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Comparison of in vitro Evaluation of Commercially Available Trimethoprim-Sulphamethoxazole Tablets.

สุมน สกลไชย
เดชพล ปรีชากูล
สุเทพ ไวยครุฑธา
ประยูร ถนอมสิทธิ์
สุทธินี คมคาย

คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น

Sumon Sakolchai PhD., Detpon Preechakoon MS., Prayoon Tanomsith BSc., Sutthinee Komkai BSc. and Suthep Wiyakrutta MS.*. Faculty of Pharmaceutical Science, Khon Kaen University, Khon Kaen Thailand 40002

Abstract

Five commercial brands of combined formulations of 1:5 Trimethoprim and Sulphamethoxazole were evaluated, *in vitro*, for their weight variation, the percent labelled amount of active ingredients, hardness, disintegration time and dissolution rate by the official pharmacopoeal methods. All brands meet the pharmacopoeal requirements with regard to content uniformity; disintegration time and the percentage of Sulphamethoxazole whereas Trimethoprim content was not within the USP range in some commercial formulations. Variation among different brands was demonstrated by diverse dissolution rates and profiles. Only brand A and B passed the USP dissolution test and no statistically-significant difference was noted for both Trimethoprim and Sulphamethoxazole. Based on the previous correlation study between *in vitro* dissolution and in vivo absorption rate of Trimethoprim, it was recommended that dissolution data could predict the bioavailability of this drug. It is concluded that only brand A and B passed all major essential requirements of the official compendium and accordingly improvement with respect to dissolution characteristic for others is needed.

บทคัดย่อ

ยาเม็ดสูตรผสมระหว่าง Trimethoprim และ Sulphamethoxazole ในอัตราส่วน 1 : 5 ซึ่งมีจำหน่ายในประเทศจำนวน 5 ชื่อ ได้รับการประเมินเปรียบเทียบคุณสมบัติในด้าน ความสม่ำเสมอของน้ำหนักเม็ดยา จำนวนร้อยละของสารสำคัญ ความแข็งของเม็ดยา ระยะเวลาการแตกตัวของเม็ดยา และอัตราละลายของยาเม็ด โดยใช้วิธีการตามที่เภสัชตำรับกำหนด ผลการศึกษาพบว่า ตัวอย่างยาทั้ง 5 ชื่อ ได้มาตรฐานตามเภสัชตำรับในแง่ความสม่ำเสมอของน้ำหนักเม็ดยา ระยะเวลาการแตกตัวของเม็ดยา และจำนวนร้อยละของ Sulphamethoxazole ในขณะที่จำนวนร้อยละของ Trimethoprim ในหลายตัวอย่างยังไม่เข้ามาตรฐาน ความแตกต่างระหว่าง

ยาจากผู้ผลิตบริษัทต่าง ๆ เห็นได้ชัดเจนในคุณสมบัติที่เกี่ยวกับอัตราการละลายและรูปแบบการละลายของยาเม็ด กล่าวคือ ตัวอย่าง A และ B เท่านั้นที่ผ่านเกณฑ์ตามที่เภสัชตำรับกำหนดและไม่มีความแตกต่างอย่างมีนัยสำคัญระหว่างตัวอย่างทั้งสองชนิด นอกจากนั้น ยังเคยมีรายงานว่า ความสามารถในการละลายของยาสูตรผสมนี้มีความสัมพันธ์เป็นเส้นตรงกับความสามารถในการดูดซึมของ Trimethoprim และเสนอแนะว่า คุณสมบัติในการละลายนี้สามารถใช้คาดคะเนคุณสมบัติในแง่ bioavailability ของยานี้ได้ ดังนั้น ข้อมูลจากการศึกษานี้สรุปได้ว่าตัวอย่าง A และ B มีมาตรฐานที่สำคัญครบเกณฑ์ตามที่เภสัชตำรับกำหนด ในขณะที่อีก 3 ตัวอย่างควรจะทำการปรับปรุงสูตร และกรรมวิธีในการผลิตโดยเฉพาะอย่างยิ่งในส่วนที่เกี่ยวกับความสามารถในการละลายของยา

Introduction

A combined formulation of Trimethoprim (5-[(3,4,5-trimethoxyphenyl) methyl] pyrimidine-2,4-diamine) and sulphamethoxazole [4-amino-N-(5-methyl-3-isoxazolyl) benzene-sulphonamide], in a relative ratio 1:5, is a widely used broad-spectrum antimicrobial agent against a diversity of gram-positive and gram-negative organism as well as selected protozoa [1,2] and used clinically for the treatment of a variety of infections in man[3.]. Comparison of bioavailability and *in vitro* dissolution evaluation of both Trimethoprim and Sulphamethoxazole from certain dosage forms reported by Meshali revealed that most parameters tested were highly brand-individualized [4]. In Thailand, at least 15 brand names of trimethoprim-sulphamethoxazole formulation with a variety of stregth and dosage forms are commercially available on a divergent price range.

Among those different commercial brands with identicle strength of identicle combination of certain active ingredients, no comparative *in vitro* studies on such formulation are reported, particularly with respect to an original product. The present study was carried out to investigate and compare physical characteristics and *in vitro* dissolution parameters of commercially available brands of 80:400 mg trimethoprim-sulphamethoxazole formulation, in reference to the innovator's product.

MATERIALS AND METHOD

PRODUCTS Five different commercial brands, and innovator's as well as locally-manufactured products, were randomly sampled from the market. They were designated as A, B, C, D and E for each brand. Each tablet contained 400 mg. of sulphamethoxazole and 80 mg. of trimethoprim and all tablets were found to be uncoated tablets.

PHYSICAL CHARACTERISTIC EVALUATION. The weight Variation of tablets were performed according to the USP XXI method [4]. The active ingredients of each brand were individually assayed for both Trimethoprim (TMP) and Sulphamethoxazole (SMZ) using HPLC technique by the method of USP XXI supplement 4[5]. Hardness of tablets was performed by Monsanto hardness tester. To determine the disintegration time of tablets, the USP XXI disintegration method for uncoated tablets was the one of choice [6], in which six tablets of each brand were evaluated using distilled water medium at 37 °C.

DISSOLUTION STUDY. To evaluate and compare the *in vitro* dissolution of tablets, the basket method of the USP XXI was assessed [7]. Each tablet was introduced to 900 ml dilute hydrochloric acid, stirred with 100 rpm speed at 37±0.5 °C. Aliquots were withdrawn at predetermined time intervals within 25 minutes and assayed for Sulphamethoxazole (SMZ) and Trimethopeim(TMP) by HPLC assay technique monitored at 255 nm with a mobile phase (pH 5.9) consisting of a mixture of acetonitrile : triethylamine : water (20:1:80 % v/v) at a flow rate of 15 ml. min^{-1}

RESULTS AND DISCUSSION

Physical Characteristics of the tablets

Weight variation of different tablet brands, in Table 1, was shown to meet the USP XXI requirement no single tablet, on an individual basis, varied 5% greater than an average weight value. The assay result as indicated by % labelled amount (%LA) showed that the average percent content of SMZ was 104.16, 100.01, 103.30, 96.28 and 97.42 for brand A, B, C, D and E, respectively. The USP limit is 93-107% of the labelled amount. All brands passed the pharmacopoeal requirement for SMZ. However, with regard to TMP, only brand A was within the USP range. The average disintegration time of all brands were 0.30, 1.06, 3.58, 2.33 and 2.68 minutes for brand A to E, respectively. All brands disintegrated completely within 30 minutes, indicating that all were shown to satisfy the USP limit. It seemed that all tested tablets exhibited relatively good physicochemical and mechanical properties with regard to hardness.

Dissolution data

The dissolution of all tested tablets was performed according to the USP XXI method in dilute hydrochloric acid at 37± 0.5 °C where not less than 50% of active ingredients must be dissolved within 20 minutes. The pronounced differences in dissolution rates and profiles of five commercial formulations were found, as given in Table 2 and 3, for Sulphamethoxazole and Trimethoprim, respectively. After 20 minutes, more than 50% of Sulphamethoxazole and Trimethoprim content were released from brand A and B, comparing to relatively low concentration of SMZ and TMP for the remaining brands. Only brand A and B passed the dissolution test of the USP XXI and no statistically significant differences were found, for both SMZ and TMP, between A and B at 20 minutes. However, Brand C, D and E showed statistically significant differences, in dissolution data, from that of brand A and B. Figure 1 and 2 illustrated dissolution profiles of SMZ and TMP released among different brands at various time intervals, respectively. It is clearly shown that brand A is slightly superior to brand B, whereas both exhibited better dissolution profiles than the remaining brands. The extent of dissolution of tested tablets at 20 minutes was not markedly affected when artificial intestinal buffer was used instead of dilute hydrochloric acid.

Meshali reported that the absorption rate of Trimethoprim was dissolution rate-limited and a correlation existed between the *in vitro* dissolution rate of Trimethoprim at acidic pH and its in vivo absorption [6]. Based on this correlation, its dissolution rate can predict the bioavailability of Trimethoprim. In this study, brand A and B would give rise to the superior bioavailability to that of the others.

CONCLUSION

The results of this study revealed that variation in drug quality with regard to physical characteristics and dissolution, still existed among five different commercial brands. In general, only brand A and B passed all major essential requirements of the official compendium whereas formula improvement and tablet technology is needed for the others, especially with respect to the dissolution property.

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References

1. Bushby SRM. Trimethoprim-Sulphamethoxazole : in vitro microbiological aspects. J **Infect Dis** 1973; 128;S442-62.
2. Wormser GP, Kausch GT and Heel DC. Co-trimoxazole. **Drugs** 1982; 24:459-518.
3. Kucers A. and Bennett NM. The Use of Antibiotics. London : William Heineman Medical Books, 1979.

4. Meshali M, Sabbagh HE, Ghanem A and Foda A. Simultaneous in vitro and in vivo Evaluation of both Trimethoprim and Sulphamethoxazole from certain Dosage forms. **Pharmazie** 1983; 38:403-6.
5. The United States Pharmacopeia XXI. Suppl 4., 2224-25.
6. The United States Pharmacopeia XXI. 1985; 1242-43.
7. The United States Pharmacopeia XXI. 1985; 1243-44.

Table 1 Physical characteristics of different commercially Trimethoprim-Sulphamethoxazole tablets.

	Brand name				
	A	B	C	D	E
Tablet weight (g)[a]	0.5056±0.0046	0.6055±0.0063	0.5165±0.0081	0.5522±0.0071	0.5783±0.0049
Labelled amount[b] (% LA)					
SMZ	104.16±1.31	100.01±2.64	103.30±3.00	96.28±1.27	97.42±4.10
TMP	97.78±1.46	84.72±0.83	87.13±2.69	78.17±0.70	84.32±3.40
Hardness[b] (kg)	6.64±0.74	11.85±0.82[c]	>14[c]	7.50±0.56	12.38±3.72
Disintegration time[b] (min)	0.30±0.01	1.06±0.03	3.58±0.48[c]	2.33±0.57[c]	2.68±0.46[c]

a : Determination of an average of 20 tablets
b : Determination of an average of 6 tablets
c : $P < 0.05$, compared with brand A

Table 2 The percentage dissolution rate of Sulphamethoxazole (SMZ) from different Trimethoprim-Sulphamethoxazole tablets.

Brand name	The extent of Sulphamethoxazole dissolved at different time* (min)					
	2	5	10	15	20	25
A	**96.20**±5.38	97.40±0.58	98.70±0.38	99.10±0.34	99.50±0.45	99.80±0.23
B	77.80±2.90	83.50±6.97	89.80±3.41	94.30±1.25	97.60±1.12	98.60±0.46
C	6.80±1.93	14.60±3.60	28.50±3.69	33.10±9.09	44.60±5.21	51.90±4.36
D	4.32±0.54	8.50±1.75	27.10±2.13	40.40±4.63	49.80±3.93	56.50±5.35
E	21.32±3.40	41.40±5.32	53.40±4.40	61.70±5.38	72.60±6.76	80.40±3.82

* Average of six determinations

Table 3 The Percentage dissolution rate of Trimethoprim (TMP) from different Trimethoprim-Sulphamethoxazole tablets.

Brand name	The extent of Trimethoprim dissolved at different time* (min)					
	2	5	10	15	20	25
A	**88.60**±2.50	94.30±2.91	95.60±3.27	97.20±3.82	99.10±3.19	99.20±0.68
B	48.50±4.49	64.10±7.62	78.50±7.30	88.30±6.83	96.60±3.70	98.20±1.66
C	6.80±1.02	9.50±2.39	22.40±2.73	30.50±1.94	37.60±3.30	45.60±5.54
D	5.50±1.60	8.30±1.36	12.50±2.22	16.60±2.82	20.00±2.35	21.60±3.38
E	26.60±5.35	31.40±4.30	41.20±4.32	53.50±5.30	62.40±3.60	68.80±5.66

* Average of six determinations