved drug, Cs is a solubility of the drug, and C is a concentration of drug [13].

The effect of three different classes of surfactants in the solubility and the dissolution rates of tested drugs were summarized in tablet 1. The dissolution rates were measured at 30 minutes after the dissolution study. A cationic surfactant, CTAB, provided the highest solubility and the fastest dissolution rate for mefenamic acid. And the higher solubility resulted in the faster dissolution rate.

The dissolution profiles of nimesulide and ibuprofen tablets in different dissolution media were shown in figure 4 and 5. We compared the effect of ionic surfactant in the dissolution rate of these drugs. The dissolution rate in medium containing cationic surfactant, CTAB, was higher than medium containing anionic surfactant, as expected. The Phenomenon also appeared in the solubility results as shown on table 1.

The effects of surfactants on acidic drug were also studied by other researcher. Solubilization of gliclazide, another poorly water soluble acidic drug, by aqueous micellar solution was investigated by Alkhamis. In that study, solubility of gliclazide was 0.8372mg/ml in 1% CTAB solution, 0.7381mg/ml in 1%SLS solution, 0.1294mg/ml in 1% PSB solution. [14] Plamodon reported that rate of decarboxylation of p-aminosalicylic acid in acidic solution was decreased by addition of surfactants. P-aminosalicylic acid had a little chance to expose to acidic environment, because p-aminosalicylic acid penetrated into the micelles of surfactant. And the order of decreasing of decarboxylation was

CTAB>SLS>PSB80. [15]

All results put in order, we could obtain a rule. The rate of incorporation of the acidic drug to the micelles of cationic surfactant was the highest among the tested surfactants, except ibuprofen. Ibuprofen didn't dissociate into ionic forms, as it was examined under strong acidic condition. Incorporation rates of acidic drug which had a lower pKa value like mefenamic acid (pKa=4.2), ibuprofen (pKa=4.4), p-aminosalicylic acid (pKa=3.25) were the lowest in the medium containing anionic surfactant, SLS. Acidic drugs with relatively higher pKa value like Nimesulide (pKa=6.5) and gliclazide (pKa=5.8) had the lowest incorporation rate in the medium containing PSB80. Acidic drugs with a lower pKa value would dissociate into anionic drug form in a large proportion in the medium. Anionic drug form had a repulsive force with the micelles consisted with anionic surfactant, SLS, so little amount of drug could penetrate into the anionic micelles. In case of acidic drugs with relatively high pKa value, proportion of undissociated form was higher as compare with those with lower pKa. So, these drugs could follow the general principle that is SLS had better solubilizing effect than PSB80 for having a lower repulsive force to anionic micelles. [16, 17]

For finding out the drug partitioning into the micelles, we measured the solubility of drugs in the surfactant solution with various concentration. The data obtained were analyzed using a pseudo phase model. The partition coefficient (Pm) between the medium and the micellar pseudo-phases was calculated using the following equation (Eq. 2)

$$\frac{S_t}{S_o} = 1 + P_m v[M] \qquad (2)$$

Where S_t is total solubility, So is basic medium solubility, Pm represents the micelles-medium partition coefficient, v means the partial molal volume of the micelles, and [M] is a micellar concentration. [18] Among the tested drugs, we selected mefenamic acid as a model drug. The graphs of relative solubility versus micellar concentration were shown in the figure 6. Partition coefficient (Pm) was calculated by dividing the slope by partial molal volume of micelles. The value of partial molal volume was taken from other research paper. [19] Partition coefficient of mefenamic acid between CTAB micelles and medium and between SLS and medium were $2.54*10^4$ and $2.31*10^2$, respectively. Base on the partition coefficient, it can be concluded that mefenamic acid could dissolve over 100 times more efficiently into micelles with cationic surfactant as compared to micelles with anionic surfactant.

Additionally, the locus of mefenamic acid in the micelles of surfactants was investigated. The effect of sodium chloride which is a neutral electrolyte on the solubility of mefenamic acid in surfactant solution was also studied. Micelles were composed of non-polar moieties at core region and polar moieties at outer region. The polar head groups of surfactant in outer region would be packed more closely by the addition of neutral electrolyte which caused in the reduction of the repulsion between similarly charged polar head group. If drug exist in the outer region of the micelles, the solubility would be decreased by addition of neutral electrolyte. Otherwise, drug would exist in the core region of micelles. [14]

The effects of neutral electrolyte on the solubility of mefenamic acid in surfactant solution were shown in the figure 7 and 8. A little difference insolubility of mefenamic acid was observed in the buffer containing CTAB when the concentration of NaCl was changed. But, the solubility in the buffer

containing SLS was significantly decreased by increasing the concentration of NaCl. These results support that mefenamic acid existed in the core region of the micelles of CTAB and in the outer region in the micelles of SLS.

We conducted dissolution tests of four different kinds of formulation of mefenamic acid tablet in the pH 6.8 buffer with 1% surfactants to compare the discriminating power of each dissolution medium. Every dissolution profile looked like similar in the buffer containing 1% SLS as shown in figure 9. When buffer containing 1% PSB80 was used, formulation A and C were discriminated to formulation B and D as shown in figure 10. Buffer containing 1% CTAB could additionally distinguish between formulation B and D, as shown in figure 11. Therefore, it's better to add 1% CTAB to the dissolution media in the dissolution test of mefenamic acid.

I-4. Conclusions

Our results clearly show that the dissolution profiles of poorly water soluble acidic drug were influenced by the class of surfactants. Cationic surfactant, CTAB, was the most efficient dissolution rate enhancer among tested surfactants. This was due to the interaction between cationic surfactant and dissociated anionic drug. Especially, in case of mefenamic acid, discriminating power was the best in the medium containing 1% CTAB. When pharmaceutical researchers develop a new dissolution medium or conduct batch to batch quality control of water insoluble drug products, these results offer the standard to selecting the most suitable surfactant.

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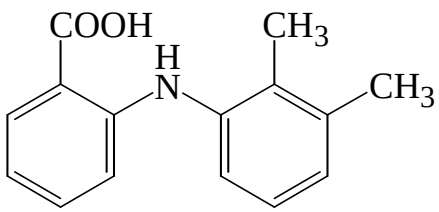
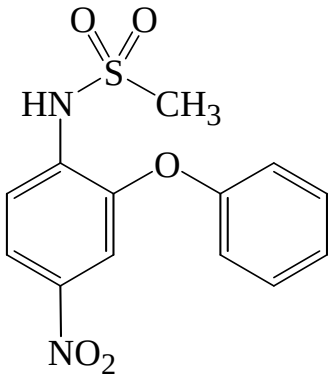
Table 1 : Effect of surfactants on the solubility and the dissolution rate (30 min) of mefenamic acid and nimesulide and ibuprofen.

Mefenamic acid	Control	PSB80	SLS	CTAB
Solubility (μg/ml)	29.6 ± 5.48	236 ± 4.89	66.7 ± 1.90	4490 ± 231.2
Dissolution rate (%)	7.30 ± 0.17	23.2 ± 0.94	13.5 ± 0.41	54.6 ± 7.81
Nimesulide	Control	PSB80	SLS	CTAB
Solubility (μg/ml)	22.8 ± 1.62	120 ± 6.78	166 ± 4.48	2530 ± 69.7
Dissolution rate (%)	21.2 ± 0.29	70.1 ± 1.29	89.1 ± 1.28	100.0 ± 2.23
Ibuprofen	Control	PSB80	SLS	CTAB
Solubility (μg/ml)	11.0 ±	1199 ±	697 ±	4371 ±
Dissolution rate (%)	1.63 ± 0.89	87.0 ± 2.53	43.5 ± 3.65	63.3 ± 6.66

(A)



(B)



(C)

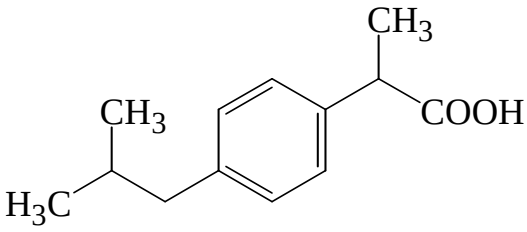


Fig. 1. Chemical structures of mefenamic acid (A), nimesulide (B), ibuprofen (C)

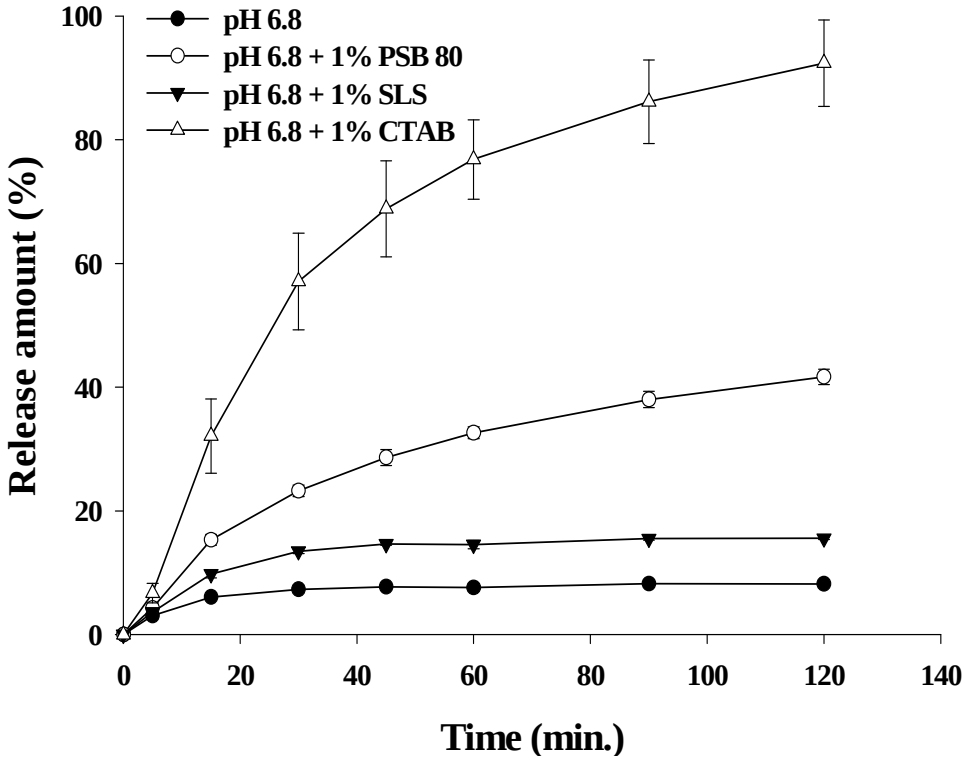


Fig. 2. Dissolution profiles of 500mg mefenamic acid tablets in pH 6.8 buffer with and without various surfactants (n=12).

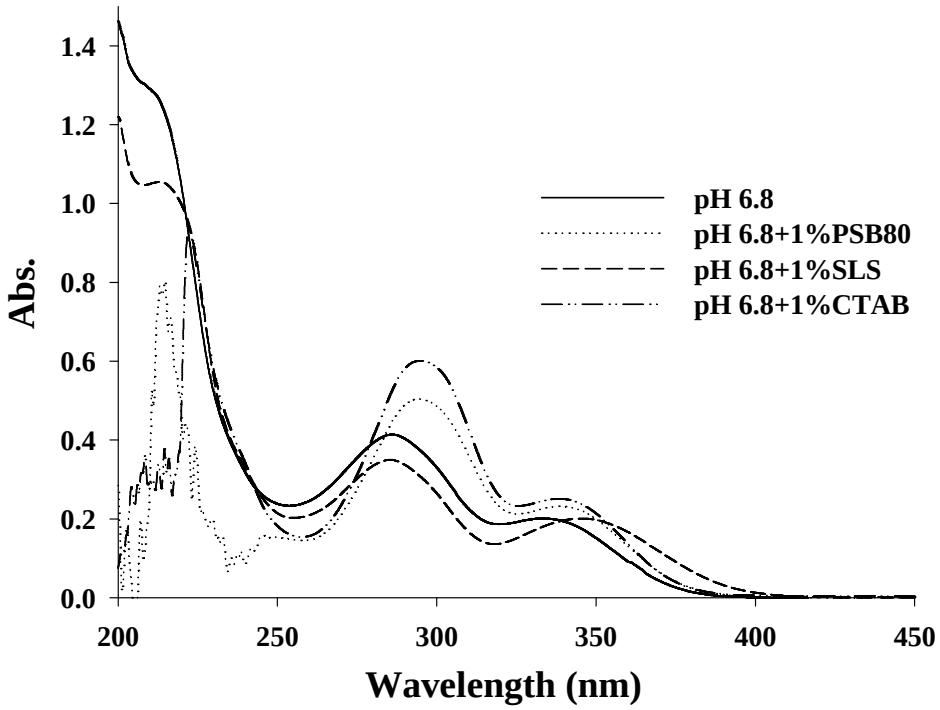


Fig. 3. UV-Visible spectrums of mefenamic acid in pH 6.8 buffer with and without various surfactants.

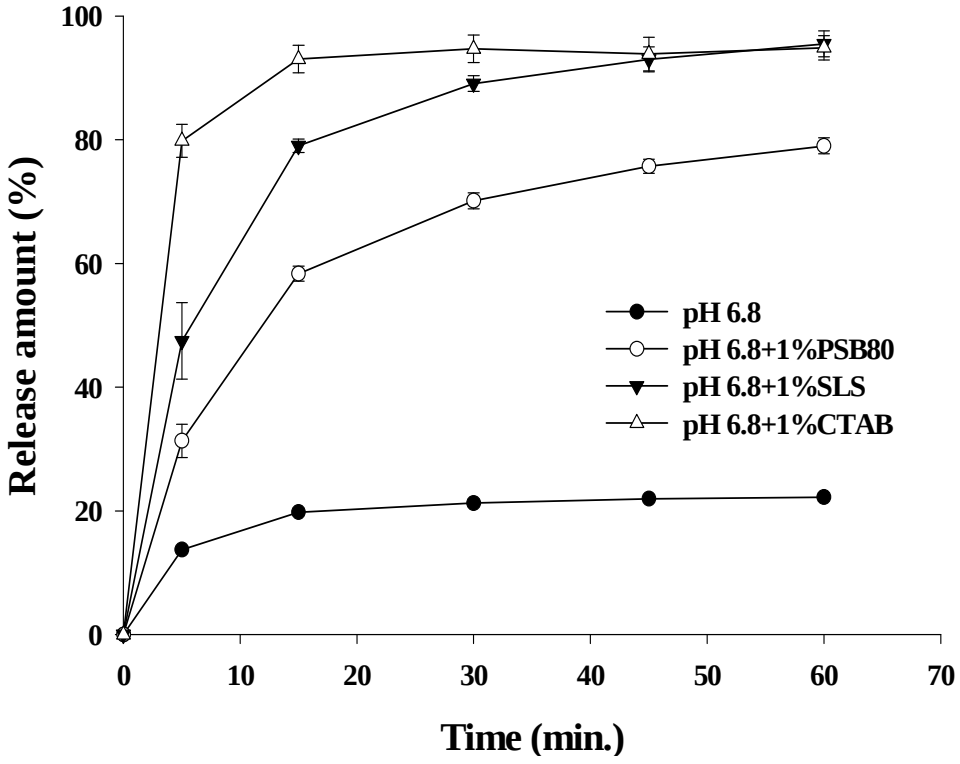


Fig. 4. Dissolution profiles of 100mg nimesulide tablets in pH 6.8 buffer with and without various surfactants (n=12).

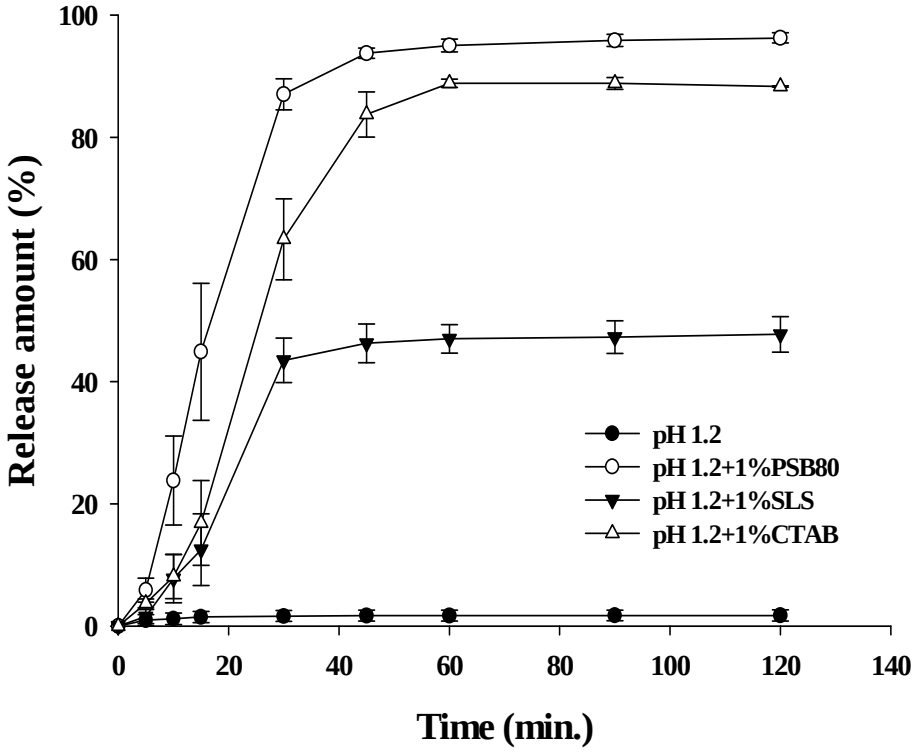


Fig. 5. Dissolution profiles of 400mg ibuprofen tablets in pH 6.8 buffer with and without various surfactants (n=12).

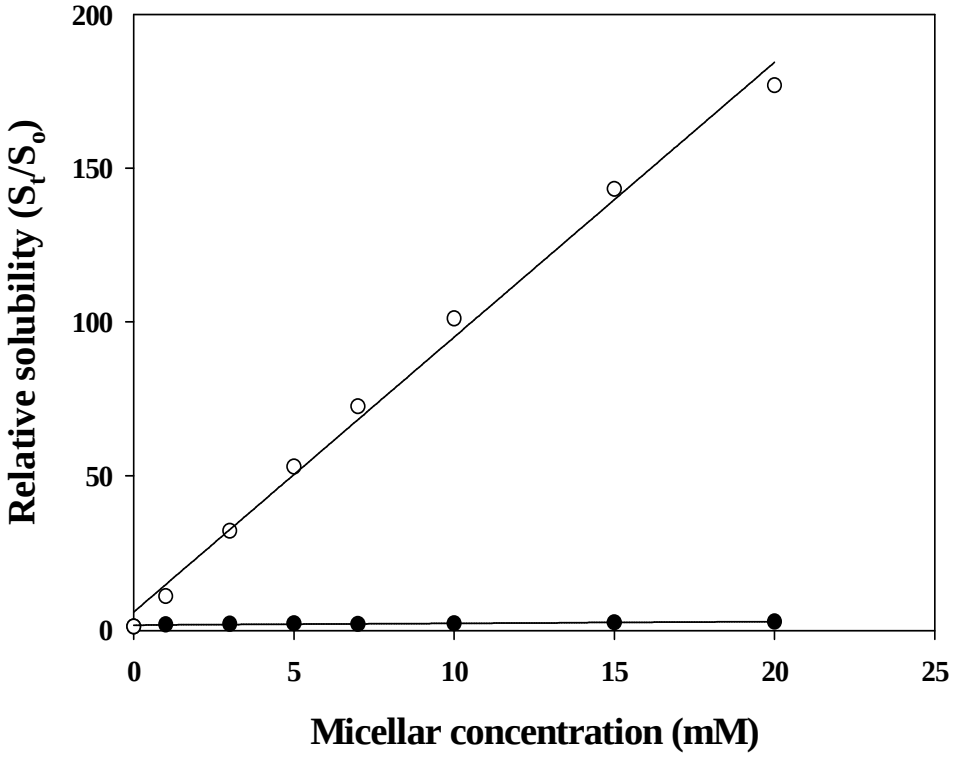


Fig. 6. Relative solubility of mefenamic acid in the media versus micellar concentration of CTAB (white circle) and SLS (dark circle).

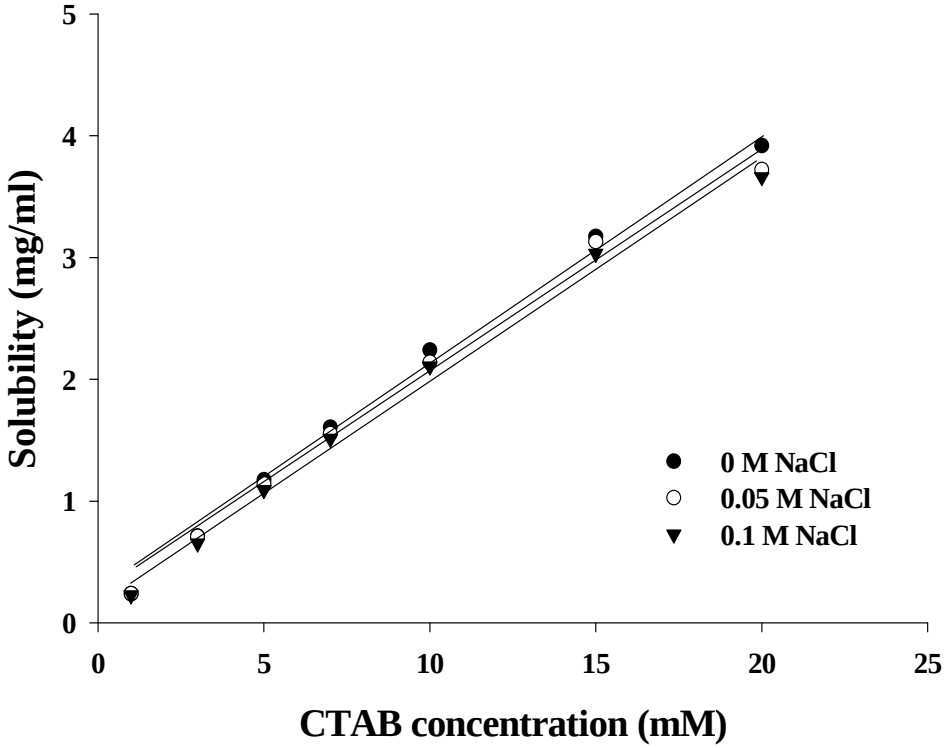


Fig. 7. Mefenamic acid solubility against CTAB concentration with different concentration of NaCl at 37℃

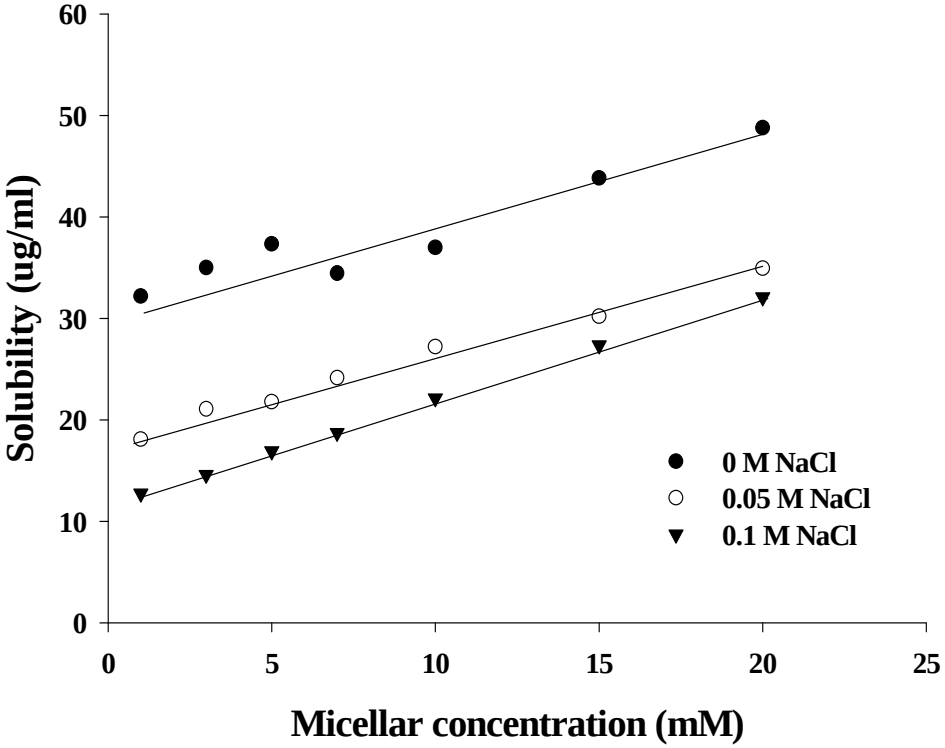


Fig. 8. Mefenamic acid solubility against SLS concentration with different concentration of NaCl at 37℃

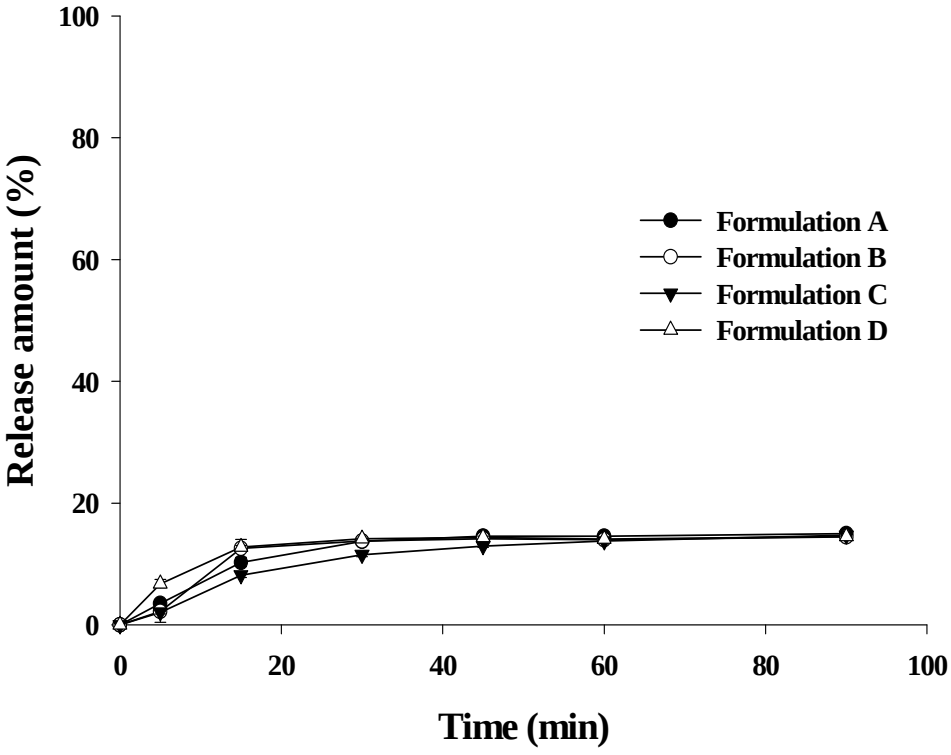


Fig. 9. Dissolution profiles of 500mg mefenamic acid tablets in pH 6.8 buffer containing 1% SLS (n=6).

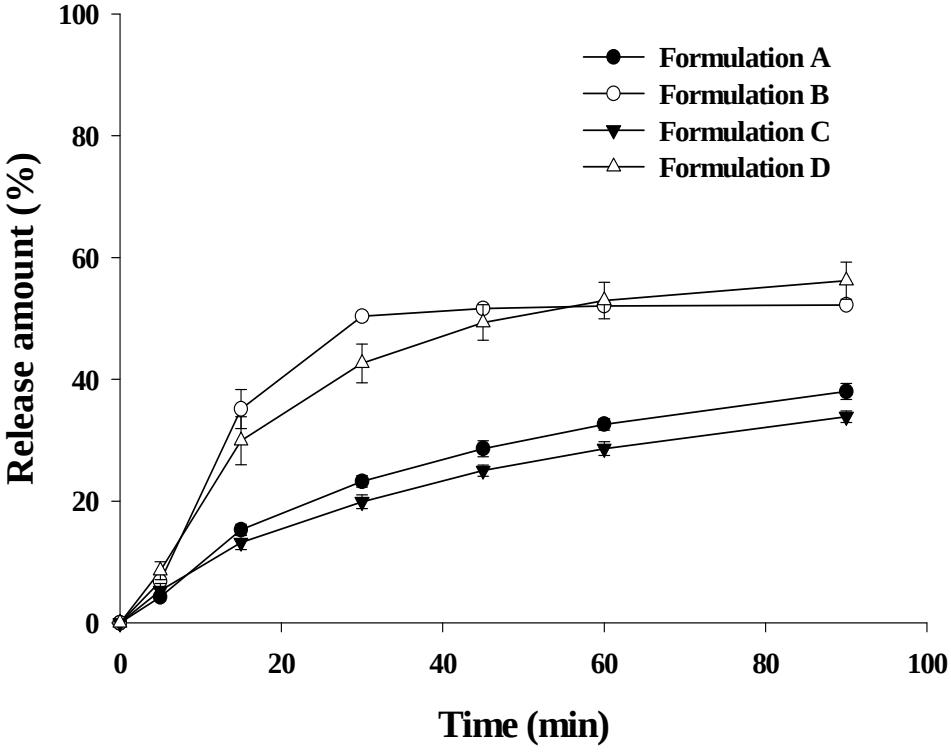


Fig. 10. Dissolution profiles of 500mg mefenamic acid tablets in pH 6.8 buffer containing 1% PSB80 (n=6).

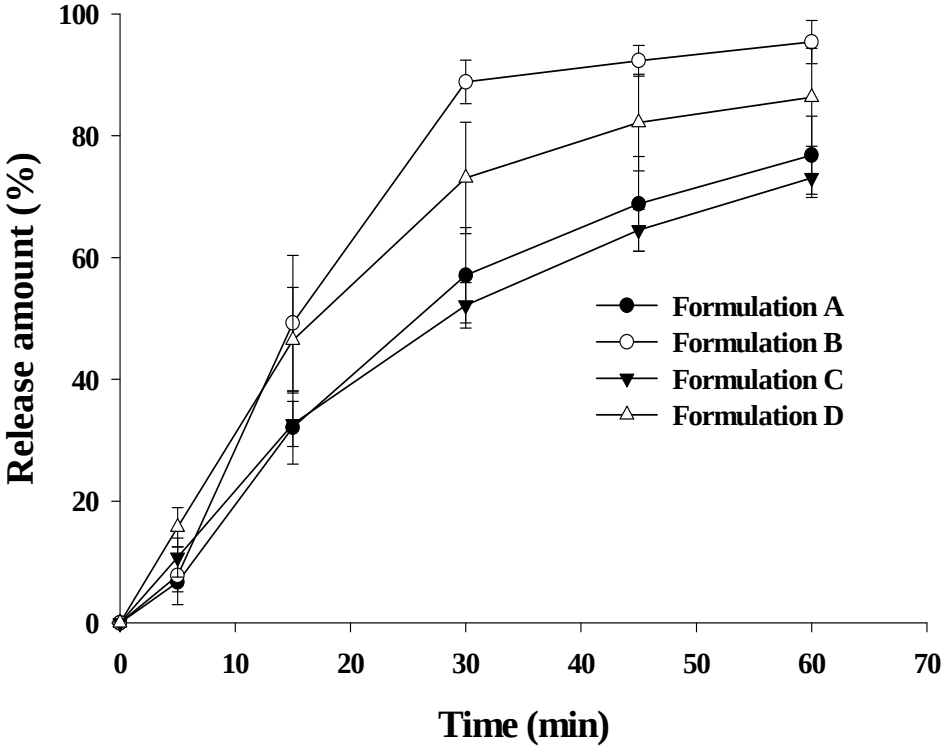


Fig. 11. Dissolution profiles of 500mg mefenamic acid tablets in pH 6.8 buffer containing 1% CTAB (n=6).

저작물 이용 허락서

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논문제목	한글 : 난용성 산성약물의 용출에 미치는 계면활성제의 영향 영문 : The Effect of Surfactants on Dissolution Profile of Poorly Water Soluble Acidic Drugs				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집·형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

2005 년 6 월 일

저작자: 장 준 호 (서명 또는 인)

조선대학교 총장 귀하