2010年 8月
博士學位論文

Development of novel drug delivery systems for oriental medicines

한약을 이용한 약물 전달 체계의 개발

朝鮮大學校 大學院

藥 學 科

金 在 日

Development of novel drug delivery systems for oriental medicines

한약을 이용한 약물 전달 체계의 개발

2010年　8月 25日

朝鮮大學校 大學院

藥　學　科

金　在　日

Development of novel drug delivery systems for oriental medicines

한약을 이용한 약물 전달 체계의 개발

指導敎授　崔　厚　均

이 論文을 藥學博士 學位申請 論文으로 提出함

2010年　4月

朝鮮大學校 大學院

藥　學　科

金　在　日

金在日의 博士學位論文을 認准함

委員長　淑明女子大學校 敎授　오 승 열 (印)

委　員　朝鮮大學校　　敎授　한 효 경 (印)

委　員　三一製藥株　　敎授　박 영 준 (印)

委　員　朝鮮大學校　　敎授　강 건 욱 (印)

委　員　朝鮮大學校　　敎授　최 후 균 (印)

2010年　6月

朝鮮大學校 大學院

Contents

국문초록 vii

Abstract ix

Chapter 1

1. Introduction 1

2. Materials and methods 4

2.1 Materials 4

2.2 Methods 4

2.2.1 Preparation of freeze dried tablets 4

2.2.2 Tablet properties 5

2.2.3 Scanning electron microscopy (SEM) 5

2.2.4 Disintegration and taste 5

3. Results and discussion 6

3.1 Screening of excipients 6

3.2 Optimization of formulation parameters 9

3.3 Effect of drying conditions 11

4. Conclusions 13

5. References 14

Chapter 2

1. Introduction 25

2. Materials and methods 28

2.1 Materials 28

2.2 Methods 28

2.2.1 Preparation of mucoadhesive microspheres 28

2.2.2 Morphology 29

2.2.3 Release of model drug from the microspheres 29

3. Results and Discussion 31

3.1 Preparation of Carbopol® 971P/Kollidon® K-90 complex microspheres 31

3.2 Effect of internal phase volume fraction 32

3.3 Effect of solvent ratios of internal phase 32

3.4 Effect of drug concentration 33

3.5 Effect of temperature 34

3.6 Effect of stirring condition..... 34

3.7 Effect of drug type 35

3.8 Morphology 35

3.9 In vitro drug release 35

4. Conclusions 37

5. References 38

Chapter 3

1. Introduction 45

2. Materials and methods 48

2.1 Materials 48

2.2 Methods 48

2.2.1 Preparation of sustained release tablets 48

2.2.2 Evaluation of tablet characteristics 48

2.2.3 Dissolution tests 49

3. Results and Discussion 50

3.1 Effect of HPMC content 50

3.2 Effect drug content 51

4. Conclusions 53

5. References 54

List of Tables

Table 1.1. Effect of solid content, on tablet characteristics. (n=5) 17

Table 1.2. Effect of Hyeonggaeyeongyotang:Kollidon®CLM ratio on tablet characteristics (n=5). 18

Table 1.3. Effect of thickness at Hyeonggaeyeongyotang:Kollidon®CLM ratio 5:1 on tablet characteristics. (n=5) 19

Table 1.4. Effect of amount of aspartame, on tablet characteristics and taste. (n=5) 20

Table 1.5. Effect of start temperature with constant drying rate (5°C/h), on tablet characteristics. (n=5) 21

Table 1.6. Effect of different drying rate with constant start temperature (0°C), on tablet characteristics. (n=5) 22

Table 2.1. Effect of various parameters on the formation of the microspheres. (n=5) 40

Table 3.1. Effect of excipient composition on tablet characteristics (n=5). ... 56

Table 3.2. Effect of drug concentration on tablet characteristics (n=5)..... 57

List of Figures

Fig. 1.1. Typical scheme to make fast dissolving tablet. 23

Fig. 1.2. Scanning electron micrographs of the fracture plane of tablets containing a) drug only; b) drug /Kollidon®CLM: 5/1 24

Fig. 2.1. Determination of drying time of complex mucoadhesive microspheres. 41

Fig. 2.2. Morphology and particle size of complex mucoadhesive microspheres. 42

Fig. 2.3. In vitro release of Sofungyangjaethang from the Carbopol® 971P/Kollidon® K-90 complex at pH 1.2 and 6.8 (n=3). 43

Fig. 3.1. Diagrammatic representation of drug release according to the Higuchi model.....58

Fig. 3.2. In vitro release of model drug from fabricated formulations 7-10 (n=3).....59

Fig. 3.3. In vitro release of model drug from fabricated formulations 11-14 (n=3).....60

Fig. 3.4. In vitro release of model drug from fabricated formulations 13, 15-17 (n=3) 61

Fig. 3.5. In vitro release of model drug from fabricated formulations 18-21 (n=3).....62

(국문 초록)

한약을 이용한 약물 전달 체계의 개발

김 재 일

지도 교수 : 최후균

조선대학교 대학원 약학과

한약의 복용과 소지의 불편함을 해결하기 위하여 새로운 제제를 개발하고자 다양한 양식의 약물전달체계를 연구하였다. 먼저 복용의 편리성과 맛의 개선을 위하여 형개연교탕(荊芥連翹湯)을 모델 한약으로 속붕해성(速崩解性) 제형을 동결건조 기술을 이용하여 개발하였다. 약물함량을 높이고, 환자의 복용성을 증진시키며 붕해시간을 단축시킬 목적으로 동결건조를 이용한 정제 제형을 개발하고자 제제 처방 및 공정변수를 연구하였다. Kollidon® CLM 은 매트릭스 형성체와 쓴맛차단제로서 사용되었다. 공용매로 사용된 에탄올은 정제의 붕해 시간을 감소시켰다. 아스파탐은 더 개선된 맛을 부여하기위해 사용되었다. 정제의 외형에 있어서 건조 조건은 중요한 영향을 미치는 것으로 나타났다. 동결건조 과정은 정제의 제조 공정 시간을 감소시키고 정제 모양의 개선을 위해 최적화 되었다. 위장체류시간을 연장하기

위해 점막점착성 미립구(粘膜 粘着性 微粒球)를 Carbopol® 971 과 Kollidon® K-90 을 사용하여 용매확산법을 이용하여 제조하였다. 분산상으로서 에탄올과 25% 암모니아 용액이 사용되었고 외부상으로 옥수수 오일이 사용되었으며 Span 80 은 계면활성제로서 사용되었다. 대략 200 μm 의 입자 크기를 갖고 내부가 완전히 채워진 구형의 미립구가 제조되었다. 최적의 분산상의 부피 비율은 5%로 나타났다. 분산상(에탄올/25% 암모니아 용액)의 용매 비율은 1/2 였다. 미립구로부터 모델약물의 방출율은 pH 6.8 보다 pH 1.2 에서 낮게 나타났다. 한약을 서방형 정제(徐放形 錠劑)로 개발하기 위하여 히드록시프로필 메틸셀룰로오스(HPMC)를 메트릭스 물질로 선택 하였다. 약물 방출 속도는 HPMC 의 느린 표면 침식 속도에 따라 방출속도가 지연됨을 확인하였다. 이는 정제의 표면층이 침식되면서 약물을 용해시킬 수 있는 물이 약물에 도달하기 위해 정제의 더 깊은 내부층으로 침투해야 하기 때문에 약물 방출속도가 감소되는 결과를 나타내었다. 부형제로 사용된 미결정셀룰로오스에 대한 HPMC 의 비율은 약물 방출속도에 중대한 영향을 미쳤다. 정제에 함유된 약물 함량은 약물의 방출속도뿐만 아니라 정제의 특성에 영향을 미치는 것으로 나타났다. 이들 결과를 최적화하여 모델약물인 수용성 약물을 12 시간 이상 지연 방출시키는 서방형 제제를 개발하였다.

Abstract

Development of novel drug delivery systems for oriental medicines

Kim Jae-Il
Advisor: Prof. Hoo-Kyun Choi, PhD
Department of Pharmacy, Graduate School of Chosun University

A fast dissolving dosage form was developed using the freeze-drying technique. Hyeonggaeyeongyotang was selected as a model oriental medicine. Formulation and processing parameters were studied to obtain freeze-dried tablet with high drug loading, good palatability, and fast disintegration time. Kollidon®CLM served as both matrix former and taste masking agent. Ethanol used as co-solvent, decreased the disintegration time of tablet. Aspartame was employed to impart better taste. Drying condition was found to have a major effect in the morphology of the tablets. Freeze-drying process was optimized to decrease the processing time and improve the appearance of the tablets. Mucoadhesive microspheres were prepared to increase gastric residence time using Carbopol® 971P with Kollidon® K-90 and a solvent diffusion method. A mixture of ethanol/25% ammonia solution was used as the internal phase, corn oil was used as the external phase of emulsion, and Span 80® was used as the surfactant. Spherical microspheres with particle size around 200μm were prepared and the inside of the

microspheres was completely filled. The optimum internal phase volume ratio was 5%. The solvent ratio of the internal phase (ethanol/25% ammonia solution) was 1/2. The release rate of model drug from the microspheres was slower at pH 1.2 than at 6.8. A simple, direct compression sustained release formulation consisting, principally, of the oriental drug and hydroxypropyl methylcellulose (HPMC) was investigated. HPMC retarded the drug release by displaying slow surface erosion. The release rate decreased because the external layers of the tablet become depleted and water must penetrate the deeper layers of the tablet to reach the remaining drug. The HPMC to diluent (microcrystalline cellulose) ratio was found to influence the rate of drug release. Drug content in the tablet affected both the tablet properties as well as release rate. It was possible to sustain the release of model water-soluble drug over a 12 h period.

Chapter 1: Development of novel drug delivery systems for oriental medicines

Part 1: Freeze-dried fast dissolving tablets

1. Introduction

Fast dissolving dosage form (FDDF) dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water or chewing (Bogner, 2002). For fast dissolving, water should be penetrated into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. Maximizing the porous structure of the tablet matrix and incorporating an appropriate disintegrating agent are the basic approaches. The freeze-drying process has been used to manufacture commercial FDDF for many drugs (Yarwood, 1990; Sastry and Nyshasham, 2005; Seager, 1998). The freeze-drying process usually involves sublimation of solvent from the frozen liquid mixture of drug, matrix former, and other excipients filled into preformed blister pockets. The advantages of FDDF are; i) improved patient compliance and bioavailability, ii) suitability during traveling, iii) accurate dosing as compared to liquids, iv) better chemical stabiliy, and v) usefulness for pediatric, geriatric and psychiatric patients (Habib et al. 2000). Increasing demand for more patient-compliant

dosage poses a constant challenge to pharmaceutical companies. Different FDDFs are reported in the literature (Bogner et al., 2002). FDDFs like Orasolv®, Durasolv®, Wowtab® are compression based systems and display higher mechanical strength than freeze-drying based system, such as Zydis®. However, the drug loading is limited due to the bitter taste of drug and/or need for rapid disintegration. Larger dose of water insoluble drugs (400mg) can be loaded in the FDDF using Zydis® method, but it is limited to an upper value of 60 mg for water-soluble drugs (Seager, 1998).

Water-soluble drugs pose various formulation challenges, especially at high solute concentration before freeze-drying. This is due to the depression in freezing point, which results in collapse of supporting structure during the sublimation process (lles et al, 1993). Such collapse could be prevented by using various matrix-forming excipients that impart rigidity into the amorphous composite. Use of gelatin as a suspending agent was reported (Kearney and Wong, 1997, Seager, 1998). Nevertheless, gelatin based FDDF lacks homogeneity and sedimentation of the liquid mixture during holding, prior to filling in the blister pockets, might occur (Kearney et al, 2003). It is noteworthy that the heating step incurred with the use of gelatin increases the processing cost. Moreover, gelatin free freeze-dried tablets should be developed to avoid the potential problems with bovine spongiform

encephalopathy infections (Marwick, 1997).

Oriental medicine has been widely used across the East Asian countries. Hyeonggaeyeongyotang (aqueous extract of various herbs) is commonly used in Korea for the treatment of atopic dermatitis. Atopic dermatitis is a representative clinical syndrome that is characterized by pruritic skin lesions, infiltrating lymphocytes, macrophage and granulated mast cells (Soter, 1989). Hyeonggaeyeongyotang is usually given as a liquid dosage form packaged in a pouch. The extreme bitterness and inconveniences related to large dose volume reduce patient compliance, especially in pediatrics.

The present study investigated the conversion of an unpalatable liquid dosage form into FDDF, which would improve portability, taste, and dose accuracy. Furthermore, FDDF could improve the acceptability in terms of ease of administration, comparable bioavailability and superior taste.

2. Materials and methods

2.1 Materials

Hyeonggaeyeongyotang, Sofungyangjethang and Sofungsan were generous gift from Daegu Hani University (Daegu, Korea). Kollidon®CLM was obtained from BASF (Ludwigshafen, Germany). Sodium carboxy methylcellulose and mannitol were purchased from Junsei Chemical (Osaka, Japan). Sucrose, trehalose and glucose were bought from Sigma-Aldrich (St. Louis, MO, USA). Ethanol was purchased from Merck (Darmstadt, Germany). All other chemicals were of reagent grade and were used without further purification.

2.2 Methods

2.2.1 Preparation of freeze dried tablets

Solution of Hyeonggaeyeongyotang was filtered and freeze-dried to powder. Drug powder and excipients were mixed geometrically and distilled water was added to the mixture. The suspension was stirred and sonicated for 30 min to remove air bubbles. Specific amount of suspension was added to the mold and freezed at -40^{o}C. The frozen matrix was dried from -40^{o}C to 40^{o}C at the rate of 5^{o}C rise per hour in programmable freeze dryer (PVTFD 10R, Shinil Lab., Korea). After the drying cycle was complete, tablets were taken out of the mold and packaged to prevent intake of the moisture.

2.2.2 Tablet properties

The hardness of the tablets was measured using a hardness tester (TBH 250, Erweka, Germany) and the thickness was assessed using a micrometer (500-115, Mitotoyo, Japan).

2.2.3 Scanning electron microscopy (SEM)

The fractured samples were adhered to the sample holder by a double-sided copper tape. The samples were mounted onto an aluminum stub and then sputter coated with gold-palladium in an argon atmosphere. The morphology of the tablets was examined by field emission scanning electron microscopy (FESEM, S-4700, Hitachi, Japan) using 3 KV accelerating voltage, a 9.2 mm working distance and an emission current of 21.6μA.

2.2.4 Disintegration and taste

Disintegration time and taste were assessed in human volunteers. Chewing or sidewise tumbling and swallowing of saliva were prohibited during the test. However, movement of the tablet against the upper palate and a gentle tumbling action was permitted (Abdelbary et al., 2005). The degree of bitterness for the formulation applied in the mouth was determined on the following criteria: 1: Bitterless, 2: Slight bitterness, 3 Strong bitterness, 4: Extremely bitter.

3. Results and discussion

3.1 Screening of excipients

Typical freeze-dried tablet consists of a drug enclosed in a structure-forming matrix. The structure-forming matrix could be hydrophilic polymers like gelatin or saccharides like mannitol (Sznitowska, 2005). In addition, many researchers have explored the possibility of using other matrix-forming agents including maltodextrins, different kinds of gelatins, xantan gum and cellulose-derivatives. The type and amount of excipients would have a significant influence on the characteristics of the lyophilized tablets. In order to formulate freeze dried tablet of satisfactory mechanical characteristics, various matrix-formers were screened for their suitability in the preparation of FDT containing water-soluble drugs. The process of making freeze dried tablet is outlined in Fig. 1.1. When sugars like mannitol, lactose, sucrose, trehalose and glucose were used, blooming occurred during the freeze-drying process. The phenomenon of blooming was the consequence of freezing point depression due to the extremely high concentration of the water-soluble drug. Selection of proper excipient is crucial in order to avoid inadequate freezing or melting of the product at the temperatures used in the freeze-drying process (Seager, 1998). Some other polymeric matrix formers were used to inhibit blooming phenomena including Kollidon®CLM, Sodium carboxymethyl cellulose (Na-CMC), Vivastar®, Vivasol® and low-substituted

hydroxypropyl cellulose (L-HPC). These excipients could be used in the lower amounts than sugars, therefore, minimal freezing point depression is expected. Kollidon®CLM was a representative example of crospovidone, Vivastar® as starch derivative, Vivasol®, Na-CMC and L-HPC as cellulose derivatives. Although formulations containing Vivasol®, Vivastar® or L-HPC did not bloom, they formed hard tablets with long disintegration time. Similarly, Na-CMC increased the viscosity of the aqueous dispersion prior to freeze-drying and also resulted in stronger lyophilized tablets. Kollidon®CLM did not cause blooming and did not show significant rise in disintegration time with increasing concentration. In contrast to many other disintegrants, Kollidon®CLM is non-water soluble. As a consequence, there is no influence on the disintegration of a tablet due to increased viscosity. Kollidon®CLM acts as disintegrant by absorbing water and subsequently swelling (Technical information, 2008). This gain in volume is in part responsible for the subsequent disintegration of the tablet. Furthermore, Kollidon®CLM provided smooth mouth feeling, which is another prerequisite for FDT. It also exhibits adsorptive properties, which can be exploited to mask the taste of bitter drugs. Especially for pediatric application, good patient compliance is a precondition for the success of a drug formulation.

The rate of disintegration is not only based on the swelling in FDT. It is a

combination of many factors; one of the most important among these is the pore size within the tablet. The pores in the lyophilized products are the space created from the sublimation of ice crystals (Corveleyn and Remon, 1997). It is obvious that the size and abundance of these pores dictate the disintegration of dosage form upon contact with the medium. Fig 1.2a shows SEM fracture plane of a tablet containing no matrix former. It looked like collection of flakes with minimal pores. Fig. 1.2b shows the SEM fracture plane of a tablet containing drug: Kollidon® CLM at the ratio of 2:1. It can be seen that the formulation forms a porous structure upon freeze drying, potentially providing an ideal route for water ingress. As seen in the figure, the unique integral networks of Kollidon®CLM and drug particles impart sufficient hardness to the tablet for handling. The micrograph shows a highly porous structure, as compared to the control tablet containing just drug (Fig. 1.2a), which accounts for the fast disintegration properties. Kollidon® CLM besides being used as a matrix former and disintegrant also is recommended as stabilizer in the suspension (Technical information, 2008). The stabilizing effect is due to increase in volume of the sediment and reducing the sedimentation rate. Furthermore, inclusion of Kollidon®CLM imparted elegant yellow color to the tablet, resulting from the mixture of dark brown color of the drug and white color of the excipient. Therefore, Kollidon®CLM was selected as a matrix forming excipient for further studies.

3.2 Optimization of formulation parameters

Solid content, which refers to the amount of solid (drug and excipients) in the aqueous dispersion, is an important factor in fabricating a FDT by freeze-drying technique. Solid content affects the compactness of the freeze-dried tablet, which results in change in tablets porosity and hence the hardness and disintegration time. Table 1.1 shows the effect of solid content in the aqueous dispersion prior to freeze-drying on disintegration time and hardness of the tablet. Freeze dried tablets from aqueous dispersion with solid contents up to 10% were too fragile and disintegrated very fast. Although reducing the amount of drug and excipients in the dosage form may reduce the disintegration time, this causes a corresponding increase in unit size in order to maintain the same effective unit dosage amount. This increase in size also contributes to an increase in processing costs. Aqueous dispersion with solid content greater than 30% produced hard tablets with longer disintegration time. Therefore, 30% w/w solid content in the aqueous dispersion was determined to have both appropriate hardness and disintegration time and selected for further studies. The resulting freeze-dried tablets contained around 80% (w/w) of Hyeonggaeyeongyotang with respect to the total weight of the tablet.

The effect of different ratios of Hyeonggaeyeongyotang and Kollidon® CLM in the aqueous dispersion on tablet properties was studied at 30% w/w

of solid content. As is shown in Table 1.2, when the weight ratio of drug: Kollidon®CLM was 7.5:1, disintegration time increased to more than a minute. In addition, somewhat bitter taste was sensible. At lower proportion (drug: Kollidon® CLM ratio 2.5: 1 and 5:1) of drug content, fast disintegrating sweet tablets could be prepared. However, at drug: Kollidon® CLM ratio of 2.5:1, the resulting tablets were too fragile to handle. Aqueous dispersion containing drug: Kollidon® CLM ratio of 5:1 formed freeze dried tablets possessing proper balance between the hardness and disintegration time and was chosen for further study of thickness.

As the thickness of the tablet increased, both the disintegration time and hardness were increased (Table 1.3). However, morphology and taste of the tablet remained unchanged. It is noteworthy that even at the tablet thickness of 19 mm, no blooming was observed.

Effect of including co-solvent in the formulation was also studied. Many of the co-solvents selected for freeze-drying increase sublimation rate due to higher vapor pressures than water (Wittaya-areekul, 1999). The most commonly used organic solvent in freeze-drying is *tert*-butanol, however, it was not easy to completely remove the solvent. Retention of volatile components during freeze-drying has also been described in the literature (Teagarden and Baker, 2002). Among the other organic solvents available for freeze-drying, ethanol was chosen based on its lower toxicity. Various studies

have demonstrated the usefulness of ethanol as cosolvent during freeze-drying process (Kaneko et al., 1993; Kamijo et al., 1987). Since Hyeonggaeyeongyotang is insoluble in ethanol, large amount of water could not be replaced by ethanol. Including 5% (v/v) ethanol in the solvent phase reduced the disintegration time from 28±9 sec to 16±3 sec, without impairing the hardness of the tablet. At higher proportions of ethanol, morphology of tablet worsened.

To improve the system in terms of palatability, effect of aspartame (sweetener) was studied. The taste enhancer did not significantly alter the properties of the tablet. As seen in Table 1.4, tablet containing 10 mg of aspartame was more acceptable than the one without aspartame. However, further increase in the amount of aspartame did not have any additional effect. Vitamin C and flavors also could be added to further improve the taste without affecting tablet properties.

3.3 Effect of drying conditions

After the optimization of formulation parameters, different drying conditions were investigated. Table 1.5 shows the effect of starting temperature on the tablet characteristics, with a constant drying rate of 5^{o}C/h. Starting temperature up to 20^{o}C could be used without much compromise in the hardness and morphology of the tablets. Higher product temperatures

result in shorter cycle times, because of an increase in sublimation rate (Pikal, 1991). Since freeze-drying is an expensive process, means to shorten the preparation time are invaluable. However, at the start temperature of 40^{o}C, large number of cracks appeared and the tablets were too fragile to handle.

Effects of different drying rates on the tablet characteristics were studied at a constant start temperature. Although satisfactory tablets were obtained using start temperature of 20^{o}C, start temperature of 0^{o}C was chosen for the study of different drying rates. It was because tablet obtained with start temperature of 20^{o}C felt into borderline of acceptance. With the start temperature of 0^{o}C, drying rate up to 10^{o}C/h produced tablets with adequate hardness and good morphology (Table 1.6). At higher rates, though there was no blooming, appearance of the tablet was changed due to increased number of cracks evident especially on the top and bottom surface of the tablet.

Based on various formulation variables studied, Kollidon® CLM was selected as the matrix former. The ratio of drug: Kollidon® CLM was fixed at of 5:1 and the solid content in the aqueous dispersion was 30% w/w. 5% (v/v) ethanol was used in the solvent phase as co-solvent. Based on the drying conditions studied, start temperature of 0^{o}C with drying rate of 10^{o}C/h was found to be optimum.

4. Conclusions

A porous dosage form containing oriental drug as active pharmaceutical ingredient was developed. Kollidon®CLM prevented blooming as well as masked the bitter taste of Hyeonggaeyeongyotang. Hence, it is a useful matrix-forming agent in the formulation of FDDF made by lyophilization. Fast dissolving tablet-containing Hyeonggaeyeongyotang has potential to improve patient compliance, especially in pediatrics.

5. References

Abdelbary, G., Eouani, C., Prinderre, P., Joachim, J., Reynier, J.P., Piccerelle, P.H., 2005. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int. J. Pharm. 292, 29-41.

Bogner, R.H., Wilkosz, M.F., 2002. Fast-dissolving tablets. U.S. Pharmacist 27, 03.

Corveleyn, S., Remon, J.P., 1997. Formulation and production of rapidly disintegrating tablets by lyophilization using hydrochlorothiazide as a model drug. Int. J. Pharm. 152, 215-225.

Habib, W., Khankari, R., Hontz, J., 2000. Fast-dissolving drug delivery systems. Critical Reviews ™ Therapeutic Drug Carrier Systems 17, 61-72.

lles, M.C., 1993. Freeze-dried dosage forms and methods for preparing the Same, U.S. Patent 5188825.

Kamijo, S., Imai, A., Kodaira, H., 1987. Preparation of crystalline lyophilized gabexate mesilate with high stability. Japanese Patent 63270623.

Kaneko, S., Kishikawa, M., Sato, T., Maeda, K., 1993. Manufacture of freeze-dried anthracycline glycoside preparations with improved solubility. Japanese Patent 07076515.

Kearney, P., Murray, O.J., Green, R., Gother, L.P., 2003. Fast dispersing

dosage forms essentially free of mammalian gelatin. U.S. Patent 6509040.

Kearney, P., Wong, S.K., 1997. Method for making freeze-dried drug dosage form. U.S. Patent 5631023.

Marwick, C., 1997. BSE stets agenda for imported gelatin. J. Am. Med. Assoc. 277, 1659-1660.

Pikal, M.J., 1991. Freeze-drying of proteins. Part I: process design. Pharm. Technol. 22, 37-40.

Sastry, S.V., Nyshadham, J.R., Fix, J.A., 2000. Recent technological advances in oral drug delivery - a review. Pharm. Sci.Technol. Today 3, 138 145.

Seager, H., 1998. Drug-delivery products and the zydis fast-dissolving dosage form. J. Pharm. Pharmacol. 50, 375-382.

Soter, N.A., 1989. Morphology of atopic eczema. Allergy 44, 16-19.

Sznitowska, M., 2005. The physical characteristics of lyophilized tablets Containing model drug in different chemical forms and concentrations. Drug Research 62, 25-29.

Teagarden, D.L., Baker, D.S., 2002. Practical aspects of lyophilization using non-aqueous co-solvent systems. Eur. J. Pharm. Sci. 15, 115-133.

Technical information, 2008. Insoluble Kollidon® grades. BASF.

Wittaya-areekul, S., 1999. Freeze-drying from non-aqueous solution. Mahidol Univ. J. Pharm. Sci. 26, 33-43.

Yarwood, R., 1990. “Zydis: A novel, fast dissolving dosage form. Manuf. Chem. 61, 36 37.

Table 1.1. Effect of solid content, on tablet characteristics.

	Solid content (%) w/w	*In vivo* DT (Sec)	Hardness (kp*)
F11	5	16±1	NA
F12	10	16±6	NA
F13	20	20±2	3±0.6
F14	30	49±3	6.1±1.1
F15	40	159±13	10.5±2.1
F16	50	390±14	24.4±3.8

*kp = kilopascal

Values are represented as mean ± standard deviation (n=5)

Table 1.2. Effect of Hyeonggaeyeongyotang:Kollidon®CLM ratio on tablet characteristics.

	Drug: Kollidon ratio	*In vivo* DT (Sec)	Hardness (kp*)
F17	2.5:1	8±2	2.0±0.2
F18	5:1	30±6	6.2±1.2
F19	7.5:1	66±4	8.6±1.7
F20	10:1	85±9	15±3.6

*kp = kilopascal

Values are represented as mean ± standard deviation (n=5)

Table 1.3. Effect of thickness at Hyeonggaeyeongyotang:Kollidon®CLM ratio 5:1 on tablet characteristics.

Thickness (mm)	*In vivo* DT (Sec)	Hardness (kp*)
4	30±6	6.2±1.2
7	52±11	7.4±2.1
11	82±4	8.3±1.7
19	138±35	9.7±2.6

*kp = kilopascal

Values are represented as mean ± standard deviation (n=5)

Table 1.4. Effect of amount of aspartame, on tablet characteristics and taste.

	Aspartame (mg)	*In vivo* DT (Sec)	Hardness (kp*)	Taste#
F21	0	28±3	5.3±0.3	2
F22	10	25±2	4.5±0.7	1
F23	20	33±5	4.9±0.8	1
F24	30	27±3	4.9±1.2	1
F25	40	27±2	4.5±0.8	1

*kp = kilopascal

1: Bitterless; 2: Slightly bitter

Values are represented as mean ± standard deviation (n=5)

Table 1.5. Effect of start temperature with constant drying rate (5°C/h), on tablet characteristics.

Start temp. (°C)	*In vivo* DT (Sec)	Hardness (kp*)
-40	31±2	5.3±0.5
-20	29±4	4.3±0.6
0	25±5	4.0±0.8
20	30±4	3.4±0.5
40	25±1	2.6±0.4

*kp = kilopascal

Values are represented as mean ± standard deviation (n=5)

Table 1.6. Effect of different drying rate with constant start temperature ($0^{o}C$), on tablet characteristics.

Rate ($^{o}C/h$)	*In vivo* DT (Sec)	Hardness (kp*)
2.5	31±2	4.4±0.5
5	25±5	4.0±0.8
10	24±2	3.3±0.2
20	23±8	2.8±0.8
40	31±4	2.1±0.7

*kp = kilopascal

Values are represented as mean ± standard deviation (n=5)

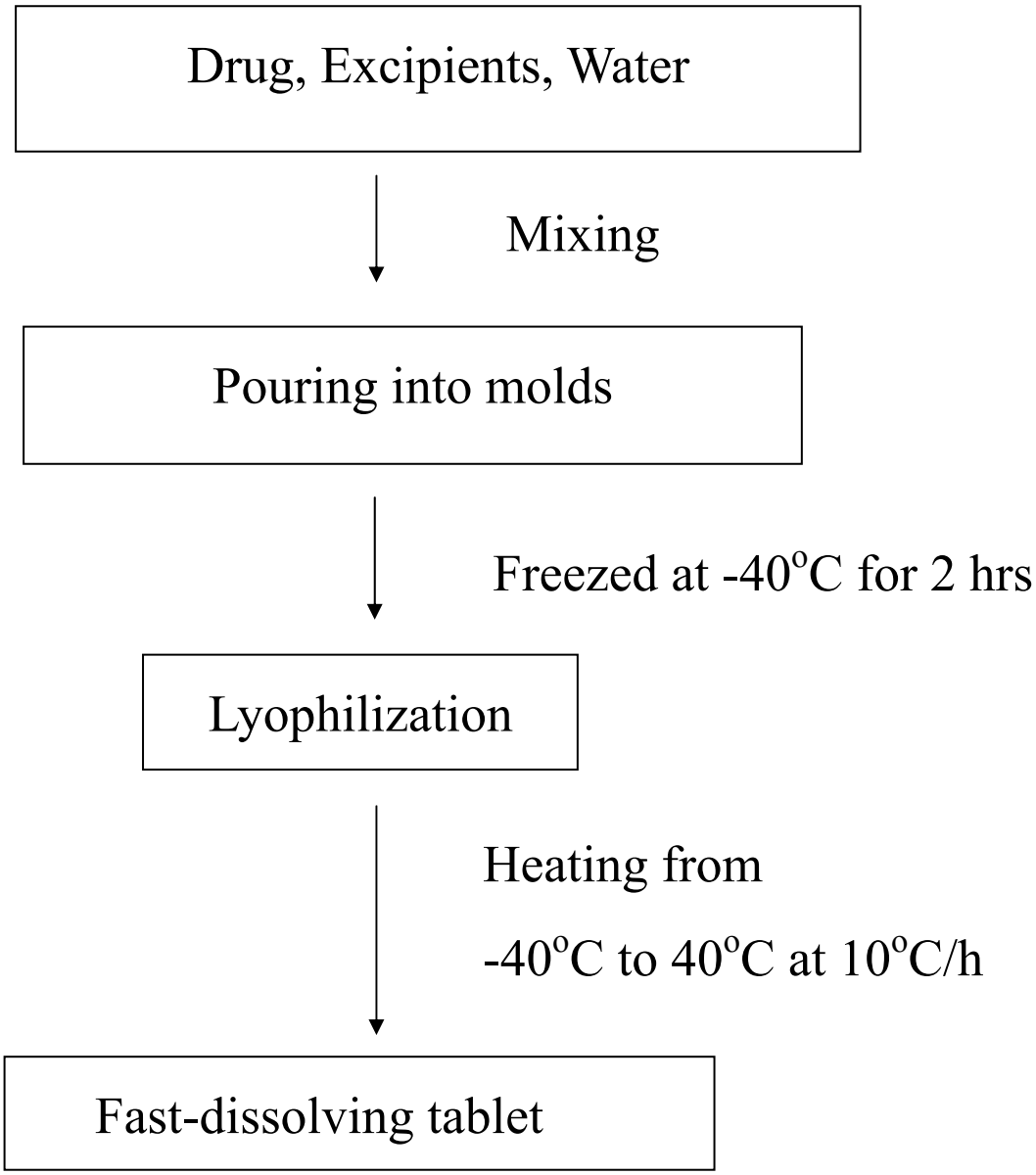
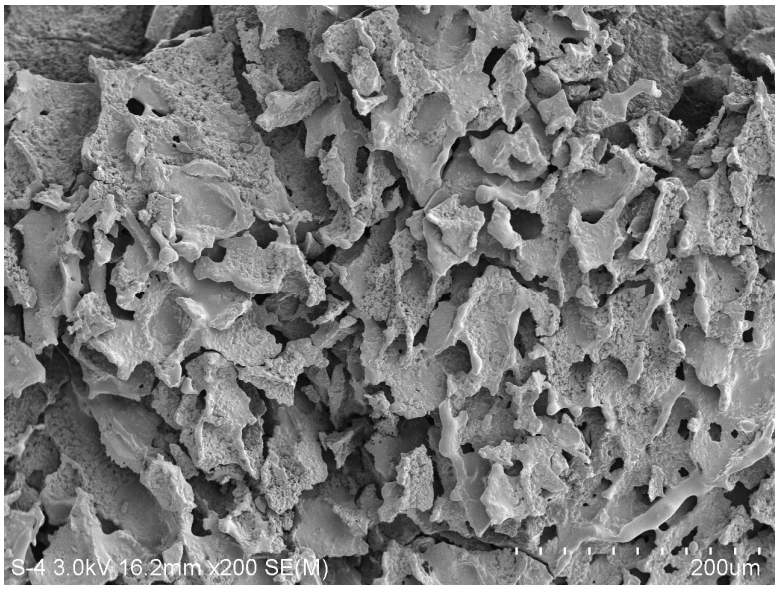


Fig. 1.1. Typical scheme to make fast dissolving tablet.

a)



b)

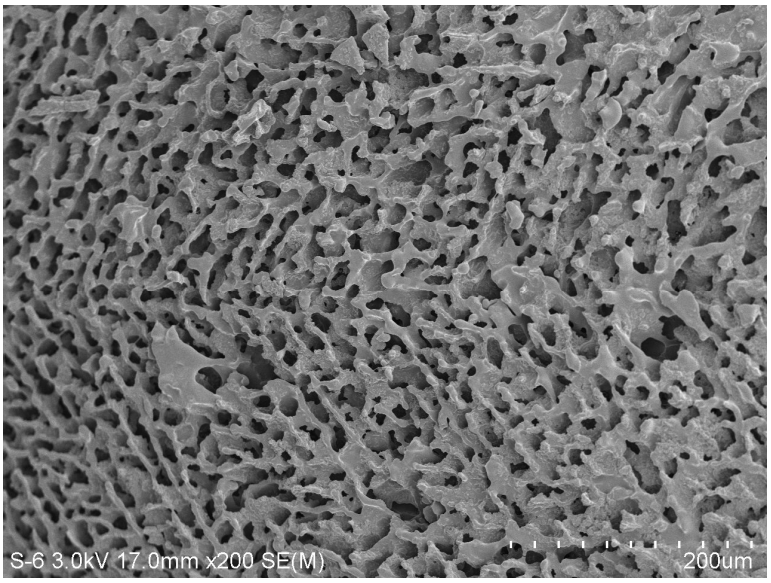


Fig. 1.2. Scanning electron micrographs of the fracture plane of tablets containing a) drug only; b) drug /Kollidon®CLM: 5/1

Chapter 2 : Development of novel drug delivery systems for oriental medicines
Part 2: Mucoadhesive microspheres

1. Introduction

In order to develop oral drug delivery systems, it is necessary to optimize both the residence time of the system in the gastrointestinal (GI) tract and the release rate of the active ingredient from the system. One of the most extensively studied methods for prolonging the residence time in the GI tract is using mucoadhesive polymers that adhere to the mucus layer and release the loaded drug in a sustained manner (Lueßen et al., 1994 and Wang et al., 2001). The intimate contact of the mucoadhesive polymer with the mucous surface can result in an increased drug retention time in the GI tract (Wang et al., 2001). Mucoadhesive dosage forms have been reported to improve the absorption and systemic bioavailability of the drugs that are normally poorly absorbed (Nagai and Machida, 1985). While the GI residence time of some of the mucoadhesive dosage forms was not extended in vivo (Khosla and Davis, 1987 and Harris et al., 1990), various mucoadhesive microspheres have been successful in extending the GI residence time (Wang et al., 2001 and Nagahara et al., 1998).

When the mucoadhesive dosage form is administered in either tablet or

capsule form, they may or may not adhere to the mucous surface due to the weight of the dosage form and the vigorous movement of the GI tract, resulting in a large variation. However, the mucoadhesive microspheres have some advantages. These include lightweight and smaller dose variations due to the large number of microspheres administered.

The widely studied mucoadhesive materials include chitosan, hydroxypropyl cellulose, poly (acrylic acid) (PAA) and their derivatives. Although, Carbopol® 971P, a derivative of PAA, is considered to be one of the best mucoadhesive polymers, the high water solubility of Carbopol® 971P critically limits its use as a carrier for the sustained release of a drug. PAA based interpolymer complexation (Choi et al., 1999, Chun et al., 2001, Chun et al., 2002a and Chun et al., 2002b) has been examined in order to reduce the water solubility of PAA. In those studies, it was shown that the water solubility of PAA could be reduced and the adhesive force could be maintained via the complexation of the PAA with proton accepting polymers such as poly (ethylene glycol), poly (ethylene glycol) macromer, poloxamer and poly (vinyl pyrrolidone) (PVP) (Choi et al., 1999, Chun et al., 1999, Chun et al., 2001, Chun et al., 2002a and Chun et al., 2002b). It was also observed that PAA and PVP aggregate and precipitate in ethanol and water in a relatively short period of time, resulting in the formation of a PVP/PAA interpolymer complex, suggesting that the intensity of hydrogen bonding

between PAA and PVP is quite strong. It was believed that this strong complexation could be utilized to prepare mucoadhesive microspheres. Each component is soluble in water. However, when they come together they form a complex and precipitate. If Carbopol® 971P solution and Kollidon® K-90 solution can be emulsified and droplets of each emulsion collides afterwards, complexation should occur, which will solidify to form microspheres.

This study investigated the effect of various preparation parameters on the formation and morphology of microspheres containing extracts from oriental medicine and optimized the preparation conditions for microspheres. In addition, the release of a drug from the prepared mucoadhesive microspheres was examined.

2. Materials and methods

2.1 Materials

Hyeonggaeyeongyotang, Sofungyangjethang and Sofungsan were generous gift from Daegu Hani University (Daegu, Korea). Kollidon® K-90 was obtained from BASF (Ludwigshafen, Germany). Carbopol® 971P was purchased from Aldrich (Milwaukee, WI). Sorbitan monooleate (Span 80®) and 25% ammonia solution was purchased from Junsei Chemical (Tokyo, Japan). Corn oil was acquired from CJ Corporation (Seoul, Korea). Ethanol was purchased from Merck (Darmstadt, Germany). All other chemicals were of reagent grade available commercially.

2.2 Methods

2.2.1 Preparation of mucoadhesive microspheres

The mucoadhesive microspheres were prepared by interpolymer complexation and solvent diffusion method. Carbopol® 971P (0.077 g) was dissolved in 7ml of ethanol/25% ammonia solution (1/2, v/v) and shaken in shaker overnight. Kollidon® K-90 (0.123 g) and model drug were dissolved in 3 ml of ethanol/25% ammonia solution (1/2, v/v) and stirred overnight. The two solutions were mixed and stirred for 3 h. Using a syringe, the mixture was sequentially dropped into 200ml of corn oil, which was used as the external phase. The external phase contained 80μl of Span 80® as a

surfactant. They were stirred with a magnetic bar at 500 rpm at an ambient temperature over 36 h. The microspheres were gradually hardened and the hardened microspheres were collected by filtration. They were washed several times with n-hexane and dried at 80^{o}C over 4 h. Drying time was determined by taking weight of microspheres at different time intervals. Fig. 2.1 shows that beyond 4 h, the weight of microspheres is constant. The yield was calculated by dividing the weight of the collected microspheres by the total weight of all the non-volatile components used for preparing the microspheres.

In order to examine the effect of the formulation parameters on the formation of microspheres, each relevant variable was changed with other variables fixed as previously described.

2.2.2 Morphology

The morphology of the microspheres was examined by camscope (Sometech Incorporated, Seoul, South Korea). The sample was mounted onto a glass slide and observed under the light source.

2.2.3 Release of model drug from the microspheres

The drug release test was carried out using a dissolution tester (DST 810, LABFINE, Inc., Korea). The drug-loaded microspheres were placed in 900

ml of a release medium and stirred at 50 rpm at 37^{o}C. The release media tested were pH 1.2 HCL solution and pH 6.8 phosphate buffer solution. An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through a 0.45 μm-syringe filter, and analyzed by UVVIS spectrometer (UV 1601, Shimadzu).

3. Results and discussion

3.1 Preparation of Carbopol® 971P/Kollidon® K-90 complex microspheres

Carbopol® 971P and Kollidon® K-90 are known to form a complex in an aqueous solution and in some organic solvents such as ethanol (Chun et al., 2002a). Once they form a complex, the aqueous solubility greatly decreases without losing the mucoadhesive properties of Carbopol® 971P and the complex formed precipitates in the solution. This principle was utilized to prepare the mucoadhesive microspheres. The mixture of Carbopol® 971P and Kollidon® K-90 solutions were sequentially dropped and dispersed in corn oil. Corn oil was chosen as the external phase because the ammonia solution as an internal phase is not miscible with corn oil and the complex is not soluble in it. The droplets of Carbopol® 971P/Kollidon® K-90 complex gradually solidified and hardened as the ammonia solution diffused out of the internal phase. The morphology and particle size of the complex microspheres is shown in Fig. 2.2.

In order to identify the optimum preparation conditions, the effects of the various experimental parameters, such as the internal phase volume fraction, the solvent ratio of the internal phase, drug concentration, elevated temperature, and the stirring condition, on the formation of microspheres were investigated.

3.2 Effect of internal phase volume fraction

The volume fractions of the internal phase tested were 5, 7.5, and 10% of the external phase with the Carbopol® 971P and Kollidon® K-90 concentrations in the internal phase being kept constant. The observation of the Carbopol® 971P/Kollidon® K-90 complex microspheres formation is shown in Table 2.1. At an internal phase volume fraction of 5 and 7.5%, the formation was relatively good. In the case of 10%, the degree of aggregation abruptly increased and the surface of microspheres obtained were irregular. As the volume fraction of the internal phase was increased, the medium became densely populated with internal droplets. Until ammonia and water inside the droplets completely diffused out and evaporated, the formed microspheres would be sticky. Due to the dense population and sticky properties of the droplets, they have a greater chance of coming in contact with each other and aggregating. Therefore, as the volume fraction of the internal phase exceeds the optimal range, larger droplets tend to aggregate and smaller droplets form microspheres, resulting in irregular shaped particles.

3.3 Effect of solvent ratios of internal phase

The effect of various solvent ratios of the internal phase (ethanol/25%ammonia solution) on the formation of microspheres were

investigated (Table 2.1). At ethanol/25%ammonia solution ratio of 1/0 as well as below a ratio of 1/3, the microspheres hardly formed. However, at the ratios of 1/1 and 1/2, most of the microspheres formed and showed spherical shape. The content of water in the internal phase appeared to play a key role in the formation of microspheres. After ethanol and ammonia preferentially diffused out into the corn oil phase, water mainly constitutes the core of emulsion droplets. As a result, the water content directly affects the solidification time of the microspheres. When the ethanol/water ratio was 1/3, the solidification time of the microspheres increased due to the relatively large amount of water, which increased the collision frequency between the incompletely solidified microspheres with adhesive property in the wet state. As a result, the degree of aggregation increased. When pure ethanol was used as an internal phase solvent, it spread over the surface of corn oil as soon as the ethanol solution was dropped into the corn oil and formed a film as the ethanol quickly evaporated from the surface of the corn oil. The film partly adhered to the wall of the beaker or aggregated.

3.4 Effect of drug concentration

The effect of drug concentration on the formation of microspheres is shown in Table 2.1. The drug concentrations tested include 20, 35 and 50%. The aggregation of the particles increased at drug concentration more than

20%. Viscosity of the internal phase increases with increasing drug concentration. As the viscosity of the internal phase increases, it becomes more difficult to break up the droplets to a smaller size and larger droplet will be formed that could settle as aggregates. It was also suggested in the literature that the stirring efficiency was reduced due to the increased viscosity with increased polymer concentration (Singh and Udupa, 1997).

3.5 Effect of temperature

Table 2.1 shows the effect of temperature on the formation of microspheres. At elevated temperature, the morphology of microspheres worsened. This could be due to rapid diffusion of the solvent that resulted in blisters on the surface of the microspheres.

3.6 Effect of stirring condition

Different types of stirring conditions had a significant impact on the particle size and yield of microspheres. When mechanical stirrer was used, smaller particle sized microspheres were obtained and the yield also reduced to 43.0%. This could be due to the deleterious action of propeller. Before and during the solidification process, the droplets were chopped when encountered with the blade.

3.7 Effect of drug type

When different model drugs were used, microsphere formation was not altered. Lowest yield was obtained when sofungsan was used as model drug (Table 2.1). However, in all the cases yield was satisfactory.

3.8 Morphology

The morphology of the microspheres was examined by camscope. The view of microspheres showed a spherical shape with smooth surface morphology (Fig. 2.2). The particle size ranged from about 130 to 230μm.

3.9. In vitro drug release

Fig. 2.3 shows the in vitro release profile of a model drug, sofungyangjaethang, from the microspheres made from Carbopol® 971P/ Kollidon® K-90 complex at pH 1.2 and 6.8. The release rate of sofungyangjaethang from the Carbopol® 971P/ Kollidon® K-90 complex microspheres was significantly slower at pH 1.2 than at pH 6.8. Hydrogen bonding between Carbopol® 971P and Kollidon® K-90 was so strong at a pH much lower than the pKa of Carbopol® 971P that they barely dissociated in to Carbopol® 971P and Kollidon® K-90. These results suggest that the Carbopol® 971P/ Kollidon® K-90 microspheres can be used as a drug-

delivery system for sustaining the release of model oriental drugs.

4. Conclusions

In the present study, mucoadhesive microspheres of oriental drugs were prepared by emulsion solvent evaporation method. Oriental drugs could remain in the stomach for an extended time and be better absorbed in the upper part of gastrointestinal tract. However, pharmacokinetic study should be done to assess whether the oral bioavailability of oriental drugs in mucoadhesive microspheres would be enhanced due to the prolonged residence time in stomach.

5. References

H.-K. Choi, O.-J. Kim, C.-K. Chung and C.-S. Cho, A novel mucoadhesive polymer prepared by template polymerization of acrylic acid in the presence of poly(ethylene glycol), *J. Appl. Polym. Sci.* **73** (1999), pp. 2749–2754.

M.-K. Chun, C.-S. Cho and H.-K. Choi, A novel mucoadhesive polymer prepared by template polymerization of acrylic acid in the presence of poloxamer, *J. Appl. Polym. Sci.* **79** (2001), pp. 1525–1530.

M.-K. Chun, C.-S. Cho and H.-K. Choi, Mucoadhesive drug carrier based on interpolymer complex of poly(vinyl pyrrolidone) and poly(acrylic acid) prepared by template polymerization, *J. Control. Release* **81** (2002), pp. 327–334.

M.-K. Chun, H.-K. Choi, D.-W. Kang, O.-J. Kim and C.-S. Cho, A mucoadhesive polymer prepared by template polymerization of acrylic acid in the presence of poly(ethylene glycol) macromer, *J. Appl. Polym. Sci.* **83** (2002), pp. 1904–1910.

D. Harris, J.T. Fell, H.L. Sharma and D.C. Taylor, GI transit of potential bioadhesive formulations in man: a scintigraphic study, *J. Control. Release* **12** (1990), pp. 45–53.

R. Khosla and S.S. Davis, The effect of polycarbophil on the gastric emptying of pellets, *J. Pharm. Pharmacol.* **39** (1987), pp. 47–49.

H.L. Lueßen, C.-M. Lehr, C.-O. Rentel, A.B. Noach, J.A.G. de Boer, J.C.

Verhoef and H.E. Junginger, Bioadhesive polymers for the peroral delivery of peptide drugs, *J. Control. Release* **29** (1994), pp. 329–338.

N. Nagahara, Y. Akiyama, M. Nakao, M. Tada, M. Kitano and Y. Ogawa, Mucoadhesive microspheres containing amoxicillin for clearance of *Helicobacter pylori*, *Antimicrob. Agents Chemother.* **42** (1998), pp. 2492–2494.

T. Nagai and Y. Machida, Mucosal adhesive dosage forms, *Pharm. Int.* **6** (1985), pp. 196–200.

U.V. Singh and N. Udupa, In vitro characterization of methotrexate loaded poly(lactic-co-glycolic) acid microspheres and antitumor efficacy in Sarcoma-180 mice bearing tumor, *Pharm. Acta Helvetiae* **72** (1997), pp. 165–173.

J. Wang, Y. Tabata, D. Bi and K. Morimoto, Evaluation of gastric mucoadhesive properties of aminated gelatin microspheres, *J. Control. Release* **73** (2001), pp. 223–231.

Table 2.1. Effect of various parameters on the formation of the microspheres.

Processing parameter	Observation
Internal phase volume fraction	
5%	Microspheres formed
7.5%	Microspheres formed
10%	Irregular surface
Solvent ratio of internal phase (ethanol/25% ammonia solution)	
1/0	Precipitation
1/1	Microspheres formed
1/2	Microspheres formed
1/3	Precipitation
Drug Concentration (%)	
50	Aggregation
35	Aggregation
20	Microspheres formed
Temperature	
Room temperature	Microspheres formed
50^{o}C	Surface irregular
Stirring condition	
Mechanical stirrer, 500 rpm	Shape unsatisfactory
Magnetic bar, 500 rpm	Microspheres formed

Model drugs	Yield (%)
Hyoungyoyoungyothang	82.4
Sofungyangjethang	89.4
Sofungsan	72.4

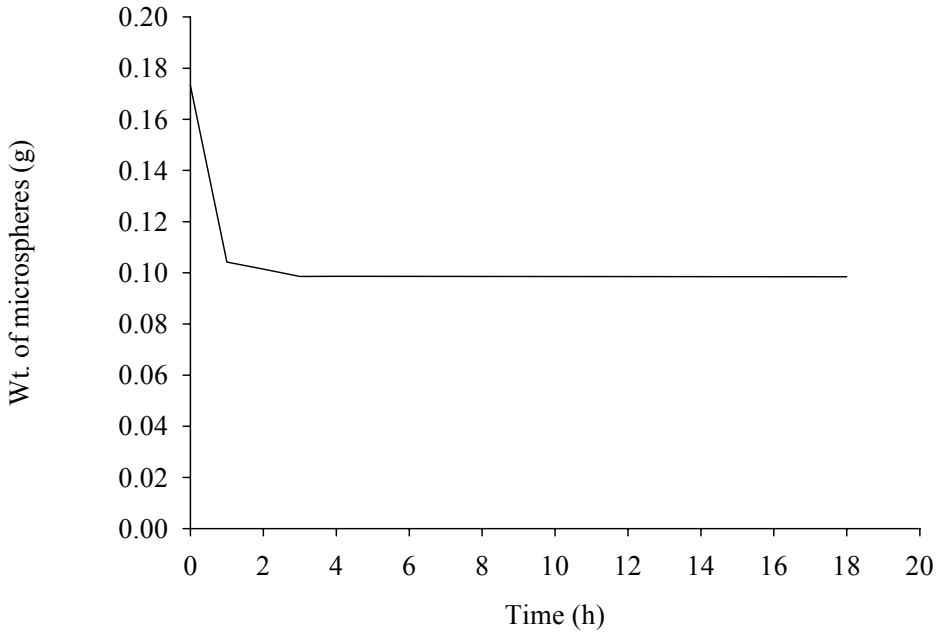


Fig. 2.1. Determination of drying time of complex mucoadhesive microspheres.

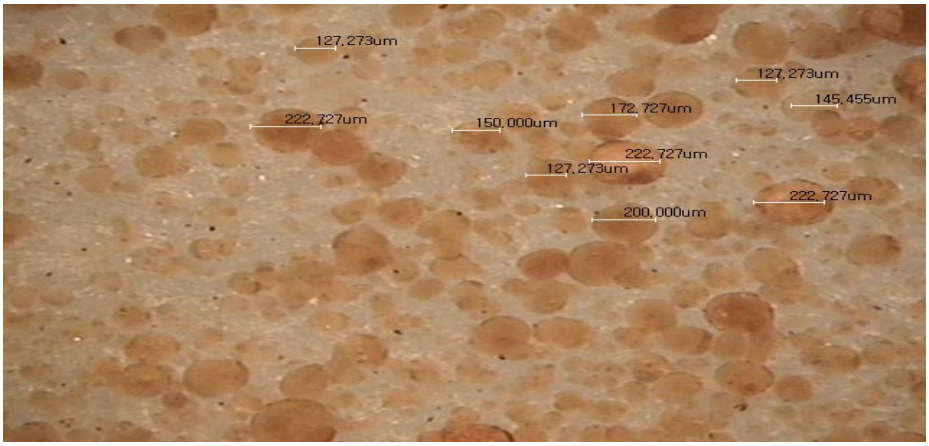


Fig. 2.2. Morphology and particle size of complex mucoadhesive microspheres.

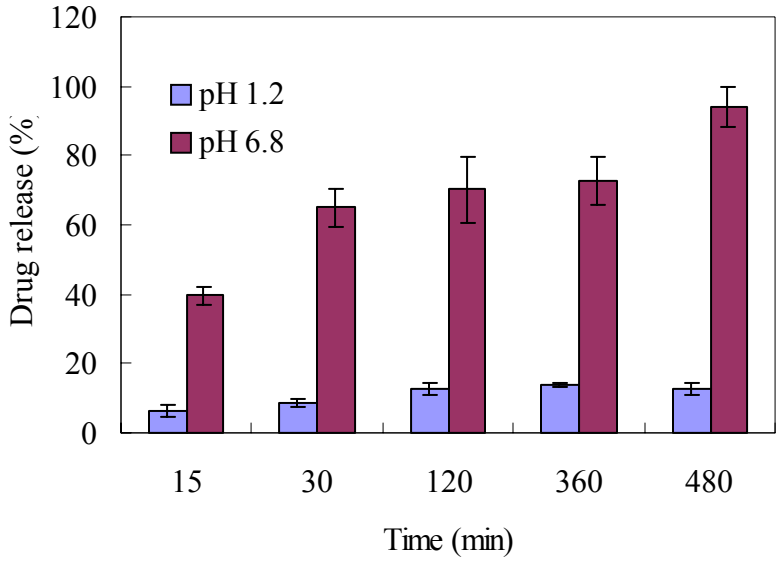


Fig. 2.3. In vitro release of Sofungyangjaethang from the Carbopol® 971P/Kollidon® K-90 complex at pH 1.2 and 6.8 (n=3).

Chapter 3: Development of novel drug delivery systems for oriental medicines
Part 3: Sustained release tablet

1. Introduction

Broadly, drug delivery system (DDS) can be classified into two types: conventional and non-conventional. Conventional DDS are simple systems where drug release is not modified. Therefore, the conventional dosage forms cannot control peak plasma concentration and provide temporal delivery of drug, which can increase toxicity and decrease therapeutic efficacy. An alternative approach to this system is the repetitive use of drug at a constant dosing interval. Although with this dosing system, drug level can be maintained within desired therapeutic range, a constant plasma concentration is not achieved. In addition, this multiple-dose therapy possesses a risk of overdosing if careful attention is not given to the plasma half-life of drug.

To counter the problems of conventional DDS, non-immediate release systems were developed. There types of DDS, do not release drug immediately after administration but rather with some control. The mechanism of this control property differ according to route of administration and intended therapeutic activity but generally it can be

divided into four categories: delayed release, site-specific release, receptor release and sustained release (Chiao and Robinson, 1995). These systems are beneficial for the maintenance of plasma drug concentration for a long period of time and therefore reduction in the dosing frequency. However, in case of failure immediate release of the drug can occur thereby producing dose dumping and localized irritation if lodged in a single area.

For many drugs, the optimal therapeutic response is only observed when adequate blood levels are achieved and maintained with minimal fluctuations. Sustained release products have become popular for the oral administration of such drugs because they give more consistent blood levels. However, increasingly sophisticated products have become so expensive that they are beyond the reach of many people. Cost containment has, therefore, become important in the pharmaceutical manufacturing industry. In the manufacture of tablets, in general, direct compression is a cost effective production method. When the technique is applied to sustained release medication, the savings in time and labor are very attractive. In keeping with the concept of reducing production costs, a simple, directly compressed formulation consisting of two principal components was envisaged. These components were the drug and a material that retards drug release. With appropriate choice of the retardant, compaction of the mixture would lead to the formation of a matrix tablet. Drug release from matrix tablets becomes

progressively slower with time (Higuchi, 1963). This is in contrast to the ideal situation in which the drug is released from the tablet at the same slow rate throughout the release period. The reason for the attenuation of the drug release rate in the Higuchi profile is illustrated in Fig. 3.1. When a matrix tablet is placed in the dissolution medium, the initial drug release occurs from the tablet's superficial layers and, consequently, the release rate is relatively fast. As time passes, the external layers of the tablet become depleted of the drug and water molecules must travel through long, tortuous channels to reach the drug remaining in the deeper layers of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium. The primary reason for the continuously decreasing rate of drug release is the increasing distance that must be traversed by water and drug molecules into, and out of, the tablet, respectively. Therefore, any mechanism that lessens the time-dependent increase in the diffusion path length would reduce the attenuation of the dissolution rate. Erosion of the tablet will gradually reduce its diameter and, hence, the diffusion path length will be reduced. The classical concept of a plastic or a hydrophobic matrix was one that was inert. More recently, however, it has been recognized that the matrix may disintegrate or erode to some extent during the dissolution process (Brossard et al., 1983). However, it has been difficult to formulate controlled release

tablets of water soluble medicaments (Evenstad et al., 1992). This may be due to leaching of the medicament from the tablet before hydration and gelling of the rate controlling excipient occurs.

This paper describes the preparation and in vitro testing of directly compressed sustained release oriental medicine tablets. Oriental medicine was chosen as the model drug because of its high water solubility and need for improvement of existing pouch type dosage form.

2. Materials and methods

2.1 Materials

Hyeonggaeyeongyotang, Sofungyangjethang and Sofungsan were generous gift from Daegu Hani University (Daegu, Korea). Hydoxypropyl methylcellulose 90SH 4000 cps was obtained from Shin Etsu, Japan. All other chemicals were of reagent grade available commercially.

2.2 Methods

2.2.1 Preparation of sustained release tablets

For the manufacture of each batch, the appropriate quantities of HPMC and drug were manually premixed for 10 min in a polyethylene bag. Microcrystalline cellulose (MCC) was added and mixed for 15 min. Then, magnesium stearate was added and mixing continued for further 3 min. Compression was accomplished using 10 stationed rotary tablet machine (Chamunda, India).

2.2.2 Evaluation of tablet characteristics

Using an Erweka hardness tester, the breaking strength of the tablets was determined. The friability and abrasion test was performed in friabilator

(Labfine Inc.) at 25 rpm for 4 min. The drug content of the tablets was measured using UV-spectrophotometry (Shimadzu, UV 1601).

2.2.3 Dissolution test

The drug release test was carried out using a dissolution tester (DST 810, LABFINE, Inc., Korea). Tablet were placed in 900 ml of a release medium and stirred at 50 rpm at 37^{o}C. The release media tested was pH 6.8 phosphate buffer solution. An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through a 0.45 μm-syringe filter, and analyzed by UVVIS spectrometer (UV 1601, Shimadzu).

3. Results and discussion

3.1 Effect of HPMC content

HPMC is an attractive non-ionic ingredient of a water-soluble cellulose ether derivative (cellulose hydroxypropyl methyl ether) for use in controlled-release preparations (Langer and Peppas, 1987; Hogan, 1989). It is available in grades containing 16.5-30% of methoxy and 4.0-32.0% of hydroxypropyl groups. HPMC is often used to prepare matrix type sustained release tablets (Shah et al., 1989; Tahara et al., 1993). The characteristics of formulations with different polymer concentrations are given in Table 3.1. Results of dissolution studies showed that drug release from the matrix tablet decreased with increase in the polymer content. Formulations 1 to 5, containing more than 29% HPMC failed to release 100 % of drug within 12 h (data not shown). Almost complete release was obtained with formulation 6 that did not contain HPMC, with in an hour.

Formulation that could release 100% drug, in a sustained manner, within 12 h could have more pragmatic value. Therefore, additional formulations containing 4 to 19% HPMC were explored. As seen in Fig. 3.2, HPMC content up to 9% did not sustain the release of model drug. When the HPMC content increased to 14%, sustained profile was obtained. To find the optimum level of polymer, formulations containing various amounts of

HPMC between 10 to 14% were explored. Fig. 3.3 shows the release profile of formulations 11-14. It was inferred that HPMC content of 12% was necessary to get the desired release of model drug.

3.2 Effect of drug content

As seen in Table 3.2, with the increase in drug content, there was increase in weight. This could be due to the fineness of the drug particles and hence the higher density. Moreover, hardness was found to be proportional with the amount of MCC in the formulations. When higher amount of drug was loaded in the formulation, tablets become more friable and abrasion value also increased. Poor compressibility of drug powder resulted in thicker tablets. Hence, drug content above 75% resulted in poor physical properties of the tablet.

Fig. 3.4 shows the release profile of formulations with various amount of drug. Formulations containing 75% drug content showed sustained release profile. However, Formulation containing 87% drug content showed rapid release. In this case, HPMC content seemed to be insufficient to sustain the release of such a large amount of drug. It was interesting to note that, formulation containing 25% drug also showed fast drug release. This could be due to the high content of MCC in the formulation, which resulted in faster disintegration of tablet and drug release at higher rate. Drug loading

between 50% and 75% seemed to impart appropriate physicochemical properties and release profile to the system. So, additional formulations containing 55% to 70% drug load were investigated. The physical properties of formulations 18-21 were quite similar (Table 3.2). Formulation containing more than 60% drug released almost 100% drug in a period of 8h (Fig. 3.5). No difference was found among the formulations 19, 20 and 21. Formulation containing 55% drug load displayed appropriate release profile. The release of water-soluble drug from the matrix type tablet prepared with HPMC is reported to occur predominantly according to square root law (Higuchi, 1963); i.e., the drug is released after dissolution by the infiltrated medium in the matrix tablet. The mechanism behind the drug release can be explained by the following process: (1) infiltration of medium into the matrix tablet; (2) hydration and swelling of the matrix; (3) dissolution of drug in the matrix, and (4) diffusion of the solubilized drug through interstitial channels. Thus, drug is released from the matrix in the soluble condition rather than the particulate condition.

4. Conclusions

Different formulation parameters were investigated to optimize the release rate of oriental drug from HPMC matrix sustained release tablet. HPMC and drug content directly influenced the device properties, such as medium infiltration rate or erosion rate of matrix and drug release characteristics. The release of oriental drug from the matrix, and tablets properties was optimized to develop a commercially viable product. However, *in vivo* studies should be conducted to further characterize the functionality of the dosage form.

5. References

C. Brossard, D., Lefort des Ylouses, D., Duchene, F., Puisieux, J.T., Carstensen, Dissolution of a soluble drug substance from vinyl polymer matrices. *J. Pharm. Sci.* **72** (1963), pp. 162-169.

C.S.L. Chiao, J.R., Robinson, Sustained-release drug delivery systems. *Remington: The science and practice of pharmacy*, 19th Edition (1995), pp. 1660-1675.

K.L. Evenstad, K.R., Malhotra and V.A., O'Neill, Controlled release tablet containing water soluble medicament, *United States Patent*, US 005126145A (1992).

J.E. Hogan, Hydroxypropyl methylcellulose sustained release technology. *Drug Dev. Ind. Pharm.*, **15** (1989), pp. 975-1000/

T. Higuchi, Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.,* **53** (1963), pp. 1145-1149.

R.S. Langer and N.A., Peppas, Present and future applications of biomaterials in controlled drug delivery. *Biomaterials*, **2** (1987), pp. 201-214.

A.C. Shah, N.J., Britten, L.S., Olanoff and N.J., Basalamenti, Gel-matrix systems exhibiting bimodal controlled release for oral drug delivery. *J. Control. Release.,* **9** (1989), pp. 169-174.

K. Tahara, M., Mikawa, S., Yokohama and T., Nishihata, Characteristics of

intestinal absorption of adinazolam and in vivo evaluation of oral sustained release tablets of adinazolam in beagle dogs. *Int. J. Pharm.*, **99** (1993), pp. 311-320.

Table 3.1. Effect of excipient composition on tablet characteristics (n=5).

S. No.	Composition (Drug/HPMC/MCC/MgSt)	Weight (g)	Hardness (kp)	Friability (%)	Abrasion (%)	Thickness (mm)
1	0.50/0.49/0.00/0.01	0.910±0.02	10.2±2.5	0.23	0.45	6.95±0.03
2	0.50/0.44/0.05/0.01	0.885±0.01	10.4±0.9	0.21	0.19	6.88±0.03
3	0.50/0.39/0.10/0.01	0.886±0.01	10.9±1.6	0.19	0.23	6.90±0.02
4	0.50/0.34/0.15/0.01	0.879±0.01	12.1±1.0	0.22	0.23	6.83±0.01
5	0.50/0.29/0.20/0.01	0.886±0.01	11.9±1.1	0.19	0.28	6.81±0.05
6	0.50/ 0.00/0.49/0.01	0.864±0.01	14.6±1.0	0.16	0.14	6.58±0.05
7	0.50/0.19/0.30/0.01	0.886±0.02	13.3±0.7	0.22	0.06	6.75±0.06
8	0.50/0.14/0.35/0.01	0.891±0.03	12.8±1.0	0.10	0.09	6.86±0.08
9	0.50/0.09/0.40/0.01	0.886±0.02	13.8±0.8	0.02	0.02	6.86±0.05
10	0.50/0.04/0.45/0.01	0.889±0.01	15.1±0.3	0.24	0.09	6.82±0.01
11	0.50/0.10/0.39/0.01	0.913±0.04	13.0±1.1	0.10	0.11	6.36±0.10
12	0.50/0.11/0.38/0.01	0.875±0.02	11.8±1.2	0.09	0.07	6.86±0.06
13	0.50/0.12/0.37/0.01	0.896±0.02	13.6±1.0	0.07	0.09	6.91±0.05
14	0.50/0.13/0.36/0.01	0.885±0.02	11.9±1.3	0.03	0.04	6.91±0.02

Table 3.2. Effect of drug concentration on tablet characteristics (n=5).

S. No.	Composition (Drug/HPMC/MCC/MgSt)	Weight (g)	Hardness (kp)	Friability (%)	Abrasion (%)	Thickness (mm)
15	0.25/0.12/0.62/0.01	831±34	13.9±1.7	0.05	0.04	7.01±0.06
16	0.75/0.12/0.12/0.01	949±25	11.2±3.1	0.07	0.15	7.07±0.03
17	0.87/0.12/0.00/0.01	953±22	3.2±1.3	0.63	0.85	7.19±0.07
18	0.55/0.12/0.32/0.01	887±12	12.3 ±1.4	0.06	0.05	7.00±0.05
19	0.60/0.12/0.27/0.01	912±8	11.8±2.5	0.08	0.07	7.04±0.02
20	0.65/0.12/0.22/0.01	925±17	11.7±0.3	0.04	0.10	7.05±0.08
21	0.70/0.12/0.17/0.01	940±24	11.5±2.7	0.10	0.13	7.08±0.04

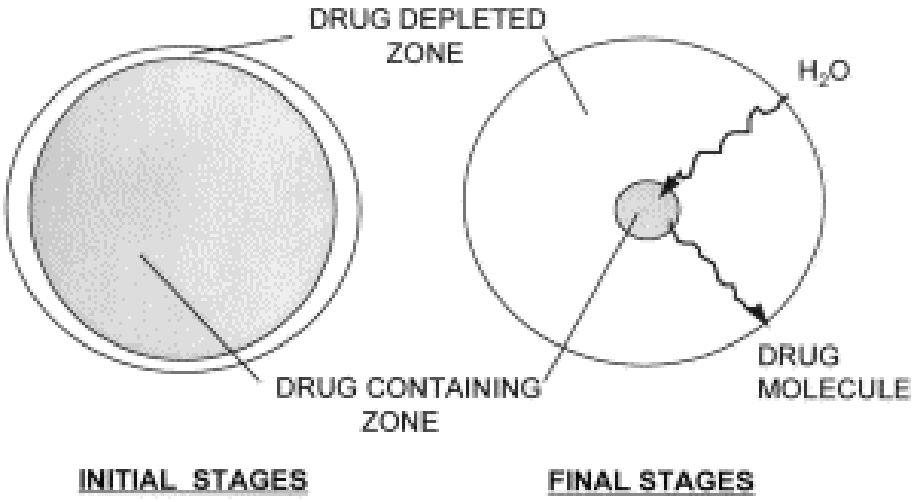


Fig. 3.1. Diagrammatic representation of drug release according to the Higuchi model.

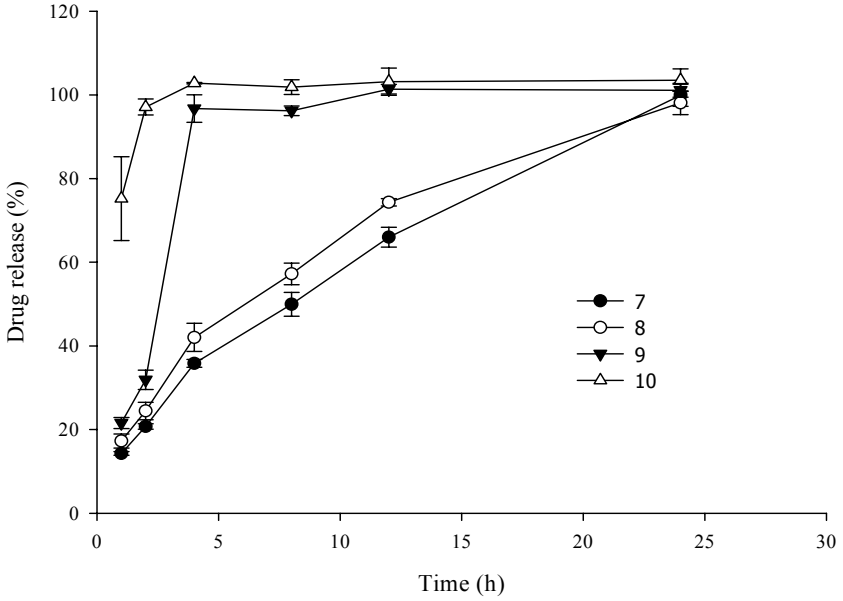


Fig. 3.2. In vitro release of model drug from fabricated formulations 7-10 (n=3).

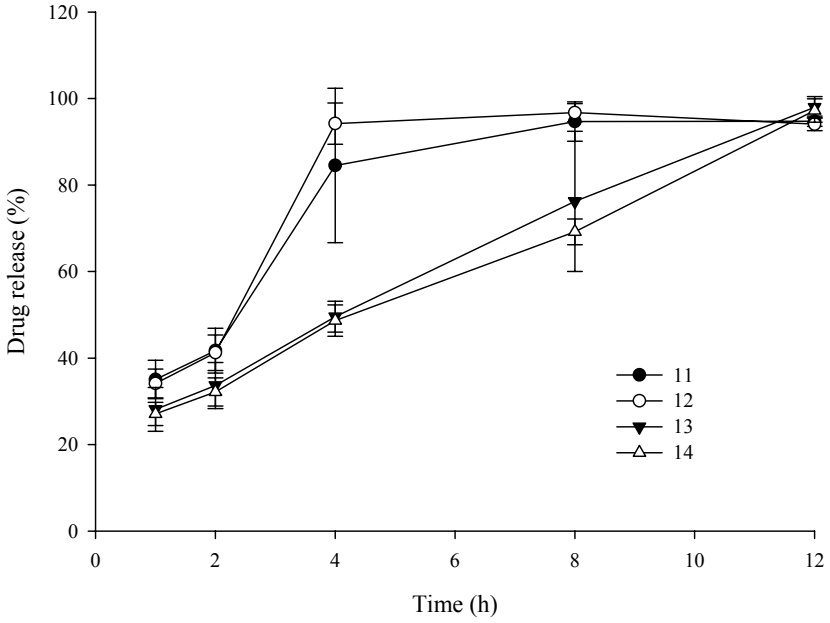


Fig. 3.3. In vitro release of model drug from fabricated formulations 11-14 (n=3).

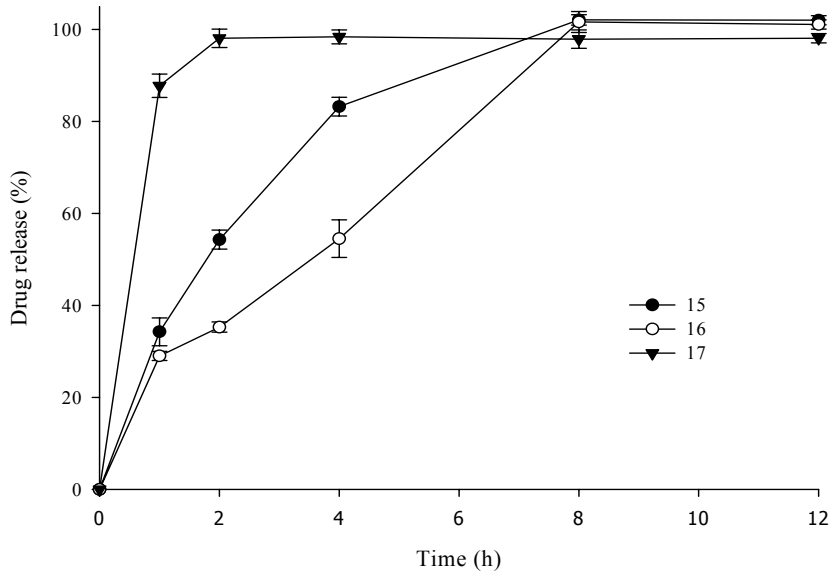


Fig. 3.4. In vitro release of model drug from fabricated formulations 15-17 (n=3).

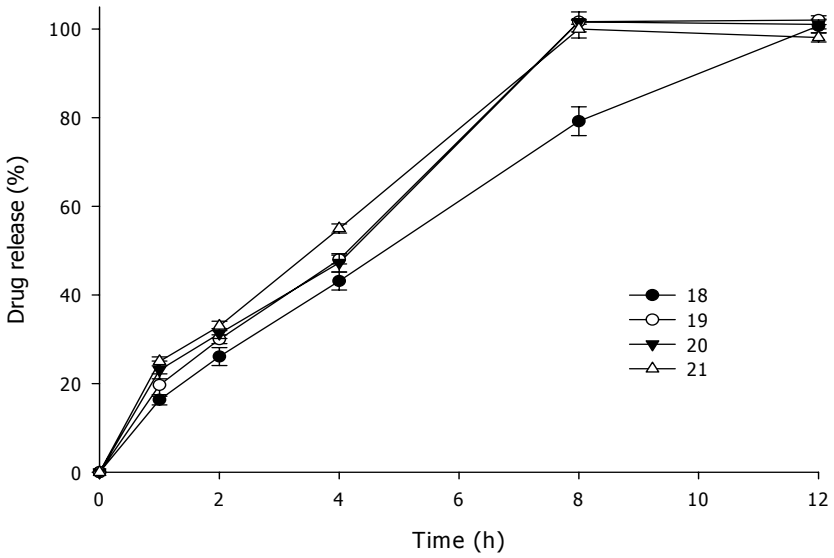


Fig. 3.5. In vitro release of model drug from fabricated formulations 18-21 (n=3).

Acknowledgements

I would like to express my sincere gratitude to my advisor Prof. Hoo-Kyun Choi, PhD, for his valuable guidance, incessant support and encouragement during my PhD degree study.

I owe special thanks to Seonja Kim for her much needed help and inspiration during my work.

I would like to thank my seniors, colleagues (especially, Robhash Kusam Subedi) and juniors in the lab for their co-operation and cheerful presence.

I wish to express my love and appreciation to my family for their endless love, understandings and support.

저작물 이용 허락서

학 과	약학과	학 번	20077533	과 정	박사
성 명	한글: 김재일 한문 : 金 在 日 영문 : Kim Jae-IL				
주 소	울산광역시 동구 전하동 301-28 번지 대경넥스빌 103 호 1003 호				
연락처	E-MAIL : kjiyhs2002kr@yahoo.co.kr				
논문제목	한글 : 한약을 이용한 약물전달체계의 개발 영어 : Development of novel drug delivery systems for oriental medicines				

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 의사 표시가 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 ( )

2010 년 8 월 25 일

저작자: 김재일 (서명 또는 인)

조선대학교 총장 귀하