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Approaches to improve dissolution of capsule containing a poorly water-soluble drug: Mefenamic acid

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Abstract

A poorly water-soluble drug, mefenamic acid (MA), in powder or granule forms was formulated in capsule dosage form. Hydrophilic and hydrophobic diluents, lactose and dibasic calcium phosphate (DCP) respectively, were used in capsules containing MA granules for preparation with polyvinylpyrrolidone K30 as a binder. The capsules containing MA granules provided faster drug dissolution profiles than did the capsules containing MA powder. Faster capsule dissolution was obtained when lactose was used as a diluent, instead of DCP, in capsules containing MA granules. Incorporation of a capsule disintegrant, sodium starch glycolate (Explotab®), into the capsule consisting of MA granules and DCP resulted in increasing dissolution of the MA capsule. However, no obvious dissolution improvement was observed when Explotab® was employed as disintegrant in the capsule consisting of MA granules and lactose. For the capsules containing MA granules, DCP and Explotab®, inclusion of a surfactant, sodium lauryl sulfate (SLS), into the formulation caused further improvement in capsule dissolution. The influences of Explotab® and SLS on dissolution of MA capsules prepared from MA powder and MA granules (with lactose or DCP as diluent) were investigated using a two-level full factorial experimental design. The use of Explotab® and SLS in the capsules consisting of MA powder yielded greater dissolution enhancing effects than their use in the capsules consisting of MA granules and each diluent. The main and interaction effects of Explotab® and SLS contents on capsule dissolution were identified using multiple linear regression analysis. The contour plots of the equations representing the relationships between the two capsule dissolution parameters, reflecting onset and completeness of capsule dissolution, and the contents of Explotab® and SLS utilized in the MA capsule formulations were constructed. From these relationships, the optimum amounts of Explotab® and SLS in the MA capsules requiring fast dissolution can be determined.

Keywords**:** *mefenamic acid, capsule dissolution, poorly water-soluble drug*

บทคัดย่อ

นำตัวยาที่ละลายน้ำยากได้แก่เมฟีนามิกแอซิด (MA) ในรูปแบบที่เป็นผงและแกรนูลไปเตรียมเป็นยาในรูปแบบแคปซูล โดยเลือกใช้แลคโตสเป็นสารเพิ่มปริมาณชนิดที่ละลายน้ำได้และไดเบสิกแคลเซียมฟอสเฟต (DCP) เป็นสารเพิ่มปริมาณชนิดที่ไม่ละลายน้ำสำหรับแคปซูลที่บรรจุด้วยแกรนูลของ MA ซึ่งเตรียมขึ้นโดยใช้โพลีไวนิลไพโรลิโดน เค 30 เป็นสารยึดเกาะ พบว่าแคปซูลที่บรรจุแกรนูลของ MA มีการละลายของตัวยาที่เร็วกว่าแคปซูลที่บรรจุผงของ MA และการใช้แลคโตสเป็นสารเพิ่มปริมาณในแคปซูลที่บรรจุแกรนูลของ MA แทนการใช้ DCP มีผลทำให้ได้การละลายของยาจากแคปซูลที่เร็วกว่า นอกจากนั้นการเติมสารช่วยแตกตัวคือโซเดียมสตาร์ชกลัยโคเลท (Explotab®) ลงในแคปซูลที่บรรจุแกรนูลของ MA และ DCP มีผลในการเพิ่มการละลายของยาจากแคปซูล อย่างไรก็ตามไม่พบการเพิ่มการละลายอย่างชัดเจนของยาจากแคปซูลที่บรรจุแกรนูลของ MA และแลคโตสเมื่อเติม Explotab® ลงไป ยังพบว่าการเติมสารลดแรงตึงผิวคือโซเดียมลอริลซัลเฟต (SLS) ลงไปในตำรับแคปซูลที่บรรจุด้วยแกรนูลของ MA และ DCP รวมทั้ง Explotab® ช่วยเพิ่มการละลายของยาจากแคปซูลมากขึ้น เมื่อทำการศึกษาถึงผลของ Explotab® และ SLS ที่มีต่อการละลายของยาจากแคปซูลที่บรรจุผงของ MA และแกรนูลของ MA (ที่ใช้แลคโตสหรือ DCP เป็นสารเพิ่มปริมาณ) โดยออกแบบการทดลองแบบฟูลแฟคทอเรียลชนิดสองระดับ พบว่าการใช้ Explotab® และ SLS ในแคปซูลที่บรรจุด้วยผงของ MA ให้ผลในการเพิ่มการละลายของตัวยาจากแคปซูลที่มากกว่าเมื่อเทียบกับการใช้สารเหล่านี้ในแคปซูลที่บรรจุแกรนูลของ MA และสารเพิ่มปริมาณแต่ละชนิด การวิเคราะห์ด้วยการถดถอยพหุคูณเชิงเส้นตรงทำให้ทราบถึงผลของอิทธิพลหลักและผลที่เกิดจากการปฏิสัมพันธ์ของ Explotab® และ SLS ที่มีต่อการละลายของยาจากแคปซูล ได้กำหนดดัชนี 2 ตัวที่บ่งชี้ถึงความรวดเร็วและความสมบูรณ์ในการละลายของยาจากแคปซูล และนำสมการที่แสดงความสัมพันธ์ของดัชนีแต่ละตัวกับปริมาณของ Explotab® และ SLS ที่ใช้ในตำรับของแคปซูลมาสร้างเป็นแผนภาพคอนทัวร์ จากความสัมพันธ์ดังกล่าวสามารถนำมาหาปริมาณที่เหมาะสมของ Explotab® และ SLS ที่ใช้ในตำรับของแคปซูลของ MA ที่จะให้การละลายของยาที่รวดเร็วตามต้องการได้

คำสำคัญ: *เมฟีนามิกแอซิด, การละลายของยาจากแคปซูล, ยาที่ละลายน้ำยาก*

1. Introduction

Hydrophobic drugs provide slow dissolution and hence capsules containing hydrophobic drugs usually exhibit slow drug dissolution from the capsule due to poor wettability of the drug (Abdou, 1989). Several approaches have been used to improve dissolution of capsules consisting of poorly water-soluble drugs. By utilizing some suitable capsule excipients such as hydrophilic diluents and suitable types of disintegrants and surfactants, the dissolution of capsules consisting of poorly water-soluble drugs can be significantly improved (Proudfoot, 1988).The optimum contents of such excipients need to be empirically determined to obtain effective dissolution enhancing effects, since usage in excessive amounts will lead to unnecessary high production costs.

A general process to improve dissolution of the hydrophobic drug from capsules is to improve the wettability of the encapsulated drug powder (Attword and Florence, 1983). There are several accepted methods to enhance wettability currently used in the pharmaceutical industry. Upon granulation of the hydrophobic drug powder with binding liquid, the drug powder is pre-wet and the dried granules become easier to wet in the dissolution medium after the capsule shells dissolve. Including hydrophilic excipients instead of hydrophobic excipients into the granules of the hydrophobic drug can also improve drug dissolution from the capsule due to higher wettability of the granules. Incorporation of a surfactant into capsule formulation is an approach to enhance the wettability of the poorly water-soluble drug. Surfactant adsorption onto hydrophobic drug particles below the critical micelle concentration can aid wetting of the particles and consequently increase the rate of solution of the particle agglomerates (Florence, 1981). Surfactants may be incorporated into solid dosage forms so that their solubilizing action comes into play as the disintegration process starts and water penetrates to form a concentrated surfactant solution around the drug particles or granules. Both facilitation of wetting through lowering of surface tension and the increase of solubility will aid dissolution of the drug. Wet granulation of a hydrophobic drug powder by a suitable binding liquid is also an alternative method utilized to improve the drug wettability (Bandelin, 1989). By wetting and granulating the hydrophobic drug powder prior to filling capsules, the drug granules can disintegrate into powder with better wettability and consequently an enhanced dissolution rate of the drug.

2. Objectives

The purpose of this paper is to study various aspects of enhancing dissolution of the capsule containing a hydrophobic drug. Mefenamic acid (MA) was chosen as a model hydrophobic drug due to its poor solubility in water (The Department of Health, Great Britain, 2008). Polyvinylpyrrolidone K30 (PVP) was employed as water-soluble granulating agent utilized to prepare MA granules due to its wide application in the wet-granulation process (Rowe, Sheskey and Quinn, 2009). In the first part of this study, the effects of a hydrophilic diluent, lactose, and a hydrophobic diluent, dibasic calcium phosphate (DCP), on dissolution of the capsule consisted of MA granule were investigated. The influences of a disintegrant, sodium starch glycolate (Explotab®) and a surfactant, sodium lauryl sulfate (SLS) on capsule dissolution were also examined.

The second part of the study focused on the combinatory effects of both Explotab® and SLS on dissolution of MA capsules prepared from MA powder and granules. The optimum amounts of both Explotab® and SLS used in MA capsule formulation were determined to obtain the most effective dissolution enhancing effects. In order to study the main and interaction effects of Explotab® and SLS on dissolution of the capsules consisting of either MA powder or MA granule (with lactose or DCP as diluent), a two-level full factorial experimental design was applied in this investigation. The optimal contents in the MA capsule formulations resulting in fast dissolution rates of the capsules consisting of MA powder or MA granule, were searched.

3. Materials and methods

The following materials were obtained from commercial sources: mefenamic acid (Lot No. 515157, supplied by Metha Group Trading Ltd., Part., Thailand), sodium lauryl sulfate (Lot No. SEP03, supplied by Srichand United Dispensary Ltd., Part., Thailand), lactose (The Lactose Company of New Zealand, Ltd., New Zealand), polyvinylpyrrolidone K30 (Lot No. PN 14/399, Germany), dibasic calcium phosphate (Lot No. 910408.1, supplied by Pharmaceutical Science Ltd., Part., Thailand) and sodium starch glycolate (Explotab®, supplied by Pharmaceutical Science

Ltd., Part., Thailand). The commercial mefenamic acid capsule, Ponstan® (Parke-Davis), was obtained from a local pharmacy as a reference capsule.

3.1 Part I. Formulation approach for enhancing MA capsule dissolution

3.1.1 Preparation of mefenamic acid capsules

MA powder was evaluated for its bulk density in order to calculate the amount of diluent needed to fill No.0 hard gelatin capsules (Lot No. 2F20-OJ, Parke Davis Capsule Division, Warner-Lambert K.K, Tokyo, Japan). For the No. 0 capsules, the MA powder of 250 mg per capsule could fill the capsule body without the use of a capsule diluent. To search for the effect of wet granulation on dissolution of MA capsule, the MA powder was wet granulated by an aqueous solution of polyvinylpyrrolidone K30 (equivalent to 2.9 mg of PVP per capsule). Two types of capsule diluent, lactose (hydrophilic diluent) and DCP (hydrophobic diluent), were used in the capsule formulations prepared from MA granule in order to fill the capsule body. To investigate the effects of other capsule excipients on dissolution of the capsules prepared from MA granules, a disintegrant, sodium starch glycolate (Explotab®) in the amount of 5 mg per capsule was incorporated into the MA capsule containing MA granule and each diluent. A surfactant, 10 mg of sodium lauryl sulfate (SLS) per capsule, was also employed in the capsule formulation consisting of MA granule, DCP and Explotab®. A capsule-filling device (Ardmore, Model CAP-FILL, U.S.A.) was used to fill the MA powder or granules into the No. 0 hard gelatin capsule. Each capsule contained the drug powder or granule equivalent to 250 mg of MA. Table 1 shows the prepared MA capsule formulations.

3.1.2 Capsule disintegration studies

Disintegration studies of the prepared MA capsules were conducted using a U.S.P. type disintegration apparatus with distilled water as medium ($37\pm1^{o}C$) according to U.S.P. 32 and NF 17 (The United States Pharmacopeia, 2009). Average disintegration time was calculated from 6 capsules obtained from each capsule formulation.

Table 1 Formulations of MA capsules

Formulation	MA powder (mg)	MA granule (mg)	Lactose (mg)	DCP (mg)	Explotab®	SLS
MA	250	-	-	-	-	-
MA granule-lactose	-	252.9	56.4	-	-	-
MA granule-DCP	-	252.9	-	52.0	-	-
MA granule-lactose+Explotab®	-	252.9	56.4		5	-
MA granule-DCP+Explotab®	-	252.9	-	52.0	5	-
MA granule-DCP+Explotab®+SLS	-	252.9	-	52.0	5	10

Table 2 Formulations of MA capsules designed according to a two-level full factorial experimental design of two variables.

Formulation	MA powder (mg)	MA granule* (mg)	Diluent		Explotab®		SLS		T_{30} (minutes)	C_{60} (%)	DT±S.D. (minutes)
			Lactose (mg)	DCP (mg)	Level	(%)**	Level	(%)**			
1	250	-	-	-	-1	2	-1	1	9	60.3	1.32±0.03
2	250	-	-	-	1	5	-1	1	15	55.6	1.71±0.39
3	250	-	-	-	-1	2	1	3	8	57.6	1.52±0.27
4	250	-	-	-	1	5	1	3	9	61.0	1.23±0.14
Control	250	-	-	-	-	-	-	-	-	4.8	1.39±0.13
5	-	257.3	56.4	-	-1	2	-1	1	21	42.4	1.35±0.11
6	-	257.3	56.4	-	1	5	-1	1	21	41.0	1.24±0.11
7	-	257.3	56.4	-	-1	2	1	3	28	36.8	1.26±0.06
8	-	257.3	56.4	-	1	5	1	3	19	45.9	1.37±0.10
Control	-	257.3	56.4	-	-	-	-	-	47	35.5	1.39±0.14
9	-	257.3	-	52.0	-1	2	-1	1	28	39.5	1.33±0.13
10	-	257.3	-	52.0	1	5	-1	1	34	37.6	1.48±0.07
11	-	257.3	-	52.0	-1	2	1	3	19	44.3	1.33±0.14
12	-	257.3	-	52.0	1	5	1	3	28	39.3	1.30±0.10
Control	-	257.3	-	52.0	-	-	-	-	70	28.6	1.43±0.14

*The MA granule consisted of PVP K30 in the amount of 7.3 mg per capsule.
** % of MA powder or % of MA granule and diluent.

3.1.3 Capsule dissolution studies

Dissolution studies of the prepared MA capsules and a commercially available MA capsule, Ponstan® (250 mg), were performed with a USP type I dissolution apparatus (Pharma Test Apparatebau GmbH, Model TW II, Hamburg, Germany) using 900 ml of pH 7.4 phosphate buffer dissolution medium prepared according to USP 32 and NF 17 (The United States Pharmacopeia, 2009). The medium was kept at 37±1°C and the basket was adjusted to rotate at 150 rpm to differentiate the dissolution of the hydrophobic drug (Mudit et al., 2011). Five milliliters of dissolution medium was withdrawn at predetermined time intervals up to 2 hours and assayed for drug content by spectrophotometry (Spectronic Instruments, Inc., Spectronic® GenesysTM, Rochester, NY, U.S.A.) at 286 nm. The volume withdrawn at each time interval was replaced with a fresh quantity of dissolution medium. The dissolution studies were conducted on 6 capsules obtained from each formulation.

3.2 Part II. The effects of Explotab® and SLS on MA capsule dissolution.

3.2.1 Preparation of mefenamic acid capsules

MA powder and granule were formulated into capsule dosage form using the No. 0 hard gelatin capsule. To prepare the MA granule, the MA powder was granulated by wet granulation process using 10% (w/v) polyvinylpyrrolidone K30 (PVP) aqueous solution as binding agent equivalent to 7.3 mg of PVP per capsule. The commonly employed capsule diluents, lactose monohydrate (hydrophilic diluent) and DCP (hydrophobic diluent), were used in capsule formulations consisting of MA granule. In order to search for combined effects of a disintegrant and a surfactant on MA capsule dissolution, Explotab® and SLS were employed in MA capsules prepared from MA powder and granule. A two-level full factorial experimental design was applied to study the effects of the two independent variables, the contents of Explotab® and SLS on MA capsule dissolution. A total of 12 formulations (Table 2) were obtained for the capsules containing MA powder, MA granule and lactose, and MA granule and DCP. The two independent variables were set as low level (coded by -1) and high level (coded by 1). The low and high levels of Explotab® and SLS contents employed in MA capsule formulations conformed to 2% and 5% of the disintegrant and 1% and 3% of the surfactant, respectively. The control capsule formulations (0% Explotab® and 0% SLS) consisting of MA powder only, MA granule and lactose, and MA granule and DCP. The prepared capsules were tested for their disintegration and dissolution by the same procedures as prescribed in Part I.

4. Results and discussion

4.1 Formulation approach for enhancing MA capsule dissolution

Figure 1 illustrates dissolution profiles of capsules consisting of MA powder and MA granules as compared to the dissolution profile of Ponstan® capsule. The Ponstan® capsule provided faster drug dissolution than did the capsule consisting of MA powder. Extremely poor capsule dissolution was obtained when the capsule was filled with MA powder only. Granulation of MA powder by PVP aqueous solution, prior to filling the capsule, resulted in significant enhancement of MA capsule dissolution as demonstrated in Figure 1. In general, wet granulation of a hydrophobic drug by an aqueous binding solution improves dissolution of a poorly water-soluble drug (Bandelin, 1989). Wetting action of the aqueous PVP solution on MA powder during wet granulation process provided better wettability. As a result, the dissolution profiles of the drug from the capsules containing MA granules were faster than that obtained from the capsule consisting of the MA powder only.

For the capsules containing MA granule, the roles of a hydrophilic diluent (lactose), and a hydrophobic diluents (DCP), on capsule dissolution are illustrated in Figure 1. DCP is a water-insoluble diluent while lactose is a water-soluble diluent. Hence, the capsule mass consisting of MA granules and lactose was more hydrophilic than the capsule mass consisting of MA granule and DCP. As a result, faster drug dissolution was obtained from the MA capsule containing lactose as compared to the one containing DCP.

Figure 1 also demonstrates the effects of Explotab® on dissolution of MA capsules consisting of MA granule and each diluent, lactose or DCP. Inclusion of Explotab® (5 mg/capsule) caused improvement in the capsule dissolution when DCP was used as diluent. However, no obvious improvement in capsule dissolution was observed when lactose was employed as diluent instead of DCP. The disintegration times of the prepared MA capsule formulations were similar, ranging from 1.22 to 1.48 minutes (Table 3). Therefore, disintegration

of the capsule mass through the 10-mesh sieve of the disintegrator was not a factor in controlling dissolution of the MA capsules. For the MA capsules containing MA granule and DCP, the particle agglomerates that passed through the 10 mesh sieve of the disintegrator contained particles of MA granules whose surfaces were covered by insoluble DCP particles that retarded drug dissolution. The presence of Explotab® within the agglomerates was responsible for further disintegration of the agglomerates into smaller particles, due to its swelling action. As a result, the use of Explotab® as disintegrant in the capsule containing MA granule and DCP improved capsule dissolution.

For the capsules containing MA granule and lactose, the presence of Explotab® caused no significant improvement in capsule dissolution. Lactose is a water-soluble diluent; hence it dissolves immediately after dissolution of the capsule shell leaving the MA granule and Explotab® powder in the medium. The swelling action of the disintegrant, Explotab®, thus did not prove to be beneficial in improving dissolution of the capsule containing MA granules and lactose.

Table 3 Disintegration times of MA capsules

Formulation	Disintegration time ±S.D. (minutes)
MA	1.39±0.13
MA granule-lactose	1.28±0.10
MA granule-DCP	1.22±0.08
MA granule-lactose + Explotab®	1.27±0.10
MA granule-DCP + Explotab®	1.28±0.08
MA granule-DCP + Explotab® +SLS	1.48±0.07

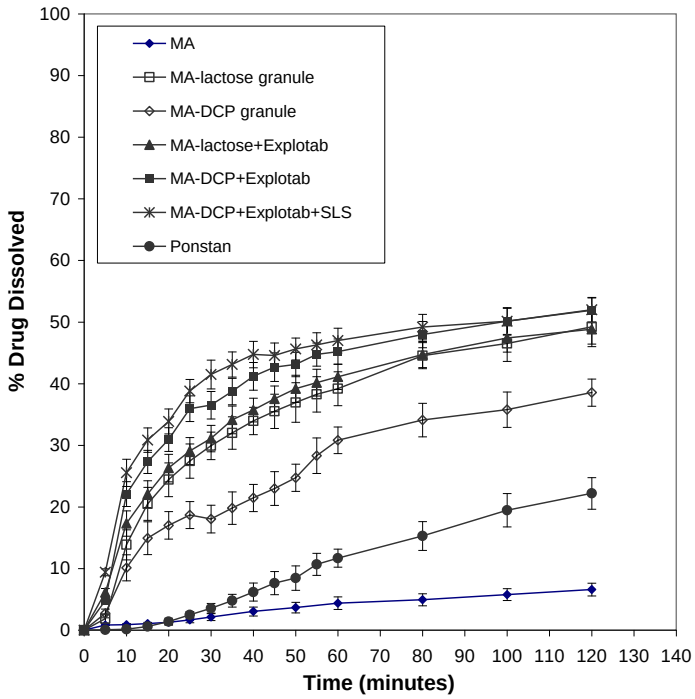

Figure 1 Dissolution profiles of MA capsules

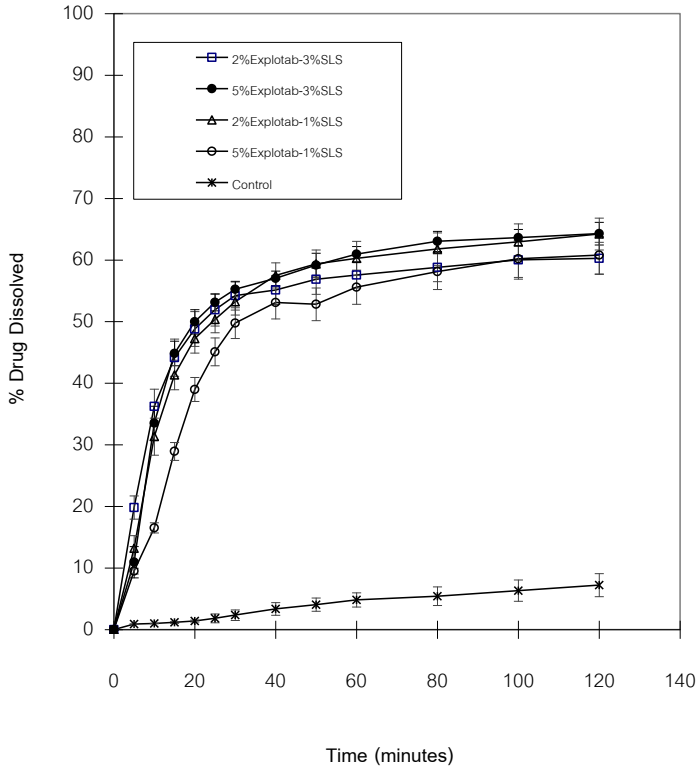

Figure 2 Dissolution profiles of MA capsules containing MA powder

The capsule containing MA granule, DCP and Explotab® provided faster dissolution than the capsule containing MA granule, lactose and Explotab®. In an effort to further enhance dissolution of the capsule, SLS was incorporated into the capsule consisting of the MA granule, DCP and Explotab®. As shown in Figure 1, the dissolution profile of the capsule containing SLS was faster than the one without SLS. As a surfactant, SLS increased wettability of the encapsulated capsule mass resulting in faster dissolution of the drug from the capsule.

From this part of the study it was demonstrated that the dissolution of the capsule containing a poorly water-soluble drug, mefenamic acid, could be enhanced. Each step of the production process could improve capsule dissolution: wet granulation of the hydrophobic drug powder and choosing of a hydrophilic diluent, also the use of a disintegrant and finally the incorporation of a surfactant in the capsule. The next part of the study focused on the coexistence of a disintegrant, Explotab®, and a surfactant, SLS, in the capsules prepared from either MA powder or MA granule (with lactose or DCP as diluent) and their effects on capsule dissolution in order to identify their optimal effective contents in the MA capsules.

4.2 The effects of Explotab® and SLS on MA capsule dissolution.

As shown in Table 2, the disintegration times of the MA capsules consisting of Explotab® and SLS, prepared from MA powder or granules were comparable ranging from 1.23 to 1.71 minutes. However, variations in capsule dissolution profiles were observed. This observation conformed to the results obtained in Part I indicating that the time needed for disintegration of the capsule mass through the 10 mesh sieve of the disintegrator was not a factor in controlling drug dissolution from the MA capsules. The lack of correlation between the observed capsule disintegration times and dissolution rates indicated that there was no effect of disintegration time on dissolution rate of the prepared MA capsules.

4.2.1 Capsules containing MA powder

For the capsules consisting of MA powder, dissolution profiles of the capsules containing Explotab® and SLS in various contents, are compared to the dissolution profile of the control capsule in Figure 2. The control capsule exhibited the slowest dissolution followed by the capsule containing 5% Explotab®-1% SLS. While the capsules containing 2% Explotab®-1% SLS and 5% Explotab®-3% SLS showed similar fastest dissolution profiles followed by the capsule containing 2% Explotab®-3% SLS.

The use of 2% Explotab® and 1% SLS in the capsule containing MA powder was sufficient to provide an acceptable capsule dissolution profile. Increased contents of both Explotab® (from 2% to 5%) and SLS (from 1% to 3%) in the capsule formulation did not provide additional dissolution enhancing effects to the MA capsule. From Figure 2, the dissolution profile of the MA capsules containing 2% Explotab®-3% SLS was slower than that of the capsule containing 2% Explotab®-1% SLS. Therefore, the amount of 1% SLS was effective for improving the wettability and consequently the dissolution of MA in the capsule containing 2% Explotab®. Increasing the amount of Explotab® from 2% to 5% while keeping the content of SLS at 1%, caused deterioration in the capsule dissolution. The 2% Explotab® content thus was suitable to act as capsule disintegrant for the MA capsule formulation. Sodium starch glycolate (Explotab®) is a starch derivative that swells up to 300 times of its volume upon contacting to water (Allen, Popovich and Ansel, 2011). If the Explotab® content is too high, it results in decreasing capsule dissolution due to its viscous nature after swelling in the dissolution medium (Rowe, Sheskey and Quinn, 2009). Hence, the suitable contents of Explotab® and SLS employed in the capsule prepared from MA powder were found to be 2% and 1%, respectively.

In order to study the effects of Explotab® and SLS content on capsule dissolution, several factors were assessed; two dissolution parameters, the time required to obtain 30% drug dissolution (T_{30}) and the percentage of drug dissolved at the 60th minute interval (C_{60}), were set as the criteria to indicate the onset and completeness of drug dissolution from the MA capsules, respectively. The T_{30} was chosen after examination of the dissolution profiles of the MA capsules that 30% drug dissolution was obtained within 10 minutes for the MA capsules consisting of MA powder with Explotab® and SLS (Figure 2). The C_{60} was chosen since the dissolution profiles of the MA powder capsule showed a small degree of increment indicating almost complete dissolution. These criteria were used as references for comparing the MA granule capsules. The T_{30} and C_{60} of the MA capsules containing MA powder are listed in Table 2.

The relationships between the levels (from –1 to 1) of two independent variables, Explotab® content and SLS content, and the T_{30} and C_{60} of the MA capsules were computed according to the principle of a statistical experimental design (a full factorial design of two variables) using multiple linear regression. The levels of both variables were transformed into real contents of Explotab® (X_1) and SLS (X_2). Consequently, the transformed relationships were calculated and represented by the equations 1.1 and 1.2. The main and interaction effects of Explotab® and SLS contents on T_{30} and C_{60} of the capsule consisted of MA powder were expressed by the beta-coefficients of X_1, X_2, and X_1X_2 in the equations, respectively.

$$T_{30} = 2.833X_1 - 0.833X_1X_2 + 1.167X_2 + 3.833 \quad (r^2 = 1.000) \quad (1.1)$$

$$C_{60} = -2.895X_1 + 1.342X_1X_2 - 4.033X_2 + 67.400 \quad (r^2 = 1.000) \quad (1.2)$$

From the above relationships, the main effect of increasing Explotab® content (X_1 from 2% to 5%) on dissolution of MA capsules was dissolution retarding effect. As indicated by the beta-coefficient of X_1, varying X_1 (from 2% to 5%) caused an increasing T_{30} and decreasing C_{60}. Similarly, the main effect of increasing SLS content (X_2) on MA capsule dissolution caused a retarding effect in dissolution. Increasing SLS content from 1% to 3% resulted in increasing T_{30} and decreasing C_{60} as illustrated by the positive and negative values of their beta-coefficients, respectively. As indicated previously, 1% SLS content was enough to provide maximum wetting effect to the drug powder. Increasing content of SLS in the capsules to 3% thus was unnecessary. Viscosity increment at high concentration of surfactant was recognized as a reason for decreased dissolution rate of a drug from solid dosage form (Florence, 1981). A viscous environment resulting from dissolution of excessive SLS content thereby was responsible for delaying capsule dissolution. Although the interaction effects of Explotab® and SLS contents on T_{30} and C_{60} (X_1X_2) were dissolution enhancing, the extent was low if the amounts of Explotab® and SLS were

inadequate. Therefore, the use of 2% Explotab® and 1% SLS in the capsules containing MA powder was found to be suitable. Higher amounts of either Explotab® or SLS employed in the capsules caused additional negative effects on capsule dissolution. If Explotab® was used at higher content then higher amount of SLS was also required in order to keep the drug dissolution from the capsule at the previous level. The use of both Explotab® and SLS in higher contents of 5% and 3% could result in enhancement of capsule dissolution due to their interaction effect as indicating by the beta-coefficient values of X_1X_2 (-0.833 for T_{30} and 1.342 for C_{60}). However, this effect was neutralized by the dissolution retarding effects. Therefore, the MA capsule containing 5% Explotab®-3% SLS yielded a similar dissolution profile to that of the MA capsule containing 2% Explotab®-1% SLS.

4.2.2 Capsules containing MA granule and lactose

Figure 3 shows dissolution profiles of capsules containing MA granule and lactose having Explotab® and SLS in various amounts, according to two-level full factorial experimental design. The presence of Explotab® and SLS in the MA capsules results in faster drug dissolution profiles as compared to the dissolution profile of the control MA capsule. The fastest drug dissolution was obtained from the MA capsule containing 5% Explotab®-3% SLS followed by the MA capsules containing 2% Explotab®-1% SLS and 5% Explotab®-1% SLS. While the capsule consisting of 2% Explotab®-3% SLS provided the slowest drug dissolution. The main and interaction effects of Explotab® and SLS contents on T_{30} and C_{60} of the capsule consisted of MA granule and lactose were expressed by the following equations.

$$T_{30} = 1.500X_1 - 1.500X_1X_2 + 6.500X_2 + 14.500 \quad (r^2 = 1.000) \quad (2.1)$$

$$C_{60} = -2.212X_1 + 1.745X_1X_2 - 6.305X_2 + 49.658 \quad (r^2 = 1.000) \quad (2.2)$$

The main effects of increasing the contents of Explotab® (X_1, from 2% to 5%) and SLS (X_2, from 1% to 3%) on capsule dissolution were found to retard dissolution as indicated by the positive values of their beta-coefficients in the equation 2.1 and their negative values of their beta-coefficients in the equation 2.2, respectively. However, their interaction effect (X_1X_2) was enhancing dissolution. Dissolution retarding effects derived from increasing SLS content were more significant than those obtained from increasing Explotab® content as indicated by its significantly higher values of the beta-coefficient in the equation 2.1 and 2.2.

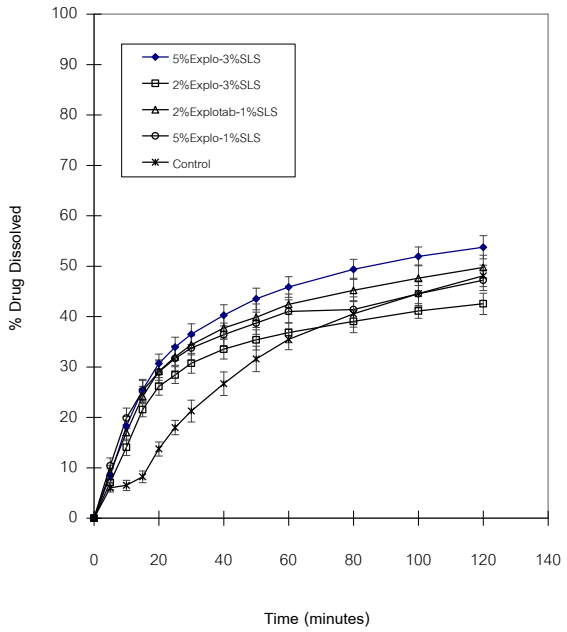

Figure 3 Dissolution profiles of MA capsules containing MA granule and lactose

The use of 2% Explotab® and 1% SLS provided the capsule having T_{30} of 21 minutes and C_{60} of 42.4%. Increasing Explotab® content from 2% to 5%, while fixing the SLS content at 1%, resulted in small degree of difference in capsule dissolution (T_{30} of 21 minutes and C_{60} of 41.0%). The dissolution retarding effect of increasing Explotab® content was counterbalanced by the dissolution enhancing effect derived from interaction between Explotab® and SLS. Therefore, the 2% Explotab® content was sufficient as a disintegrant in the capsule consisting of MA granule and lactose containing 1% SLS.

Increasing SLS content from 1% to 3%, while fixing Explotab® at 2%, caused slower capsule dissolution. Higher SLS content led to a large dissolution retardation effect that overcame the dissolution enhancing effect derived from the interaction between Explotab® and SLS. However, when both Explotab® and SLS contents were increased from 2% to 5% and 1% to 3%, respectively, the resulting capsule dissolution profile was found to be faster than the dissolution profile of the capsule consisting of 2% Explotab®-1% SLS. The main effects of high amounts of Explotab® and SLS content on retarding capsule dissolution were overcome by their interactive effect on enhancing capsule dissolution. In such cases, the T_{30} and C_{60} of the capsule containing 5% Explotab® and 3% SLS were 19 minutes and 45.9% while the T_{30} and C_{60} of the capsule containing 2% Explotab® and 1% SLS were 21 minutes and 42.4%, respectively. Therefore, the suitable contents of Explotab® and SLS utilized in the capsule formulation should be chosen after balancing the beneficial effect of capsule dissolution improvement to the economic disadvantage of higher production costs.

The negative effect of SLS on capsule dissolution was higher in the capsule consisting of MA granule and lactose than in the capsule consisting of MA powder. The beta-coefficient values were greater in equations 2.1 and 2.2, compared to those in the equations 1.1 and 1.2. The mass of the capsule containing MA granule and lactose was more hydrophilic than the mass of the capsule containing MA powder alone since both MA granule and lactose are more hydrophilic than MA powder. The wettability of the MA granule and lactose was higher than the wettability of the MA powder therefore, less surfactant effect derived from SLS was required to improve the wettability. Consequently, the dissolution enhancing effect of SLS due to its surfactant effect was more important in the capsule consisting of MA powder than that in the capsule containing MA granule and lactose. As mentioned, SLS also imparted dissolution retarding effects to the MA capsule if being used in high concentration. As a result, the greater dissolution retarding effect of SLS was obtained in the capsule containing MA granule and lactose since its dissolution enhancing effect was less significant in this case.

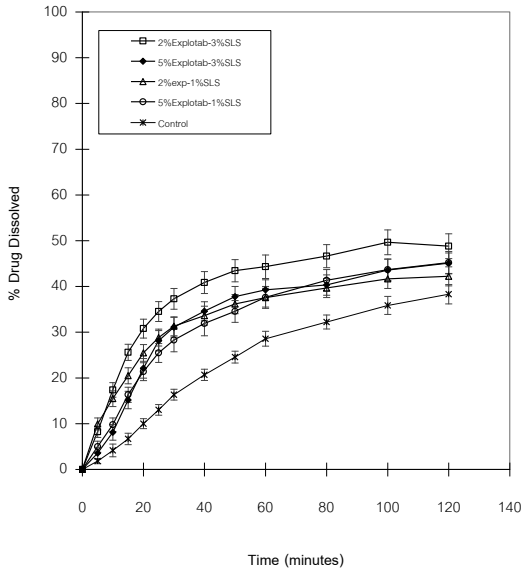

Figure 4 Dissolution profiles of MA capsules containing MA granule and DCP

4.2.3 Capsules containing MA granule and DCP

Figure 4 demonstrates the dissolution profiles of the capsules containing MA granule and DCP having various amounts of Explotab® and SLS as compared to the dissolution profile of the control capsule of MA granule and DCP. The slowest drug dissolution was obtained from the control MA capsule. Hence, the inclusion of Explotab® and SLS in the capsule containing MA granule and DCP improved drug dissolution. The fastest drug dissolution was obtained from the MA capsule having 2% Explotab®-3% SLS, while comparable dissolution profiles were obtained from the MA capsules having 2% Explotab®-1% SLS, 5% Explotab®-3% SLS, and 5% Explotab®-1% SLS. The equations represented the relationships between two dissolution parameters (T_{30} and C_{60}) and the contents of Explotab® and SLS were as the following.

$$T_{30} = 1.500X_1 + 0.500X_1X_2 - 5.500X_2 + 29.500 \quad (r^2 = 1.000) \quad (3.1)$$

$$C_{60} = 0.885X_1 - 0.858X_1X_2 + 5.107X_2 + 32.380 \quad (r^2 = 1.000) \quad (3.2)$$

From the equations 3.1 and 3.2, the main effects of increasing Explotab® content (from 2% to 5%) on T_{30} and C_{60} were indicated by their beta-coefficient values. Increasing Explotab® content from 2% to 5% provided dissolution retarding effect in the initial period of drug dissolution as illustrated by its positive beta-coefficient value in the T_{30} equation. The main effect of increasing Explotab® content also caused higher C_{60}. However, this effect was quite low as indicated by its low beta-coefficient value of 0.885. Increasing SLS content from 1% to 3% resulted in opposite effects on T_{30} and C_{60}, with T_{30} decreasing and C_{60} increasing. So, increasing SLS content provided a dissolution enhancing effect. While the interaction effects between Explotab® and SLS (X_1X_2) on T_{30} and C_{60} were found to be dissolution retarding since the values of their beta-coefficients were 0.500 and -0.858 for equations 3.1 and 3.2, respectively.

At a low content of SLS (1%), increasing Explotab® content from 2% to 5% caused higher T_{30} and lower C_{60} (Table 1). The positive effect of increasing Explotab® content on C_{60} was counterbalanced by the negative interaction effect between Explotab® and SLS. Conversely, when a higher content of SLS (3%) was used, the magnitude of this negative interactive effect was magnified. Hence, the use of a higher concentration of Explotab® (5%), and SLS remaining constant at 3%, provided a much lower C_{60} value than did the use of a lower content (2%).

Since DCP is a hydrophobic diluent while lactose is a hydrophilic diluent, the hydrophobicity of the capsule mass containing MA granule and DCP was higher than that of the capsule mass consisting of MA granule and lactose. The effect of SLS on increasing wettability of the MA capsule mass was found to be more dominant in the capsule containing DCP. Thus, the use of 1% SLS was not sufficient to provide the fastest drug dissolution in the capsule consisting of MA granule and DCP. Increasing the content of SLS from 1% to 3% caused the most improvement in capsule dissolution in the capsule containing 2% Explotab®. However, lower capsule dissolution improvement derived by using 3% SLS was observed in the capsule containing 5% Explotab®. In the latter case, higher content of Explotab® caused a delay in capsule dissolution due to high negative interaction effect between Explotab® and SLS on C_{60}. This effect was derived from increased viscosity around the capsule mass resulting from excess amount of Explotab® and SLS being employed. This dissolution retarding effect thus opposed the dissolution enhancing effect of increasing SLS content. Therefore, the 2% Explotab® and 3% SLS were suitable to be used in the capsule containing MA granule and DCP in order to provide fast drug dissolution.

4.2.4 Optimization of Explotab® and SLS contents in MA capsule formulation

The contour plots of T_{30} and C_{60} as functions of Explotab® and SLS contents for the capsules containing MA powder, MA granule-lactose, and MA granule-DCP are illustrated in Figures 5. From these contour plots, the optimum contents of Explotab® and SLS yielding the required T_{30} and C_{60} can be chosen. The fastest T_{30} and the maximum C_{60} are the most required ideal dissolution parameters. The graphical analysis of the contour plots provided the overview of how to obtain the most possible ideal requirements for both criteria.

For the MA capsule, fast onset of action is needed. Therefore, the low value of T_{30} is set as the primary objective. The C_{60} then is maximized in order to achieve the most complete drug dissolution. For the capsule consisting of MA powder, the effects of Explotab® and SLS content on T_{30} and C_{60} are shown as contour plots (constructed from equations 1.1 and 1.2) in Figure 5a and 5b, respectively. From

the contour plots, various contents of Explotab® (between 2 % and 5%) and SLS (between 1% and 3%) that resulted in the satisfied fast T_{30} and high C_{60} can be chosen. For example, the T_{30} of about 9 minutes and C_{60} of about 60% can be obtained by employing 2% Explotab® and 1% SLS or 4% Explotab® and 3% SLS. While the use of 5% Explotab® and 3% SLS is also found to yield T_{30} of about 9 minutes and C_{60} of about 61%. However, the use of 2% Explotab® and 1% SLS is the most suitable choice since the lowest contents of Explotab® and SLS are used and subsequently a lower production cost is expected.

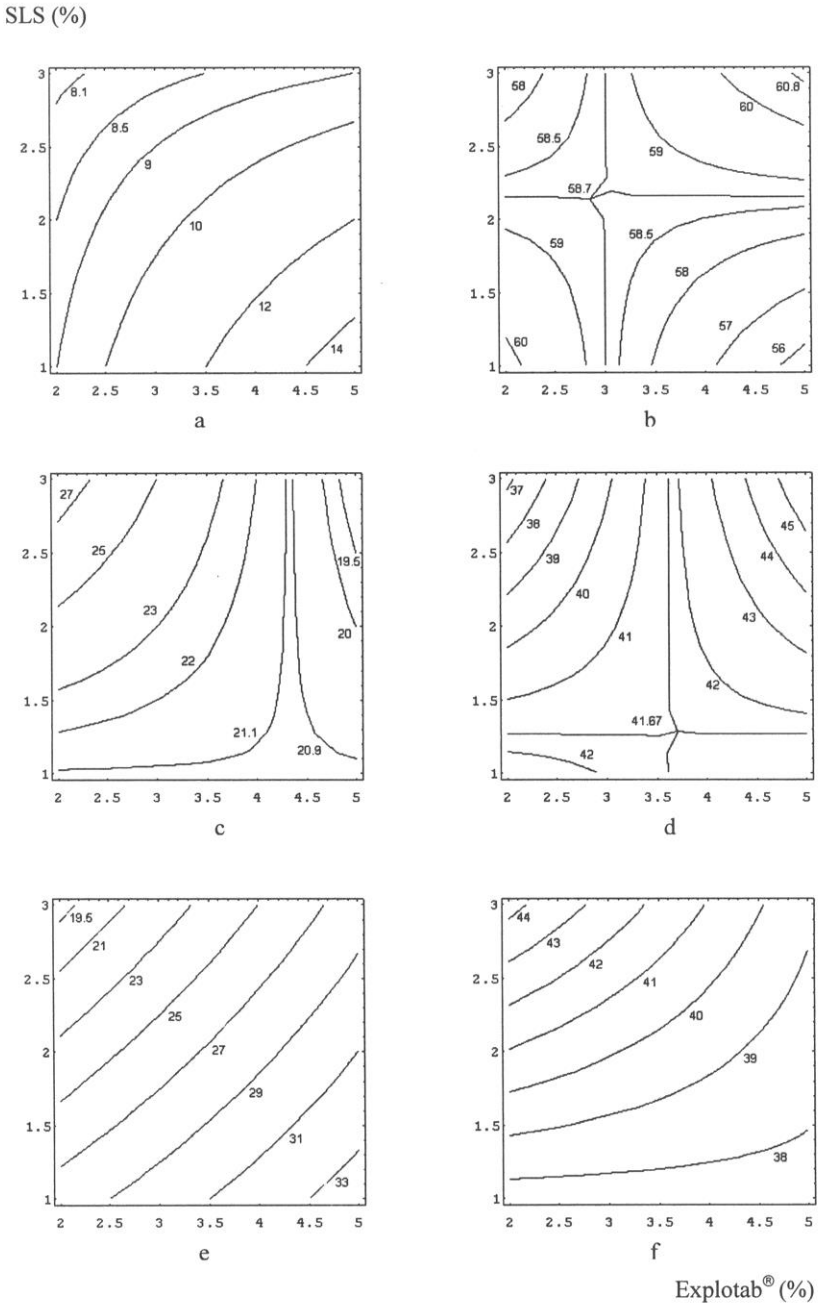

Figure 5 Contour plots of T_{30} and C_{60} as functions of Explotab® and SLS of capsules containing MA powder; (a) T_{30} and (b) C_{60}, MA granule-lactose; (c) T_{30} and (d) C_{60}, and MA granule-DCP; (e) T_{30} and (f) C_{60}

Figures 5c and 5d show the contour plots of T_{30} and C_{60} as functions of Explotab® and SLS contents of the capsules containing MA granule and lactose (constructed from equations 2.1 and 2.2). While Figures 5e and 5f show contour plots of the capsule containing MA granule and DCP (constructed from equations 3.1 and 3.2). For the capsule consisting of MA granule and lactose, if the criteria set for fast T_{30} and high C_{60} are about 20 minutes and 42%, respectively, then T_{30} of 20 minutes and C_{60} of 42% can be obtained from various sets of Explotab® and SLS contents such as 2% Explotab® with 1% SLS, 4.5% Explotab® with 1.5 % SLS, and 5% Explotab® with 1.25% SLS. From the contour plots (5c and 5d), faster T_{30} and higher C_{60} can be obtained by fixing Explotab® content at a high level of 5% while increasing SLS content from 1% to 3%. By fixing Explotab® content at 2% while decreasing SLS content from 3% to 1%, a faster T_{30} and higher C_{60} are realized. Thus, fast T_{30} and high C_{60} can be obtained by using both Explotab® and SLS contents at low levels or by employing both of them at high levels. For the capsule consisting of MA granule and DCP (5e and 5f), the T_{30} of faster than 21 minutes and C_{60} of greater than 42% can be obtained when the content of Explotab® in the range of 2% to 2.5% is chosen and the SLS content is increased from 2.5% to 3%.

5. Conclusion

In this study, several approaches were applied to formulate a poorly water-soluble drug, mefenamic acid, into capsule dosage form of fast dissolution. These formulations included granulation of mefenamic acid by an aqueous binding solution of polyvinylpyrrolidone K30 and the usage of lactose as hydrophilic capsule diluent. The application of a disintegrant, Explotab®, and a surfactant, sodium lauryl sulfate, in the capsule was proven to provide further capsule dissolution improvement. The use of both Explotab® and sodium lauryl sulfate in the capsule consisting of mefenamic acid powder yielded greater dissolution enhancing effects than their use in the capsule containing mefenamic acid granule and a diluent, either lactose or dibasic calcium phosphate. The results of this investigation can be applied as a guideline to formulate a poorly water-soluble drug into capsule dosage form with the fastest dissolution.

6. References

Abdou, H. M. (1989). Factors effecting the rate of dissolution of solid dosage forms. *Dissolution, bioavailability & bioequivalent* (pp. 73-105). Easton, USA: Mack Publishing Company.

Allen, L. V., Popovich, N. G., & Ansel, H. C. (2011). Tablets. *Ansel's pharmaceutical dosage forms and drug delivery systems*, 9th ed. (pp. 225-256). Philadelphia, USA: Lippincott Williams & Wilkins.

Attword, D., & Florence, A. T. (1983). Biological implications of surfactant presence in formulation. *Surfactant systems. Their chemistry, pharmacy and biology* (pp. 381-468). New York, USA: Chapman and Hall.

Bandelin, F. J. (1989). Compressed tablets by wet granulation. In H. A. Lieberman, L. Lachman & J. B. Schwartz (Eds.), *Pharmaceutical dosage forms, tablets, Volume 1,* 2nd ed., (pp. 131-194). New York, USA: Marcel Dekker.

Florence, A. T. (1981). Drug solubilization in surfactant systems. In S. H. Yalkowsky (Ed.), *Techniques of solubilization of drugs* (pp. 60-63). New York, USA: Marcel Dekker.

Mudit, D., Bhardwaj, Y., Keshavarao, K. P., & Selvam, P. (2011). Enhancing solubility and dissolution of mefenamic acid by freeze drying using β-cyclodextrin. *International Research Journal of Pharmacy*, *2*(9), 146-150.

Proudfoot, S. G. (1988). Factors influencing bioavailability: factors influencing drug absorption from the gastrointestinal tract, In M.E. Aulton (Ed.), *Pharmaceutics: The science of dosage form design* (1st ed.), (pp. 135-173). London, UK: Churchill Livingstone.

Rowe, R. C., Sheskey, P. J., & and Quinn., M. E. (2009). *Handbook of Pharmaceutical Excipients*, 6th ed. Chicago, USA: Pharmaceutical Press.

The Department of Health, Great Britain. The Department of Health, Social, Services and Public Safety, Northern Ireland. (2008). *British Pharmacopoeia*. *Volume II*. London, UK: The Stationary Office.

The United States Pharmacopeia. The National Formulary. (2009). *USP 32 and NF 27*. *Volume 1.1*. Rockville, USA: The United States Pharmacopeial Convention.