2009 년 2 월

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Preparation of Carbopol/chitosan interpolymer complex as a controlled release tablet matrix; effect of complex formation medium on drug release characteristics

조선대학교 대학원

약 학 과

이 명 학

제어 방출형 기제로서의 키토산/카보풀 복합체의 제조: 복합체 제조 pH가 약물 방출에 미치는 영향

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지도교수 최 후 균

이 논문을 약물학 석사학위신청 논문으로 제출함

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이 명 학

이명학의 석사학위논문을 인준함

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이 명 학

지 도 교 수: 최 후 균

조선대학교 대학원 약학과

키토산과 카보풀®971NF 의 혼합 비율을 조정하여 pH3.0, 4.0 5.0 에서 분자간 인력에 의한 복합체(interpolymercomplex)를 제조하였다. 그리고 제조된 복합체가 키토산의 NH_3^+기와 카보풀®971NF 의 COO^- 기의 정전기적 인력에 의하여 형성되었음을 퓨리에 변환 적외선분광기(FT-IR)를 이용하여 확인하였다. 제조 pH 를 각각 3.0, 4.0, 5.0 으로 변화시켜 생성한 복합체들은 원료물질의 제조 pH 가 증가할수록 복합체 내에서 키토산의 결합비율이 증가하는 경향을 보였다. 생성된 복합체는 제조 pH 가 3.0, 4.0,

5.0 에서 키토산과 카보폴의 반응 비율이 각각 1/10, 1/5, 1/4 일 때 최대의 수득률을 보여주었다.

pH 1.2 medium 에서 용출실험 결과 각각의 복합체는 약물 방출에 큰 차이를 보이지 않았다. 하지만 pH 6.8 medium 에서 용출실험 결과 pH5.0 에서 제조된 복합체는 pH4.0 에서 제조된 복합체에 비해 약물을 더 빨리 방출시켰다. 한편 pH3.0 에서 제조된 복합체의 경우에는 시간이 지남에 따라 약물의 방출속도가 증가하는 모습을 보였다. 복합체로부터의 약물 방출 기전을 연구한 결과 제조된 복합체의 제조 pH 가 pH 3.0, 5.0, 4.0 순으로 relaxation 에 의한 약물의 방출이 pH 6.8 medium 에서 지배적이었다. 확산에 의한 약물 방출은 용출시험의 처음에만 나타났고 시간이 지날수록 relaxation 에 의한 약물의 방출이 주를 이루었다.

Abstract

Preparation of Carbopol/chitosan interpolymer complex as a controlled release tablet matrix; effect of complex formation medium on drug release characteristics

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Chitosan/Carbopol®971NF (poly acrylic acid) interpolymer complexes were prepared in pH 3.0, 4.0 and 5.0 medium to control the ratio of chitosan and Carbopol®971NF in the interpolymer complex. FT-IR analysis confirmed that the mechanism of complexation involved an electrostatic interaction between the NH_3^+ of chitosan and COO^- of Carbopol®971NF. An increase in the pH of the preparation medium was accompanied by an increase in the ratio of chitosan in the

chitosan/Carbopol®971NF complex. The maximum yield of interpolymer complexes prepared at pH 3, 4, and 5 (IPC3, IPC4, IPC 5) were obtained at ratios of 1/10, 1/5, and 1/4 (chitosan/Carbopol®971NF), respectively. At pH 1.2, the overall drug release from IPC tablets did not show significant differences. However, at pH 6.8, the rate of drug release from the IPC5 tablet was higher than that from the IPC4 tablet. The release rate from the IPC3 tablet was observed to increase with time. The release mechanism was increasingly dominated by the relaxational contribution in the order of IPC3, IPC5, and IPC4 at pH 6.8. The diffusional contribution was dominated only in the early stage of drug release and the relaxational contribution gradually increased with time.

Keywords: Carbopol, chitosan, interpolymer complex, pH, tablet, matrix.

1. Introduction

Various controlled drug delivery systems have been developed for reasons of improving the efficacy of an administered drug, decreasing undesired side effects and increasing patient compliance (Donini et al., 2002; Langer et al., 2003). Among various polymers, hydrogels have been widely used in the development of various controlled release matrix tablets (Kim et al., 2006; Noble et al., 1999). The hydrogel in a swollen state maintains a soft and rubbery state comparable to living tissues and displays excellent biocompatibility (Ju et al., 2002). Among various hydrogels, chitosan-based hydrogels have been the focus of study by many investigators (Kim et al., 2006; Ahn et al., 2002) due to its relatively high biocompatibility and ability to be cross-linked, thereby rendering a three-dimensional network structure to it. The network structure prevents a dosage form from dissolving easily in the medium, and the extended drug release from the swollen gel structure

can thus be achieved. To create a network structure, two different methods are available namely, covalent cross-linking and non-covalent cross-linking. Covalently cross-linked hydrogels have the obvious drawback of their limited biodegradability and this is one of the reasons why more research has been invested in the study of non-covalently cross-linked chitosan-based hydrogels (Noble et al., 1999; de la Torre et al., 2003a,2003b).

In this study we investigated chitosan/Carbopol®971NF interpolymer complexes as one of non-covalently crosslinked hydrogels and applied them to the controlled release tablet matrix (Park et al., 2008). The main driving force of this interpolymer complexation was the electrostatic interaction between the NH_3^+ of chitosan and COO^- of Carbopol®971NF.

In particular, we investigated the effect of the ratio of chitosan/Carbopol®971NF within the complex on drug release. In order

to control the ratio of chitosan/Carbopol®971NF, the interpolymer complex was formed in the medium under three different pH conditions. Prepared complexes were characterized by FT-IR. Furthermore, the release characteristics of theophylline from the chitosan/Carbopol®971NF interpolymer complex matrix tablet was evaluated in pH 1.2 and 6.8 medium. The swelling and wetting ability of chitosan/Carbopol®971NF interpolymer complex was also evaluated.

2. Materials and Methods

2.1. Materials

Chitosan (low molecular weight) and theophylline were purchased from Aldrich (St. Louis, MO, USA). Carbopol®971NF was obtained from Noveon (Cleveland, OH, USA). All other chemicals were of reagent grade or above and were used without further purification.

2.2. Preparation of chitosan/Carbopol®971NF interpolymer complexes

Various concentrations of Carbopol®971NF and chitosan were dissolved in distilled water and 2% acetic acid, respectively. The pH of the resulting solution was adjusted to 3.0, 4.0 or 5.0, respectively. These pH adjusted solutions were mixed together as a function of the monomer mole ratio of chitosan to Carbopol. The resulting precipitates

(chitosan/Carbopol interpolymer complexes) were washed with distilled water and lyophilized for 24 h. The dried complex was ground using a grinder (A11 basic, IKA, Germany) and sieved through 200 μM pore size. The yield of the formed complex was calculated by $[W_{IPC}/(W_{Carbopol} + W_{chitosan})] \times 100$, where W_{IPC} was the weight of chitosan/Carbopol interpolymer complex produced, and $W_{Carbopol}$ and $W_{chitosan}$ were the weights of Carbopol and chitosan used, respectively. The chitosan/Carbopol interpolymer complexes prepared in pH 3.0, 4.0 and 5.0 were abbreviated hereafter as IPC3, IPC4, and IPC5, respectively.

2.3. FT-IR spectroscopy

Infrared (IR) absorption spectra of chitosan, Carbopol and their complexes were obtained using a FT-IR spectrophotometer (LX30-7012, Perkin Elmer, MA, USA). The samples were pressed into the

potassium bromide pellet prior to analyzing their IR absorption spectra.

2.4. Preparation of matrix tablet

Theophylline-loaded tablets (250 mg) were prepared by compressing the mixture (1:1) of theophylline and IPC3, IPC4, or IPC5 using a hydraulic press and a punch with 13-mm diameter. The compression force was fixed at 10 kN/cm^2 with a dwell time of 1 sec.

2.5. Release of theophylline from the matrix tablet

Dissolution tests were carried out using a dissolution tester (DST 810, Labfine Inc., Korea). Theophylline-loaded tablets were placed in 900 mL of the pH 1.2 or pH 6.8 buffer at 37^oC using the USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. Samples collected at predetermined time intervals were analyzed by HPLC (Shimadzu Scientific Instruments, MD, USA), using a UV detector

(SPD-10A), a pump (LC-10AD), and an automatic injector (SIL-10A), to determine the amount of theophylline released from the matrix tablet. The wavelength of the UV detector was 280 nm and a reversed-phase column (Luna C-8, Phenomenex, CA, USA) was used. The column temperature was maintained at 30^{o}C and the flow rate was 1.2 mL/min. The composition of the mobile phase was 100 mM acetate buffer/acetonitrile=93/7.

2.6. Determination of wettability

Wettability was evaluated using 1 g of IPC (IPC3, IPC4, IPC5) tablets. The tablets were placed in a stability test chamber (FLP-650S, Labfine Inc., Korea) maintained at 37^{o}C and 75% of relative humidity. The tablets were pulled out at predetermined time intervals and weighed. The degree of water absorption was calculated using Eq. (1).

$$Water\ absorbed\ (\%) = \frac{T_w - T_d}{T_d} \times 100 \quad (1)$$

T_w refers to the weight of the water-absorbed tablet after the test, while T_d is the weight of the dried tablet before the test.

2.7. Determination of degree of swelling

The degree of swelling of the theophylline-loaded IPC tablet was evaluated using a dissolution tester (DST 810, Labfine Inc., Korea). The tablet was placed in 900 mL of pH 6.8 medium at 37^{o}C using the USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. The swollen tablets collected at predetermined time intervals were weighed after removing extra medium from the surface of the tablet. The resulting swollen tablets were dried under the vacuum for 24 h and weighed. The degree of swelling was calculated using Eq. (2)

$$Degree\ of\ Swelling\ \ (\%) = \frac{W_h - W_d}{W_d} \times 100 \quad (2)$$

W_h refers the weight of the swollen tablet after the test, while W_d is the weight of the dried tablet after the test. W_d was compensated by subtracting the weight of solutes originating from buffer solution such as KH_2PO_4, NaOH and NaCl.

3. Results

3.1. Formation of interpolymer complex

Fig. 1 shows the IR spectra of chitosan, Carbopol®971NF and the Carbopol®971NF/chitosan IPCs. Since the degree of deacetylation of chitosan used was 85%, the amine group of the 2-aminoglucose unit and the carbonyl group of the 2-acetaminoglucose unit of chitosan showed absorption bands at 1595 and 1656 cm^{-1}, respectively (Park et al., 2008; Tien et al., 2003). The peak at 1715 cm^{-1} in the IR spectrum of Carbopol®971NF was assigned to the carbonyl group of carboxylic acid. The IR spectrum of the IPC showed that the peak of 1595 cm^{-1} assigned to the amine band of chitosan was shifted to 1640 cm^{-1}, indicating that the amine group was protonated to a NH_3^+ group in IPC (de la Torre et al., 2003 a, Park et al., 2008). The bands at 1550 and 1408 cm^{-1} were assigned to the symmetric and asymmetric stretching of

the COO^- group (de la Torre et al., 2003 a; Nunthanid et al., 2004). However, the NH_3^+ peak was known to appear between 1600 and 1460 cm^{-1} (Pretsch et al., 2000). Moreover, the peak of NH_3^+ groups in the complex between chitosan and poly(acrylic acid) was known to appear at 1520 cm^{-1} (Chavasit et al., 1988) Therefore, the broad peak around 1550 cm^{-1} was deduced to be the overlapped peak of COO^- and NH_3^+ peak, indicating that the Carbopol®971NF/chitosan IPC was formed by an electrostatic interaction between the COO^- group of Carbopol®971NF and the NH_3^+ group of chitosan (Park et al., 2008). It was also observed that as the pH of the preparation medium increased, the ratio of the carbonyl peak in carboxyl group of Carbopol®971NF over NH_3^+ peak of the complexes decreased. This result suggested that as the pH of the preparation medium increased, the ratio of chitosan in the chitosan/Carbopol®971NF complex increased.

3.2. Optimization of mole ratios of chitosan and Carbopol

Since the main mechanism of interpolymer complexation between chitosan and Carbopol®971NF was found to be based on ionic interactions, chitosan and Carbopol®971NF have to be ionized before forming an interpolymer complex. The ratio of chitosan/Carbopol®971NF in the complex may vary in accordance with the environmental pH since these polymers have different charge densities depending on pH. As a result, the characteristics of interpolymer complexes and the drug release profiles from each interpolymer complex may be different. As the pH decreases, the charge density of the carboxyl group in Carbopol®971NF decreases and that of the amine group of chitosan increases.

In order to find a complexation ratio as a function of pH, various ratios of chitosan/Carbopol®971NF were fed into the medium. Once the Carbopol®971NF solution was mixed with the chitosan solution, the

interpolymer complex would be formed and precipitated due to low solubility in the medium. The unreacted Carbopol®971NF or chitosan in the medium would remain in the solution. As the amount of unreacted Carbopol®971NF or chitosan in the medium increases, the yield of complex formation was expected to decrease. Therefore, the complexation ratio of chitosan/Carbopol®971NF in each medium could be determined from the ratio that provided maximum yield in each medium. The effect of the monomer mole ratio of chitosan to Carbopol®971NF upon yield of complex formation was measured to determine the complexation ratio of both polymers in the medium with different pH and the results are shown in Fig. 2. The maximum yields of IPC3, IPC4 and IPC5 were obtained at the ratio of 1/10, 1/5, and 1/4 (chitosan/Carbopol®971NF), respectively. For further studies, the optimal ratios of chitosan/Carbopol®971NF in each pH medium were used to prepare IPC3, IPC4 and IPC5.

3.3. Release of theophylline from the complex tablets

The release of theophylline from IPC tablets was measured at pH 1.2 and 6.8, and the results are shown in Fig. 3. At pH 1.2, the overall drug release profiles from each IPC tablet did not show significant differences from each other although the release from IPC3 tablet was slightly lower than that from IPC4 and IPC5 tablets (Fig. 3a). At pH 6.8, the release rate from IPC5 tablet was higher than that from IPC4 tablet (Fig. 3b). However, drug release from IPC3 tablet showed a somewhat different tendency to the other two. While the release rate from the IPC3 tablet was similar to that from the IPC4 tablet in the early stage, it increased with time in the later phase. These results appeared to be related to the wettability and the swelling degree of the IPC tablets. To confirm this, the degrees of water absorption and swelling were measured as a function of time and are shown in Fig. 4. IPC5 tablet showed the highest water absorption rate while IPC4 tablet showed the

lowest water absorption. The initial release rate of the drug appeared to be correlated with the water absorption rate of the tablet. In the early phase, the drug located at the outer side of the tablet dissolved in the water that penetrated into the tablet and was released into the medium. As the length of diffusion path increased with time, the extent of swelling started to play more an important role in the release of the drug from the tablet. The swelling of the tablet matrix was predicted to increase the diffusion rate of the drug due to a larger amount of unbound water. Therefore, the release rate of the drug in the later phase depended on the extent of swelling of the matrix. The initial release rate of the drug from IPC3 tablet was slower than IPC5 tablet because of a slower water absorption rate, although it became faster than that of IPC5 tablet because of a higher extent of swelling in the later phase. In the early stage, the extent of swelling did not show significant differences in all the IPC tablets. However, the extent of swelling of the

IPC3 tablet was significantly increased in the later phase and the drug release rate from the IPC3 tablet increased accordingly.

3.4. Drug release mechanism from the IPC tablets

The drug release mechanism from polymeric devices could be determined using equation (3) by which the diffusional and relaxational contributions of the drug dissolution kinetics could be determined. (Peppas et al., 1989).

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (3)$$

M_t/M_∞ is the fractional drug dissolution at time t, t is the drug dissolution time, m is the purely Fickian diffusion exponent for a device of any geometry shape, k_1 and k_2 are the kinetic constants for the diffusional and relaxational drug dissolution, respectively. In order to obtain the Fickian diffusion exponent, the aspect ratio was calculated by dividing the diameter (13 mm) of the tablet by its thickness (1.61

mm). Based on the calculated aspect ratio (8.1), the Fickian diffusion exponent (0.47) was obtained from the correlation graph between the Fickian diffusion exponent and the aspect ratio reported in the literature (Peppas et al., 1987; Ritger et al., 1987). Table 1 shows the kinetic constants obtained by fitting the release data up to the first 60% of the drug release as shown in Fig. 5. Based on these values, the ratio of the diffusional to the relaxational contribution as a function of time was calculated by Eq. (4) (Peppas et al., 1987) and plotted in Fig. 6 to investigate the dependency of the diffusional and the relaxational contribution on the drug release mechanism in pH 6.8.

$$\frac{R}{F} = \frac{k_2}{k_1} t^m \quad (4)$$

R/F is the ratio of the relaxational to the diffusional contribution at time t. As can be seen in Fig. 6, the diffusional contribution was dominated only in the early stages of drug release and the relaxational contribution gradually increased with time. The result also showed that

the release mechanism was increasingly dominated by the relaxational contribution in the order of IPC 3, IPC5, and IPC4 at pH 6.8.

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Table 1. Kinetic constants for the diffusional (k_1) and relaxational drug release (k_2) from the theophylline-loaded IPC tablets at pH 6.8 at 37^{o}C.

Kinetic constant	Drug-loaded IPC tablets used		
	IPC3	IPC4	IPC5
k_1	0. 9924	1.2185	1.3705
k_2	0.1265	0.0817	0.1384

Figure legends

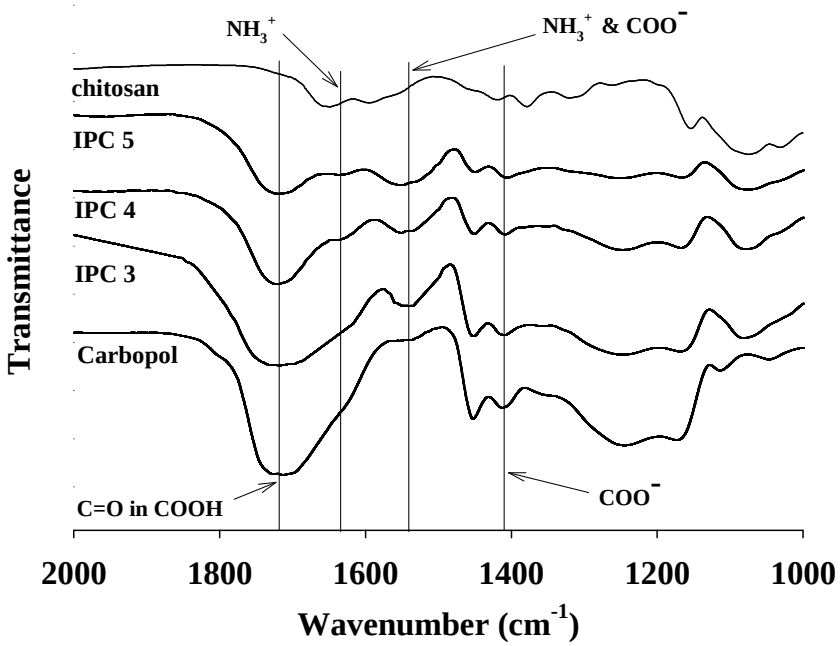


Fig. 1. FT-IR spectra of chitosan, Carbopol®971NF, and chitosan/Carbopol®971NF interpolymer complexes formed under different pH conditions (pH 3.0, 4.0 and 5.0).

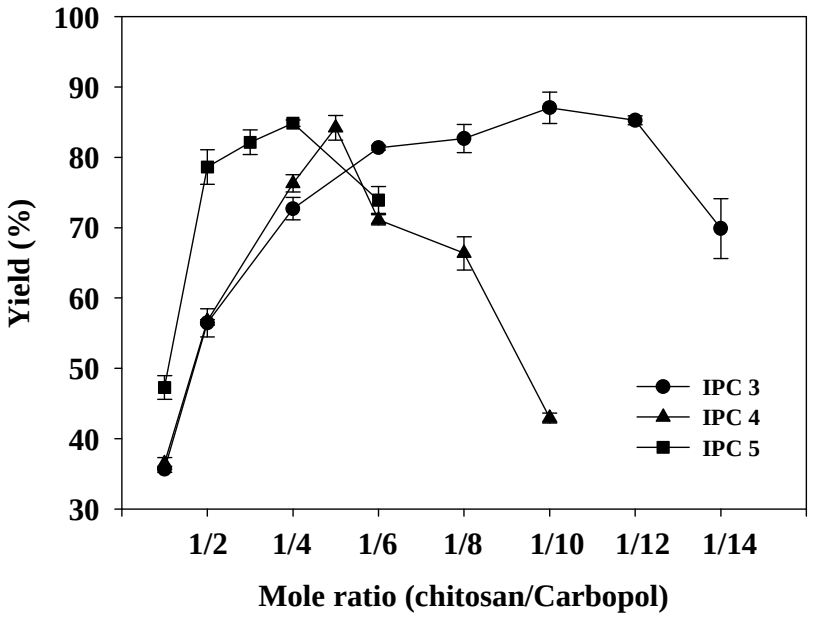
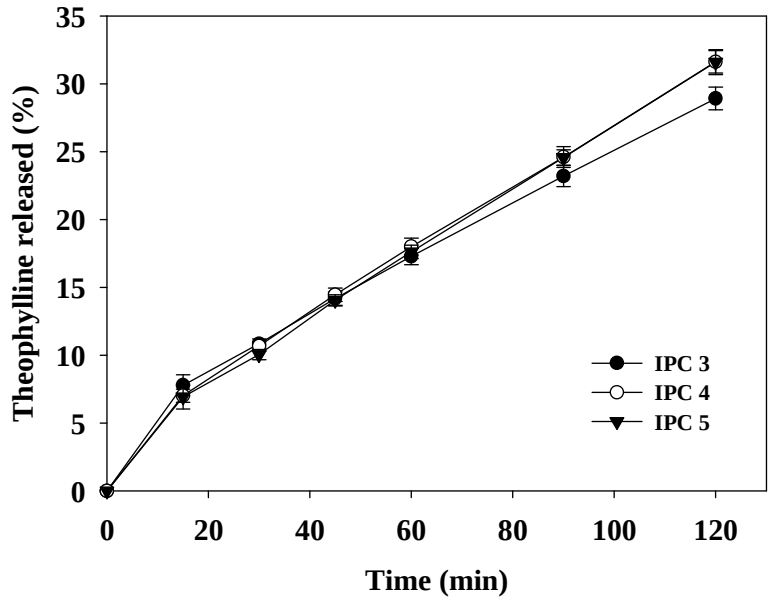
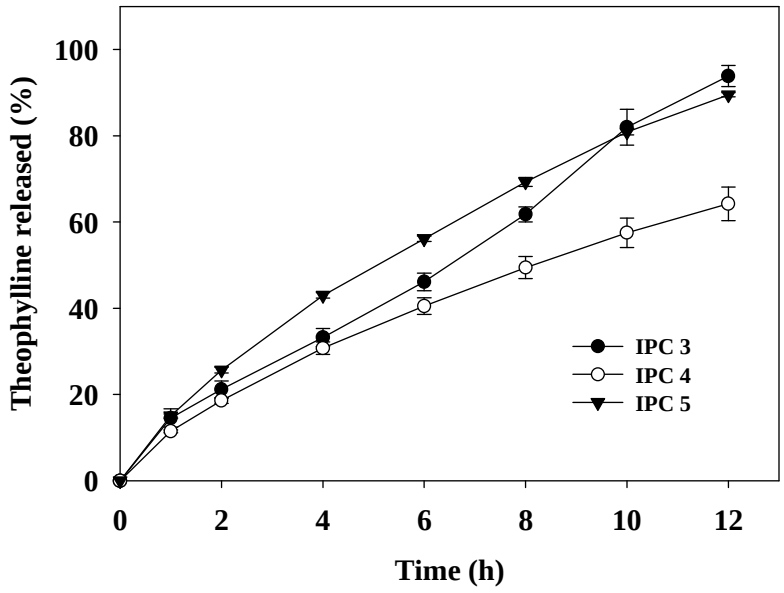


Fig. 2. Effect of the monomer mole ratio of chitosan to Carbopol®971NF on the yield of complex-formation in different pH media. (n=3)

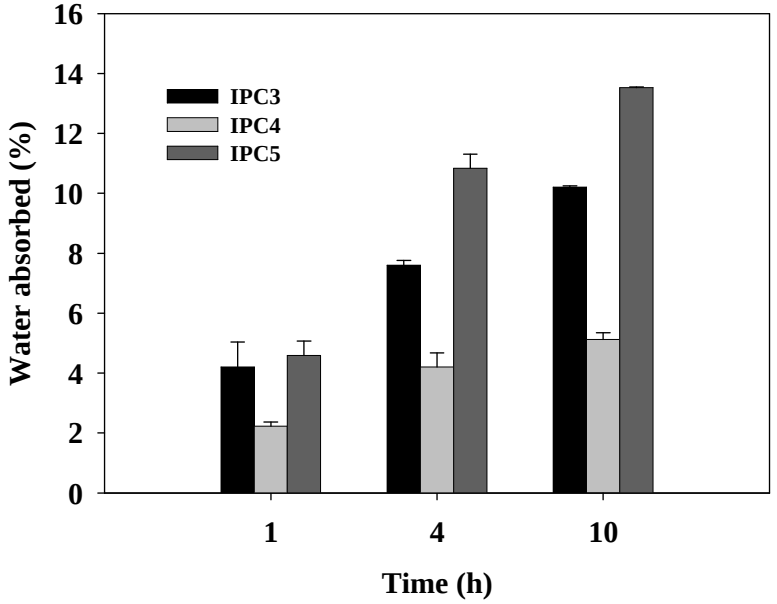

Theophylline released (%)
Time (min)
IPC 3
IPC 4
IPC 5

(a)

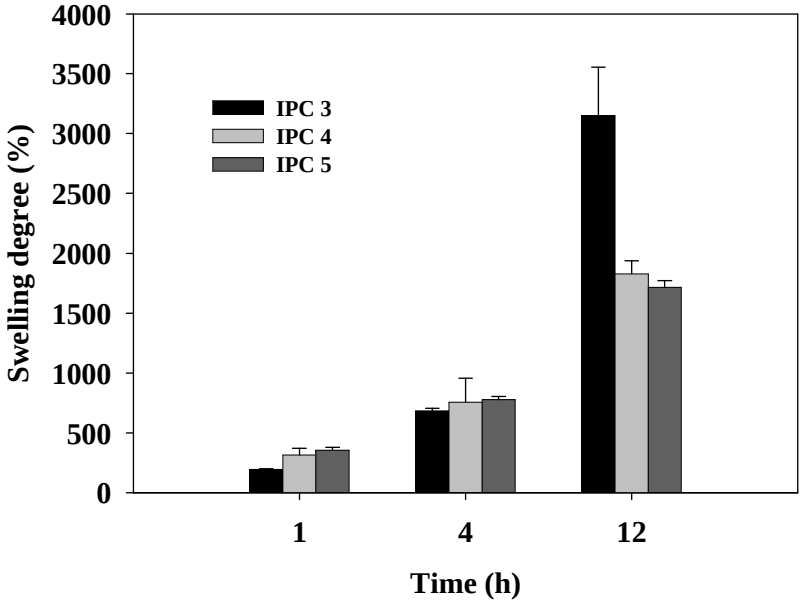

Theophylline released (%)
Time (h)
IPC 3
IPC 4
IPC 5

(b)

Fig. 3. Release of theophylline from the chitosan/Carbopol®971NF interpolymer complex (IPC3, IPC4 and IPC5) matrix tablets in pH 1.2 (a) and 6.8 (b) medium. (n=3)


Water absorbed (%)
16
14
12
10
8
6
4
2
0
IPC3
IPC4
IPC5
1
4
10
Time (h)

(a)


Swelling degree (%)
4000
3500
3000
2500
2000
1500
1000
500
0
IPC 3
IPC 4
IPC 5
1
4
12
Time (h)

(b)

Fig. 4. Wettability (a) and swelling degree (b) of the chitosan/Carbopol®971NF interpolymer complexes (IPC3, IPC4 and IPC5) in pH 6.8 medium.(n=3).

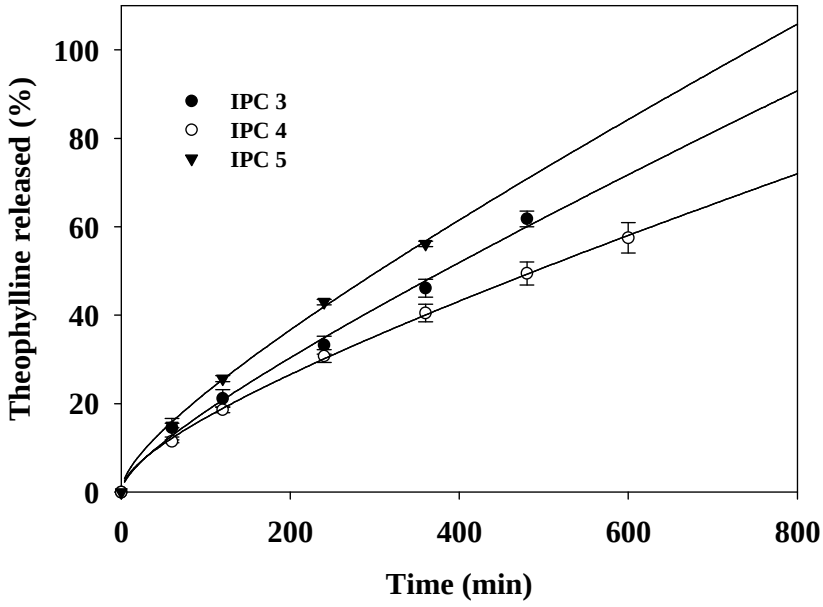


Fig. 5. Curve-fitting of release profile from theophylline-loaded IPC tablets in pH 6.8 medium using the Peppas and Sahlin model. The drug release data were used up to the first 60% of the release.

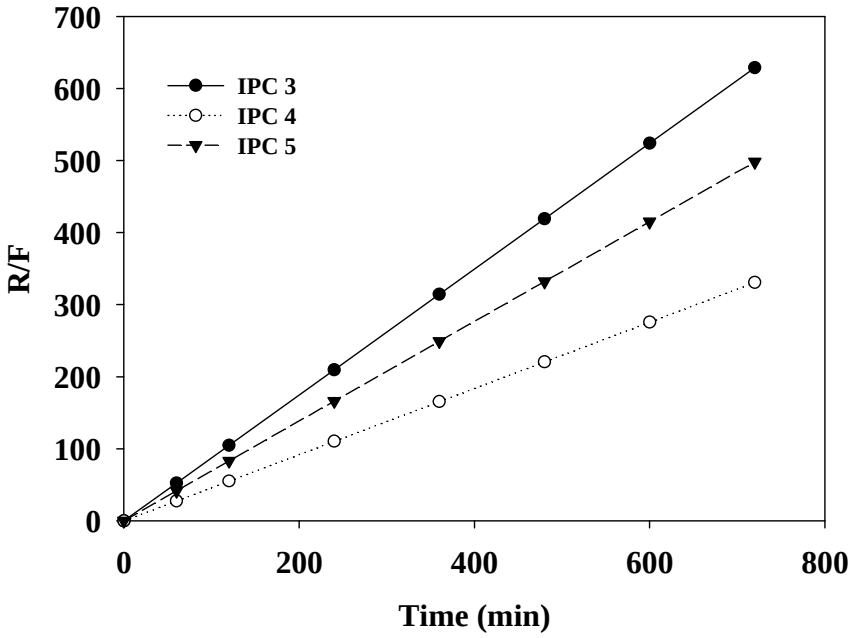


Fig. 6. Dependency of the diffusional and the relaxational contribution on the drug release mechanism in pH 6.8. R/F is the ratio of the relaxational to the diffusional contribution at time t.

저작물 이용 허락서

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논문제목	한글 : 제어 방출형 기제로서의 키토산/카보풀 복합체의 제조: 복합체 제조 pH 가 약물 방출에 미치는 영향 영어 : Preparation of Carbopol/chitosan interpolymer complex as a controlled release tablet matrix; effect of complex formation medium on drug release characteristics				

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

- 다 음 -

1. 저작물의 DB 구축 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 5 년으로 하고, 기간종료 3 개월 이내에 별도의 의사표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1 개월 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.

동의여부 : 동의(○) 반대( )

2009 년 2 월 25 일

저작자: 이 명 학 (서명 또는 인)

조선대학교 총장 귀하