CHAPTER IV
RESULTS AND DISCUSSION

4.1 Effect of Blend Composition on Drug Release

The effect of blend composition on drug release is shown in Figure 4.1-4.4. Silk fibroin contents of 0, 20, 40, 50 and 60% in drug-loaded blend films were used in this study. The blend films with silk fibroin contents higher than 60% were not reported because the films were brittle and difficult to handle without cracking.

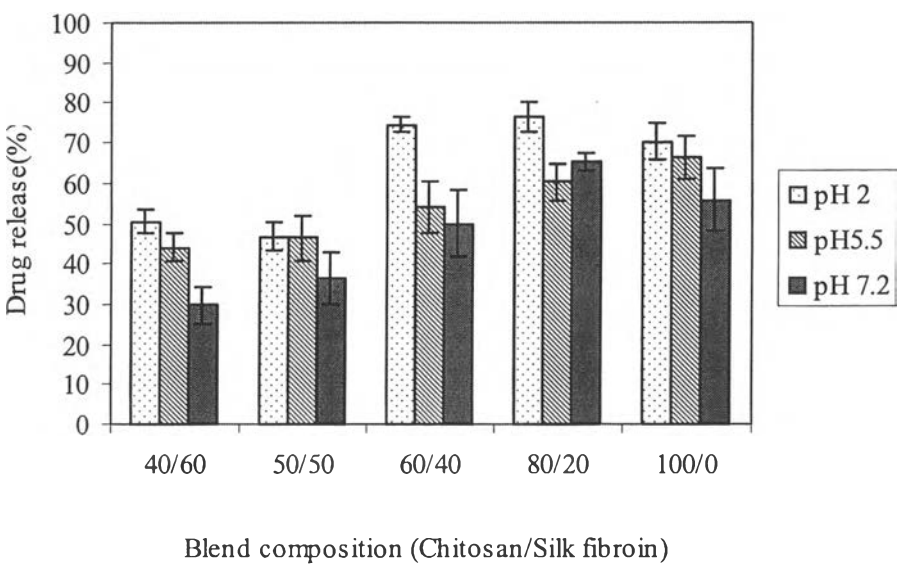

Figure 4.1 Effect of blend composition at various pH on releasing of diclofenac sodium.

It was found that the maximum release of drug was observed for the blend film with 80% chitosan content for all types of model drugs. This could be explained by the term of swelling behavior of the blend films. It was found that the blend film with 80% chitosan content showed the maximum degree of swelling (Table 4.1).

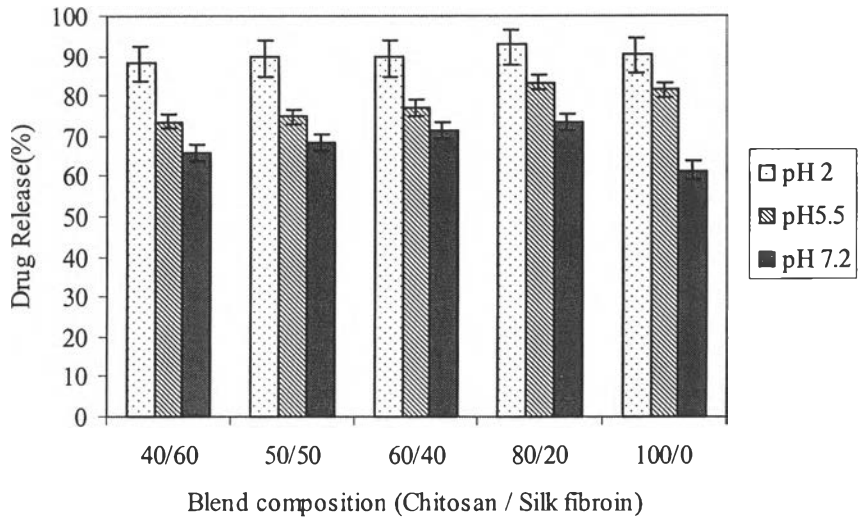

Figure 4.2 Effect of blend composition at various pH on releasing of salicylic acid.

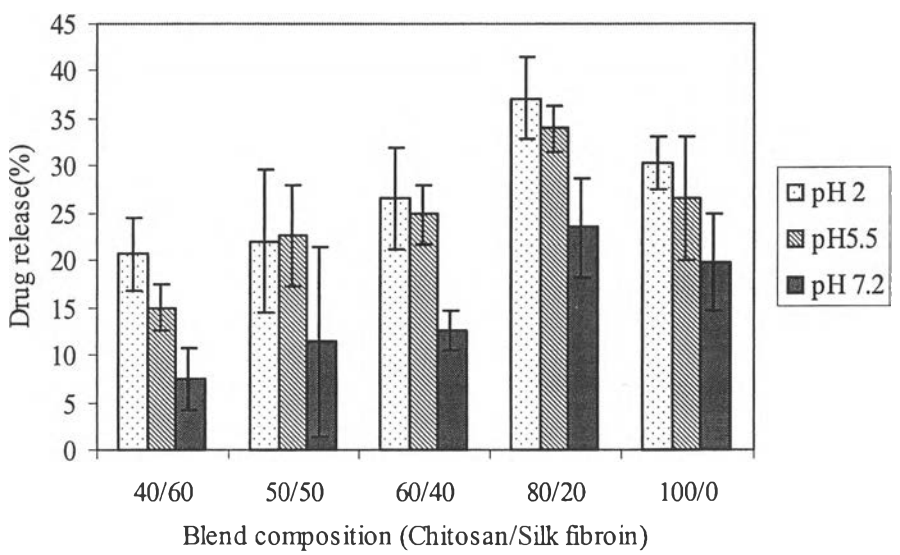

Figure 4.3 Effect of blend composition at various pH on releasing of amoxicillin.

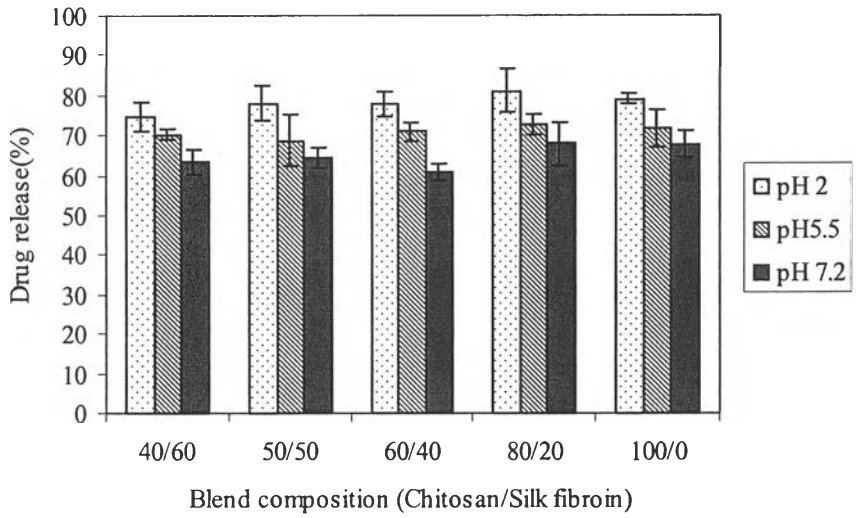

Figure 4.4 Effect of blend composition at various pH on releasing of theophylline.

Peppas *et al.* (1983) suggested that hydrogel delivery system was controlled by swelling behavior of hydrogel. Risbud *et al.* (2000) concluded that the release of amoxicillin from the air-dried and freeze-dried chitosan/poly(vinyl pyrrolidone) hydrogels was related to the degree of swelling of the hydrogels. Furthermore, Yao *et al.* (1993 and 1994) studied the release of chlorhexidini acetas and cimetidine from chitosan/polyether semi-interpenetrating hydrogel. They found that the higher degrees of swelling, the higher amounts of drug released. Chen *et al.* (1997) reported that the maximum degree of swelling of the blend films was observed for chitosan/silk fibroin blend film with 80% chitosan content. The swelling of chitosan/silk fibroin blend films may be occurred due to the dissociation between chitosan and silk fibroin chains caused by the protonation of amino groups of chitosan. However, the lower amounts of released drug were obtained when silk fibroin content in the drug-loaded blend films was increased. Suesat *et al.* (2000) reported that there was no change in the degree of swelling of pure silk fibroin film immersed in buffer solutions for the whole pH range from pH 3 to pH 11. Therefore, swelling ability of the blend films depended on the amounts of chitosan content in the blend films.

Table 4.1 Degree of swelling and percent weight loss of drug- loaded crosslinked chitosan and blend films

Drug	Weight Ratio of Chitosan to Silk Fibroin	Degree of Swelling (%)[a]			Weight Loss (%)[a]		
		pH 2	pH5.5	pH 7.2	pH 2	pH5.5	pH 7.2
Salicylic acid	100:0	840	662	185	34.20	24.27	17.60
	80 : 20	1152	974	199	39.50	27.81	24.32
	60 : 40	763	535	179	35.20	24.21	15.4
	50 : 50	539	495	173	28.10	20.04	14.2
	40 : 60	582	471	169	23.70	19.86	13.8
Amoxicillin	100:0	643	492	194	20.38	19.98	17.73
	80 : 20	736	587	197	28.25	27.24	18.67
	60 : 40	639	472	168	22.30	20.75	18.25
	50 : 50	553	431	145	19.93	18.50	19.10
	40 : 60	504	409	129	18.10	17.63	17.98
Diclofenac sodium	100:0	753	653	167	35.43	30.07	28.6
	80 : 20	809	721	173	37.85	35.18	28.8
	60 : 40	783	600	125	30.53	30.01	23.4
	50 : 50	722	534	108	29.93	28.56	20.6
	40 : 60	687	497	102	21.20	20.01	17.5
Theophylline	100:0	306	252	167	38.87	35.54	26.14
	80 : 20	376	325	175	40.05	37.75	27.22
	60 : 40	360	289	159	36.67	32.23	23.44
	50 : 50	303	277	151	33.32	28.87	20.5
	40 : 60	232	221	142	30.01	25.34	18.7

[a] the average value from three experiments

4.2 Effect of pH on Drug Release

The effect of pH on drug released from chitosan and blend films is shown in Figure 1. Drug release profile was studied at pH 2.0, pH 5.5 and pH 7.2. It was found that the amount of drug released from the systems was highest at pH 2.0 for all types of model drugs. This is in good agreement with the result of swelling as shown in Table 1. It appeared that the degree of swelling was the highest at pH 2.0 and tended to decrease when pH of swelling solution was increased. This result corresponded to the previous works, which also reported that the degree of swelling of the crosslinked chitosan/silk fibroin blend films was maximum at pH 2.0 and decreased when pH of the swelling solution was increased. It can be explained by the fact that in an acidic medium the amino groups of chitosan were protonized, resulting that the hydrogen bonds between chitosan and silk fibroin were broken and the network was dissociated. The blend films exhibited lower degree of swelling when pH was higher than 5. This may be due to the number of protonated amino groups of chitosan become lower at neutral and alkaline pH. The pK_a of chitosan is 6.3-6.5, which indicates that chitosan tends to protonate in acidic solution. Therefore, the degree of swelling of the blend films in alkaline solution was very low as compared to that of the blend films in acidic solution. Risbud *et al.* (2000) reported that the degrees of swelling of chitosan/poly(vinyl pyrrolidone) hydrogels were high in acidic solutions (pH 1.0, pH 2.0 and pH 3.0) and became lower in neutral and alkaline solutions (pH 7.2 and pH 9.2). The release of amoxicillin was found to be maximum at pH 1.0. Besides the release of drug is controlled by swelling condition of the carrier, drug release may be concerned with the erosion process. This process is associated with macroscopic changes in the appearance of the device, changes in the physicomechanical properties of the polymeric material, deformation or structural disintegration, weight loss, and the eventual loss of functions. Table 1 shows the weight loss of chitosan and blend films. It was found that the weight loss of the films was highest at pH 2. This indicated that drug release by erosion process could be occurred in this system.

4.3 Effect of Drug Types on Drug Release

The effect of drug molecules on drug release is shown in Figure 2. The releases of model drugs, theophylline, salicylic acid, diclofenac sodium and amoxicillin, were studied at pH 2.0, pH 5.5 and pH 7.2.

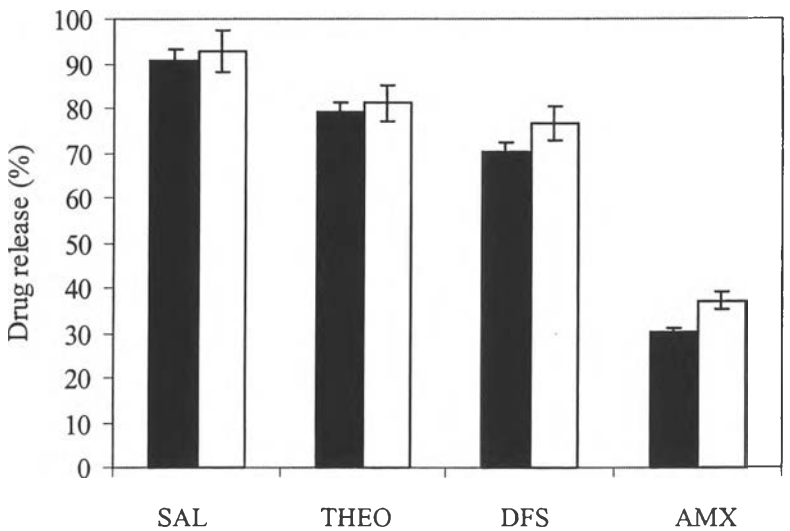

Figure 4.5 Comparison of the amounts of drugs released from chitosan and the blend film with 80% chitosan content at pH 2.0. ■ chitosan film □ blend film with 80% chitosan content.

It was found that the blend film at 80% chitosan content gave the highest amount of released drugs. The amounts of released salicylic acid at pH 2.0, pH 5.5 and pH 7.2 from blend film with 80% chitosan content were 92.7%, 83.4% and 73.5%, respectively. The amounts of theophylline released at pH 2.0, pH 5.5 and pH 7.2 from the blend film with 80% chitosan were 81.1%, 73.6% and 69.0%, respectively. The maximum amount of released salicylic acid at equilibrium was higher than that of theophylline. One factor that can affect the penetration of a drug from a polymer matrix is the molecular size of the drug. The molecule of salicylic acid was smaller than theophylline. Thus, the penetration of salicylic acid from the matrix was easier than theophylline. Diclofenac sodium released at pH 2.0, pH 5.5

and pH 7.2 from the blend film with 80% chitosan content were 76.6%, 66.1% and 65.1%, respectively.

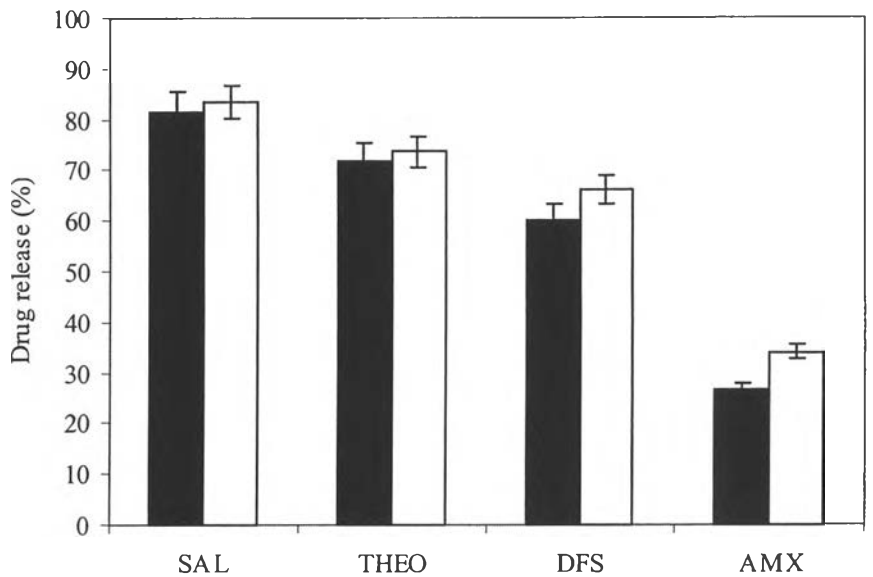

Figure 4.6 Comparison of the amounts of drugs released from chitosan and the blend film with 80% chitosan content at pH 5.5. ■ chitosan film □ blend film with 80% chitosan content.

The amount of diclofenac sodium released was less than those of theophylline and salicylic acid because diclofenac sodium did not dissolve in the blend solutions and appeared in the blend films as solid particles. Therefore, the diffusion of diclofenac sodium to the solution took longer time than salicylic acid and theophylline.

Among the drugs investigated in this study, the amounts of amoxicillin released from the blend films was the least values for all pH studied. It was found that the amount of amoxicillin released at pH 2.0, pH 5.5 and pH 7.2 were 37.2%, 34.0% and 23.5%, respectively. This may be due to the interaction between the drug molecule and polymer matrix. Risbud *et al.* (2000) reported the amoxicillin released from crosslinked chitosan-poly(vinyl pyrrolidone) air-dried hydrogel was about 31.68% and 27% at pH 1.0 and pH 2.0, respectively. They explained that the low amounts of drug released might be due to non-porous nature of the air-dried films.

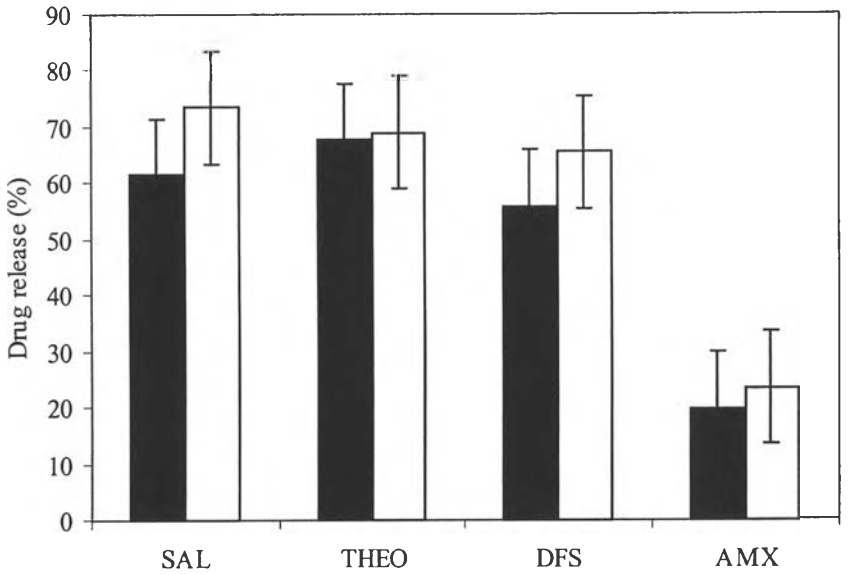

Figure 4.7 Comparison of the amounts of drugs released from chitosan and the blend film with 80% chitosan content at pH 7.2. ■ chitosan film □ blend film with 80% chitosan content.

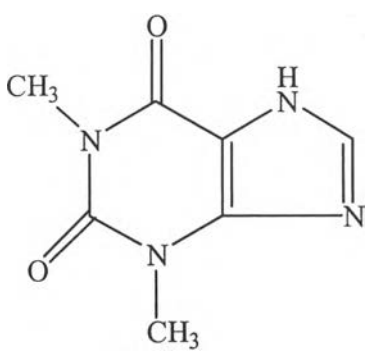

Figure 4.8 Chemical structure of anhydrous theophylline.

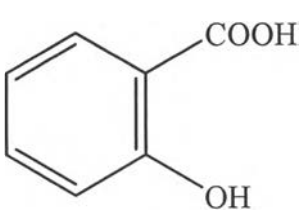

Figure 4.9 Chemical structure of salicylic acid.

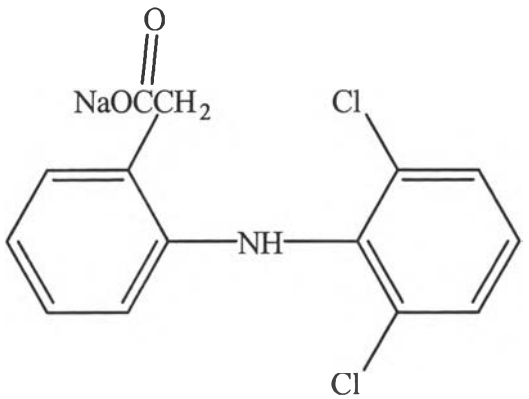

Figure 4.10 Chemical Structure of diclofenac sodium.

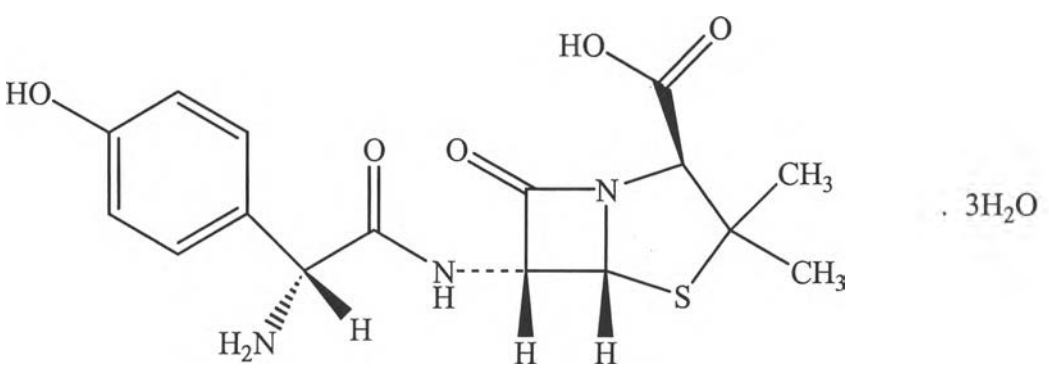

Figure 4.11 Chemical structure of amoxicillin trihydrate.

4.4 Effect of Immersion Time on Drug Release

The release profiles of each type of drug in buffer solutions at pH 2.0, 5.5, and 7.2 from the blend films with 80 % chitosan content as a function of immersion time are illustrated in Figure 4.12-4.14. The initial rates of drug releases were then calculated and the results are shown in Table 4.2. It was found that the release of theophylline from the blend films with 80% chitosan content was faster than the releases of other model drugs at all pH studied. Puttipipatkhachorn (2001) studied the drug-polymer interaction between theophylline and chitosan by Fourier Transform Infrared Spectroscopy and solid sate ^{13}C NMR spectroscopy. It was concluded that there was no interaction between theophylline and chitosan. Therefore, theophylline

was the fastest released drug in this study because there was no interaction between theophylline and chitosan.

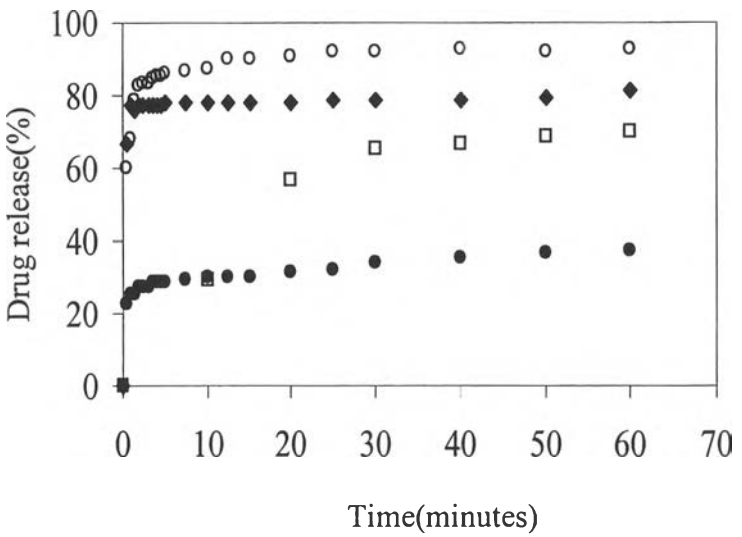

Figure 14.12 Drug release profiles from the blend films with 80% chitosan content at pH 2.0. ○: salicylic acid, ◆: theophylline, □: diclofenac sodium ,●: amoxicillin trihydrate.

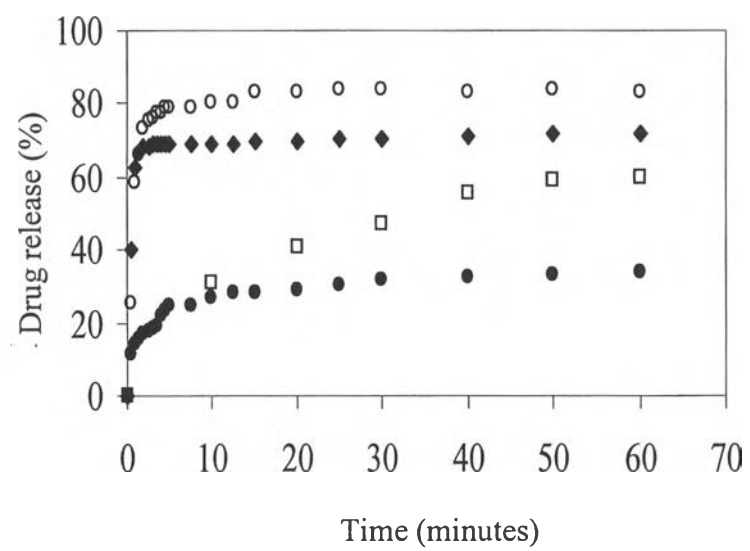

Figure 14.13 Drug release profiles from the blend films with 80% chitosan content at pH 5.5. ○: salicylic acid, ◆: theophylline, □: diclofenac sodium ,●: amoxicillin trihydrate.

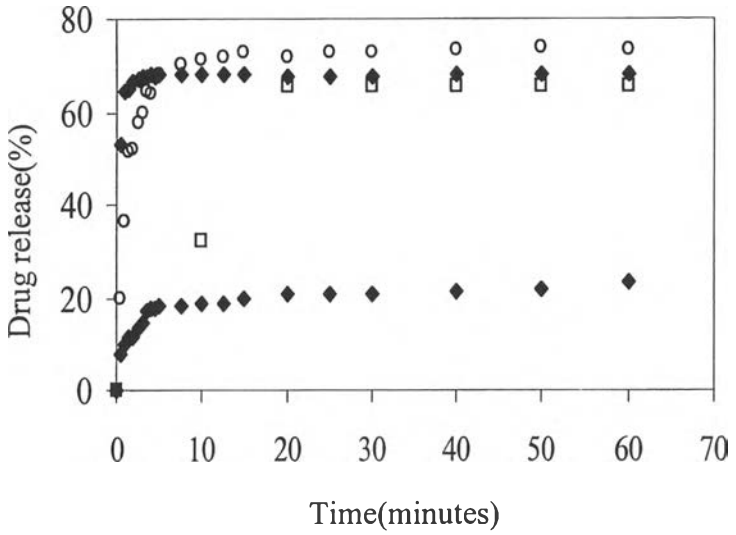

Figure 14.14 Drug release profiles from the blend films with 80% chitosan content at pH 7.2. ○: salicylic acid, ◆: theophylline, □: diclofenac sodium ,●: amoxicillin trihydrate.

Table 4.2 Initial rate of drug release from the blend films with 80% chtiosan content

Model drugs	Drug release rate (10^{-5}/sec)		
	pH 2.0	pH 5.5	pH 7.2
Salicylic acid	1.83	0.80	0.55
Theophylline	2.28	1.33	1.07
Diclofenac sodium	0.76	0.37	0.25
Amoxicillin	0.05	0.05	0.04

Moreover, the molecular size of theophylline was rather small compared with the other model drugs used. Then, theophylline could penetrate from the film easily than the others did.

The salicylic acid released from the blend films with 80% chitosan content was slower than theophylline. It could be noticed that the amount of salicylic acid

released was greater than that of theophylline. However, the initial releasing rate of salicylic acid was slower than that of theophylline. Puttipipatkhachorn (2001) was also studied the interaction between salicylic acid and chitosan by using Fourier Transform Spectroscopy. It was found that there was the salicylate formation, which was occurred by the interaction between carboxylic groups of salicylic acid and amino groups of chitosan. Therefore, the rate of salicylic acid release was slower than theophylline due to the interaction between salicylic acid and chitosan.

Diclofenac sodium release was slower than theophylline and salicylic acid release. It can be explained that because the molecular size of diclofenac sodium is bigger than theophylline and salicylic acid. Therefore, diclofenac sodium released slower due to its difficulties of diclofenac sodium for penetrating to the external swelling media.

Among the model drugs used, amoxicillin release was the slowest released drug in all pH studies. Risbud (2000) investigated the surface morphology of the amoxicillin-loaded air-dried hydrogel of crosslinked chitosan and poly(vinyl pyrrolidone) by using glutaraldehyde as crosslinking agent. It was revealed that the surface morphology of the air-dried hydrogel showed non-porous nature and non-open channel structure. Accordingly, the amoxicillin was released from the polymer matrix very slowly. In addition, the molecular size of amoxicillin is the biggest compared with the other model drugs used. Therefore, the penetration of amoxicillin through the polymer matrix was slow.

4.4.5 Effects of Concentration of Crosslinking Agent on Drug Release

The effect of crosslinking agent concentration on drug release from the blend films is shown in Figure 4.15.

To study the effect of concentration of crosslinking agent on drug release, the salicylic acid-loaded blend films with 80% chitosan content containing glutaraldehyde concentrations of 0.001, 0.01, and 0.5 mole/glucosamine unit were used. It was found that the amount of salicylic acid released was decreased with the increasing concentration of glutaraldehyde at all pHs studies. It could be possibly

explained by the term of degree of swelling as shown in Table 4.3. It indicated that the degree of swelling of the salicylic acid-loaded blend films was decreased with the

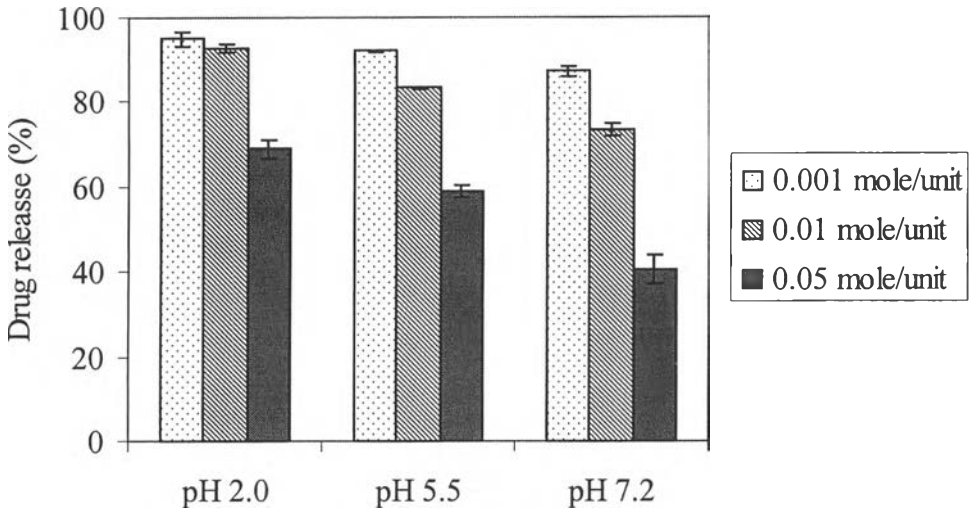

Figure 4.15 Salicylic acid released from the blend films with 80% chitosan content containing glutaraldehyde concentration of 0.001, 0.01, and 0.5 mole/glucosamine unit at pH 2.0, 5.5 and 7.2.

Table 4.3 Degree of swelling and percent weight loss of salicylic acid- loaded blend films with 80% chitosan containing various glutaraldehyde concentrations

pH	Degree of Swelling (%)[a]			Weight Loss (%)[a]		
	0.001 mole/unit	0.01 mole/unit	0.05 mole/unit	0.001 mole/unit	0.01 mole/unit	0.05 mole/unit
2.0	1453	1152	825	42.21	39.50	32.13
5.5	1213	974	672	33.16	27.81	22.81
7.2	320	199	123	25.19	24.32	19.25

[a] the average from three experiments

increasing glutaraldehyde concentration. In 1990 Peppas and Korsmeyer investigated the effect of crosslinking concentration and the release properties of poly(vinyl alcohol) on diffusion of theophylline by using glutaraldehyde as crosslinking agent. They discovered that at low concentration, the effect of crosslinking agent on the release of drug was very small, while at high crosslinking concentration a much larger effect on the drug diffusion was observed. This was attributed to the swelling behavior of the crosslink network. At low crosslinking concentration of crosslinking agent, the density of crosslinking was low that make hydrogel swell extensively. While the mesh size of the network was then big resulting in high penetration of drug particle to external environment. But at high crosslinking concentration, the degree of swelling was limited. Therefore, the mesh size of the network is closer to the size of drug, and the drug is difficult to penetrate to the external environment.