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A simplified stability assessment for selection of a suitable package for microporous osmotic tablets

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ABSTRACT

The aims of this study were to investigate the effects of moisture and temperature on microporous osmotic tablets containing metformin hydrochloride and to predict stability for optimization of packaging. Unpackaged microporous osmotic tablets were stored under four conditions: 25 °C/60% relative humidity (RH), 40 °C/75% RH, 40 °C/95% RH, or 60 °C/75% RH for 192 h using a stability chamber. The tablets were then evaluated for hygroscopicity, hardness, dissolution, and degradation. Furthermore, morphology and crystallinity were studied for confirming the change of physicochemical stability. As seen in the stability test, the microporous osmotic tablets were chemically stable under all of the tested conditions. However, the hardness of the microporous osmotic tablets was considerably affected by higher humidity and temperature conditions, as the critical quality attribute in the stability. This was due to the characteristics of the drug and excipients, as seen in the sorption study. It was confirmed the change of morphological properties of microporous osmotic tablets. However, the crystallinity of the microporous osmotic tablets did not change. Based on these experimental results, it is possible to select appropriate packaging taking into consideration the predicted water vapor transmission rate of the packaging determined through simple stability test involving exposure to various environmental conditions.

1. Introduction

Pharmaceutical products need to be protected and packaged in a way that conforms to control standards. Especially, the tablet, which is the most conventional pharmaceutical formulation, has many important factors that affect its stability. For example, tablet properties such as friability, disintegration, *in vitro* release, and hardness can be changed under different conditions [1]. Therefore, packaging plays an important role in assuring pharmaceutical stability and protection against biological contamination, physical damage, and all adverse external influences that can alter the properties of the product, such as moisture, light, oxygen, and temperature variations. Many articles have studied the influence of these parameters on the quality of specific types of packaging and package designs [2–6]. However, the complexity of packaging materials and the variety of dosage forms are significant challenges for pharmaceutical manufacturers.

Pharmaceutical packaging provides protection from various moisture and temperature conditions, major causes of instability [4,7]. Hygroscopicity, which is the capacity of a pharmaceutical product to react to moisture in the air by absorbing or desorbing water vapor, depends on the physicochemical properties of both the active pharmaceutical ingredients (API) and the excipients in the product. Moisture absorption is one of the factors that should be considered when determining the optimum packaging material because it influences the long-term moisture absorption characteristics of a particular pharmaceutical formulation [3,8–10]. Also, moisture absorption greatly depends on temperature and RH conditions. Therefore, moisture absorption was considered together with moisture and temperature to allow for proper package selection.

The process of packaging selection for pharmaceutical products involves the use of detailed stability studies, such as those in the ICH guidelines. Generally, long-term studies are conducted at

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25 °C/60% RH for 12 months and accelerated studies are conducted at 40 °C/75% RH for 6 months [11]. Conventional packaging selection involves significant time and high cost due to the need to conduct multiple stability studies. However, if the stability of a product can be predicted based on the stability conditions, the process can be modified to be simple and efficient. Samples for stability testing are exposed to various stability conditions on short period to evaluate hygroscopicity, physical and chemical degradation tendencies, and product properties. Based on the results obtained from experimental studies, optimum packaging options are derived from equations, including the moisture-modified Arrhenius equation, water vapor transmission rate (WVTR) equation, and Guggenheim-Anderson-de Boer (GAB) model [4]. The stability prediction based on these scientific methods saves considerable time and cost compared to conventional stability studies. By exposing the pharmaceutical product in various environments, it is possible to predict the thresholds of properties such as hygroscopicity, drug release, and degradation of the product itself. Therefore, it can ultimately assist the selection of a suitable packaging for the pharmaceutical product.

While there are published studies of stability test, there were few studies concerning package selection [1,4,5,12]. They have focused only on conventional tablets such as immediate release tablets or sustained release tablets. However, there are many tablets with advanced drug delivery mechanism such as osmotic tablets or delayed release tablets, which all essentially incorporate coating of tablets [13–17]. It is necessary to study the prediction of the optimal package based on the physicochemical properties of various types of tablets. Therefore, the osmotic tablet was selected as the specific type of tablet as this type of tablet represents one of the most complex and advanced dosage forms. In microporous osmotic tablet as drug delivery system, various drugs have been studied [13,18–20]. Metformin hydrochloride (HCl) was selected as the model drug in this study. It has high solubility in water and high hygroscopicity [21,22]. Therefore, it is an interesting model drug as the experimental data was expected to change under accelerated conditions in stability study.

In this study, microporous osmotic tablets containing metformin HCl were evaluated under various stability conditions. We investigated the effects of moisture and temperature and predicted how these factors would affect tablet properties in the long term. Considering all of these influences, optimal packaging for microporous osmotic tablets was determined.

2. Material and methods

2.1. Materials

The following materials were used in this study: metformin HCl (Farmhispania S.A., Spain), povidone-K30 (BASF, Germany), Kollicoat® SR 30D (BASF, Germany), magnesium stearate (Dangschat T.O.H. GmbH & Co. KG, Germany), hypromellose (Shin-Etsu Chemical Co., Ltd., Japan), propylene glycol (Dow Chemical Co., U.S.A.), sodium lauryl sulfate (Cognis, Germany), talc (Matsumura Sangyo Co., Ltd, Japan), and titanium dioxide (Univar Ltd., U.S.A.).

2.2. Tablet sample

Microporous osmotic tablets containing metformin HCl were manufactured by high shear granulation and tablet coating. The composition of the microporous osmotic tablets is listed in Table 1. First, metformin HCl and povidone-K30 were mixed and kneaded with purified water in a high shear mixer (Alexander granulator, Alexanderwerk AG, Germany). This mixture was then dried in a fluid bed dryer (WSD120, Glatt, Germany) and passed through a 1.5 mm sieve (Bohle BTS 200, L.B. Bohle LLC, U.S.A.). The inlet air temperature was set to 80 °C, and the granule loss on drying was targeted from 1 to 3%. After drying and sieving, the granules were blended with magnesium stearate, and this mixture was compressed using a tablet press (Kilian compression M/C T300, Romaco Kilian, Germany) with an oval tablet punch (18.0 mm × 8.5 mm). Second, the tablets were coated in a process of osmotic coating. During the osmotic coating, a coating solution containing hypromellose, talc, Kollicoat® SR 30D, and propylene glycol was prepared. The core tablets were coated using a tablet coater (PC1500, Glatt, Germany) with drum speed at 2 rpm. The coating solution was sprayed at a rate of 70 g/min (nozzle diameter: 0.5 mm, cap diameter: 1.5 mm, gun to tablet bed distance: 25 cm). The coated tablets were dried at 55 °C for 1 h. All tablet samples were prepared by Handok Pharmaceuticals Co., Ltd.

Table 1
Composition of microporous osmotic tablet.

Composition (mg)		
Core tablet	Metformin HCl	1000.0
	Povidone (K30)	85.0
	Mg. stearate	15.0
Osmotic coating layer	Kollicoat® SR 30D	48.1
	Hypromellose (HPMC 2910, 4.5 cP)	25.9
	Propylene glycol	7.5
	Talc	18.5
Total weight		**1200.0**

2.3. Stability test

Unpackaged microporous osmotic tablets were stored at 25 °C/60% RH, 40 °C/75% RH, 40 °C/95% RH, and 60 °C/75% RH for 192 h in a stability chamber (BS-21, JEIO Tech, Republic of Korea). The sampling time was modified to simplify stability test period from that in other literature [23,24]. Initial tablets before being subjected to stability tests were used as the control.

2.4. Hygroscopicity

The microporous osmotic tablets were exposed to various environmental conditions for 192 h, and the weights of the tablets were measured at specific time intervals (0, 4, 6, 8, 12, 24, 48, 72, 96, 144, 168, and 192 h). Moisture absorption rates, moisture absorption at equilibrium, and moisture absorption capacity were then derived from these results.

2.5. Tablet hardness

The hardness of the microporous osmotic tablets was evaluated using a texture analyzer (TA-XT2, Stable Micro Systems, England) fitted with a 100-mm-diameter aluminum plate. For each of the time points mentioned above, the microporous osmotic tablet was centered on the major axis of the analyzer. The hardness of the microporous osmotic tablet was analyzed using a compression method (trigger force: 0.05 N, maximum force: 600 N) at 1.0 mm/s, with the tablets compressed by 5 mm. The failure strength of the microporous osmotic tablets was characterized by breakage. The degree of hardness was defined as the maximum force in each profile. The hardness of the core tablet before osmotic coating was about 240 N, which was 40% of tablet hardness after osmotic coating. Therefore, it was regarded as a threshold for a significant difference as it was equivalent to the hardness of the initial core tablet in this study. The threshold value of tablet hardness was set