CHAPTER IV

DISCUSSION AND CONCLUSION

Preliminary investigation on suitable concentration of coating solution and coating condition

In this study, one of proposed objectives was to prepare controlled-release propranolol hydrochloride core tablets by osmotic pressure technique. It is fabricated by coating a core reservoir of an active drug or of a combination of an active drug and osmotically active agents by a semipermeable polymer to form a semipermeable film and shape-retaining coating. A passageway with a controlled diameter is drilled by a laser beam through the coating film for the release of drug solutes(Ramandan and Tawashi, 1987 ; Kelbert and Bechard, 1992 and Özdermir and Sahin, 1997).

The suitable concentration of coating solution should not exceed 1 % w/v due to the spray nozzle was obstructed when the concentration of solution was exceeded 1 % w/v. It could be clarified that the high polymer content led to high viscosity of the feed solution, so a large amount of the feed solution retained and dried in the spray nozzle.

The optimal inlet air temperature in this study was 40 °C. If the temperature of air inlet was less than 40 °C, overwetting of coated tablets occurred due to the spray rate of coating solution was more than the volatile rate of organic solvent. In the other way, when the temperature of air inlet was more than 40 °C, the orange peel was displayed. This problem occurred because the coating solution was dried before came in contact with the tablets.

For the atomizing air pressure, the suitable atomizing air pressure was 1.0 kg/cm^2. At lowering atomizing air pressure of about 0.5 kg/cm^2, the spray nozzle was obstructed because the feed rate of coating solution was more than the spray rate. If the atomizing air pressure was increased from 1.0 kg/cm^2 to 1.5 kg/cm^2, the result was similar to that obtained from atomizing air pressure at 1.0 kg/cm^2. It could be explained that the range of atomizing air pressure between 1.0 - 1.5 kg/cm^2 was corresponded to the feed rate of coating solution.

The physical appearance of core tablets

The physical appearance of tablets was dependent mainly on the nature of the raw materials and their color. Avicel PH 102, lactose, mannitol, magnesium sterate and propranolol hydrochloride are white or off-white powder. Hence, the drug, drug-lactose and drug-mannitol tablets are white with rather smooth surface and without crystals on the surface of tablet. When sodium chloride or sucrose was used as a osmotic agent within tablet. The tablets were also white with rather smooth surface but the crystals of osmotic agent appeared on the surface of the tablets. This result occurred because sodium chloride and sucrose were colorless crystal (Wade and Weller, 1994).

The scanning electron microscope of osmotic tablets

The scanning electron photomicrographs (SEM) of osmotic tablets coated with cellulose acetate without a plasticizer before exposure with water revealed that it has smooth surface and the cross-sectioned photomicrograph was not defected. In consideration of the photomicrograph of osmotic tablets coated with cellulose acetate without a plasticizer after exposure with water, the rough surface and defect of the

cross-sectioned were shown. It may be possible that because the cellulose acetate film without a plasticizer was fragile. This reason is supported by Odemir and Sahin (1997).

In the part of the photomicrographs of the osmotic tablets coated with cellulose acetate plasticized PEG 400 before contact with water, the surface was also smooth and the cross-sectioned was not defected. This results indicated that PEG 400 are compatible with cellulose acetate polymer. When photomicrographs of osmotic tablets coated with PEG 400 plasticized film after exposure with water were observed, the photomicrograph displayed a microporous film and sponge-like structure. It could be clarified that PEG 400 is water soluble owing to both hydroxyl groups of PEG 400 at the terminus and can be bonded with water by using hydrogen bridge (Okhamafe and York, 1982). So, it may be possible that PEG 400 can be leached out from cellulose acetate film leaving pores in the film after the osmotic tablets were placed in water (Lindstedt and coworkers, 1991 and Kelbert and Bechard, 1993).

When the levels of PEG 400 in the coated film of osmotic tablets coated with cellulose acetate plasticized with PEG 400 increased, the photomicrographs of osmotic tablets after contact with water demonstrated that the pore size on the membrane was increased with increasing levels of PEG 400 in coated film although the number of pore was decreased. Moreover, the thickness of membrane was increased with increasing levels of PEG 400 in coated film. The result may be possible that PEG 400 can be coalesced between the molecules by using the hydrogen bridge more than PEG 400 coalesced with cellulose acetate polymer, that is at hydroxyl side chain and methyl carboxyl side chain. Then, if the level of PEG 400 in coated film increase, the size of pore on membrane will increase.

Using scanning electron photomicrographs of osmotic tablets coated with cellulose acetate plasticized with DBP before exposure with water, the smooth surface and the cross-sectioned were not shown. The photomicrographs of osmotic tablets after contact with water, the surface and cross-sectioned of osmotic tablets was also smooth and without scar or crack. This results can be explained that DBP is very slightly soluble in water due to the major compartment is hydrophobic such as benzene ring and both dibutyl side chains. Moreover, it is possible that DBP could interact with cellulose acetate polymer, that is only the hydroxyl group using resonance effect and hydrogen bridge, more than the DBP interact with water. So, the surface and cross-sectioned was perfect although the osmotic tablets were in water.

Dissolution study

When comparing the influence of plasticizer type, that is PEG 400 and DBP, on release of drug from osmotic tablets, PEG 400 supported the amount of drug released from reservoir systems whereas DBP suppressed the release of drug. The result could be clarified that PEG 400 is soluble in water (Wade and Weller, 1994) and could be leached from the cellulose acetate film leaving pores (channels) in the film (Kelbert and Bechard, 1992). By having porous membrane, the water permeability of film was increased. Increasing the water-permeability of film supported the release of drug from the reservoir systems. This reason was in agreement with several authors who studied the effect of membrane composition (Theeuwes and Ayer, 1978 and Zentner et al., 1990).

In the part of DBP, it is very slightly soluble in water, that is 1 in 2,500 of water (Wade and Weller, 1994). When observed under SEM the surface of osmotic tablets after exposure with water, the porous film was not apparent. Hence, it was possible that

DBP could not increased water-permeability of cellulose acetate film because it could not be leached from the film.

The comparative release characteristics of drug from osmotic pump tablets coated with cellulose acetate plasticized with various levels of DBP were shown that the amount of drug released from osmotic tablets was not dependent on the level of DBP in coated film. It may be possible that the water-permeability of film was not decreased with increasing levels of DBP.

In consideration of the influence of various levels of PEG 400 in coated film on release of drug from osmotic tablets, the release of drug from osmotic tablets was increased with increasing levels of PEG 400 in coated film. It could be explained that increasing the levels of PEG 400 in coated film increased the water permeability of the film. When the water-permeability of the film was increased, the release of drug from osmotic tablets was increased.

The release profiles of drug from osmotic tablets coated with cellulose acetate plasticized with various levels of PEG 400 were found to be dependent on the level of PEG 400 in coated film. Increasing the level of PEG 400 resulted in corresponding increase in the amount of drug released from osmotic tablets. This result has been found by several authors, who studied the influence of membrane composition on release of active material from osmotic tablets (Theeuwes and Ayer, 1978, Zentner et al., 1989 and Ozdemir and Ordu, 1990). The result could be explained by increasing the proportion of PEG 400 in the membrane increased the water permeability of film, and by increasing the water-permeable of film, the amount of drug release from osmotic tablets were increased.

In consideration of the effect of various levels of PEG 4,000 in coated film on release of drug from osmotic tablets, the release profiles displayed that the amount of drug release from osmotic tablets were increased with increasing level of PEG 4,000 in coated film. It could be explained that the water permeability of film was increased with increasing the level of PEG 4,000 in coated film. When the water-permeability of film was increased, the release of drug from osmotic tablets was increased too. This result has been found by several authors who studied the influence of membrane composition on water-permeability of film (Okhamafe and York, 1982 ; Li and Peck, 1989 ; Kelbert and Bechard, 1992 and Guo et al., 1993).

The investigation of the influence of the passageway size that reflects on the amount of drug released from osmotic tablets, coated with cellulose acetate without plasticizer film, showed that the size of passageway dose not affect the amount of drug released, although the size of passageway was increased to four times. This results indicated that the amount of drug released from osmotic tablets does not depend on the size of passageway.

The result can be confirmed by increasing the hydrodynamic condition of dissolution medium, that is by changing the rotating type or increasing the rotating speed. When the hydrodynamic conditions were increased, the results shown that the amount of drug released from osmotic tablets was also independent on the passageway size. This result supported that the size of passageway in range of 400-1,500 μm does not affect the amount of drug released from osmotic tablets.

Theeuwes (1975) interested the influence of the passageway size on release rate of drug from osmotic devices. He discovered that the passageway size does not affect the release rate of drug from osmotic tablets when the cross-sectional area of the

passageway is larger than or equal to a minimum value and smaller than or equal to a maximum value.

He explained that the passageway size must be larger than or equal the minimum value to minimize hydrostatic pressure inside the osmotic devices that would affect the zero-order release rate in the following ways. Hydrostatic pressure within the osmotic devices not only decreases the osmotic influx but also it can increase the volume of the system. During the time that the osmotic devices volume is increasing, the outflow would be smaller than the inflow, resulting in a depressed release rate. In the part of the maximum value, the passageway size must be smaller than or equal to a maximum value to minimize the contribution to the release rate made by solute diffusion though the passageway (Theeuwes, 1975).

In consideration the influence of passageway size on release of drug from osmotic tablets coated with 20 % PEG 400 plasticized film and 60 % PEG 400 plasticized film coated osmotic tablets, the release profiles displayed that the passageway size affects the amount of drug released from osmotic tablets. When the hydrodynamic conditions were increased. The results demonstrated that the amount of drug released from osmotic tablets was also dependent on the passageway size. This results may occur due to the effect of film component.

The release of drug from osmotic tablets was dependent on the osmotic pressure of the dissolution medium. The release pattern showed that the amount of drug release from osmotic tablets was decreased when the dissolution medium was changed from water to pH-changed system. This result can be clarified by using Equation 8.

The equation indicated that the release of drug from osmotic devices is proportional to the difference of osmotic pressure within osmotic devices and the dissolution medium. If the osmotic pressure within osmotic devices is constant, then the amount of drug released from osmotic devices is directly related only to the osmotic pressure of dissolution medium. In case of water, the osmotic pressure is zero whereas the osmotic pressure of pH-changed system is more than the osmotic pressure of water. Hence, the amount of drug released from osmotic tablets in water is more than the amount of drug released from osmotic tablets in pH-changed system.

Ozturk et al.(1990), Nesbitt et al. (1994) and Rekhi et al. (1995) observed similar trends in release pattern as a function of osmotic pressure of dissolution medium.

In consideration of the effect of osmotic agent within osmotic tablets on release of drug, the release profiles showed that the amount of drug released from osmotic tablets increased as the osmotic pressure within osmotic tablets increased. Increasing the amount of drug released from osmotic tablets was found to be corresponded with the total osmotic pressure within the osmotic tablets. It could be explained by using the Equation 8. Form the Equation 8, the amount of drug released from osmotic devices is proportional to the difference in osmotic pressure within osmotic devices and the dissolution medium. In this experiment, the dissolution medium is water and the osmotic pressure of water is zero. So, the amount of drug released from osmotic devices is proportional only to the osmotic pressure within osmotic devices.

Conclusions

The amount of drug released from osmotic devices could be increased by using the microporous membrane when compared with the non-porous membrane. In case of the influence of plasticizers, PEG 400 could enhanced the amount of drug released from osmotic tablets whereas DBP suppressed the release of drug. The release of drug from osmotic devices were increased with increasing level of PEG 400 due to the water-permeability of the film increased. For DBP, the amount of drug released from osmotic devices was not altered when the level of DBP in coated film increased. In the part of PEG 4,000, the release of drug increased as the level of PEG 4,000 in coated film increased.

The size of passageway in range of 400-1,500 μm was not affected on the release of drug from osmotic devices although the hydrodynamic condition was changed. The amount of drug released from reservoir system could increased with increasing osmotic pressure within osmotic devices. The amount of drug released from osmotic tablets could be decreased when the osmotic pressure decreased.