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RESEARCH PAPER

Application of Similarity Factor in Development of Controlled-Release Diltiazem Tablet

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ABSTRACT

Controlled-release grade hydroxypropylmethylcellulose (HPMC) or xanthan gum (XG) and microcrystalline cellulose (MCC) were employed to prepare controlled-release diltiazem hydrochloride tablets. The similarity factor f_2 was used for dissolution profile comparison using Herbesser 90 SR as a reference product. Drug release could be sustained in a predictable manner by modifying the content of HPMC or XG. Moreover, the drug release profiles of tablets prepared using these matrix materials were not affected by pH and agitation rate. The f_2 values showed that only one batch of tablets (of diltiazem HCl, HPMC or XG, and MCC in proportions of 3.0:3.0:4.0) was considered similar to that of the reference product, with values above 50. The unbiased similarity factor f_2^* values were not much different from the f_2 values, ascribing to a small dissolution variance of the test and reference products. The amount of HPMC or XG incorporated to produce tablets with the desired dissolution profile could be determined from the curves of f_2 versus polymer content. Hence, the f_2 values can be applied as screening and optimization tools during development of controlled-release preparations.

Key Words: *Controlled-release diltiazem tablet; Hydroxypropylmethylcellulose; Similarity factor; Xanthan gum.*

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INTRODUCTION

In vitro dissolution has been recognized as an important parameter of drug products because of its association with drug bioavailability. Furthermore, it can also be employed as a surrogate for assessment of bioequivalence under certain conditions. In view of the significance of dissolution, it is therefore essential to investigate the drug release characteristics of preparations. In the development of oral controlled-release preparations, an ethical (proprietary) product, which has been available in the market for some time and has established its efficacy clinically, is usually selected as a reference. The generic preparation is always formulated with its dissolution profile as closely similar as possible to that of the proprietary product.

Several methods have been proposed for the comparison of dissolution profiles (1–5). Shah et al. (1) proposed a multivariate analysis of variance method to test for the difference between two dissolution profiles. Chow and Ki (2) proposed dissolution difference measurement and similarity testing based on parameters after fitting a one-degree autoregression time series model. On the other hand, Sather et al. (3) employed parameters of profiles after fitting a selected mathematical model, and Tsong et al. (4) used multivariate ''Mahalanobis'' distance between two dissolution data sets for dissolution profile comparison.

The statistical methods proposed in most of these examples involved the complicated estimation of covariance matrix. Recently, Moore and Flanner (5) proposed a simple model-independent approach using mathematical indices to define the difference factor and similarity factor to compare dissolution profiles. This approach has also been recommended for dissolution profile comparison in the FDA Guidance for Industry (6–9). The similarity factor appears to be simple and can be easily adopted by the industry. Application of the similarity factor has been exemplified and reported in the literature (10,11). Moreover, some statistical properties of the similarity factor were also delineated (12,13). The advent of the similarity factor has undoubtedly allowed more precise measurement of the product similarities. The FDA defines similarity of the dissolution profiles between two drug products as when f_2 is between 50 and 100. As such, the dissolution profile of the test preparation is considered similar to that of the reference product if the f_2 value obtained is above 50.

In the present study, we attempted to relate the development of controlled-release diltiazem HCl tablets using two different polymers, xanthan gum (XG) and hydroxypropylmethylcellulose (HPMC), as matrix materials. In addition, the effect of pH and agitation rate on the rate of drug release of tablets prepared using these two polymers was determined. The similarity factor was applied for the dissolution profile comparison of the different batches of tablets and a reference product.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (MCC) was purchased from Wei Ming Pharmaceutical Manufacturing, South Korea. Controlled-release-grade HPMC (Methocel K15M) was a gift from Colorcon (Kent, UK). Xanthan gum was purchased from Rhone-Poulenc Ghimie (Paris, France). Diltiazem HCl was purchased from Xiamen Chemical Industrial Corporation (Xiamen, China). Magnesium stearate was purchased from Nutech Drugs, Karnataka, India. Herbesser 90 SR capsules (Tanabe Seiyaku, Osaka, Japan) were purchased from a local pharmacy. All the materials were used as received.

Preparation of Controlled-Release Tablets

Two series of tablet formulations employing different polymers as matrix materials were prepared. One consisted of diltiazem HCl, HPMC, and MCC in proportions of 3.0:1.5:5.5, 3.0:3.0:4.0, and 3.0:4.5:2.5, while the other comprised diltiazem HCl, XG, and MCC in proportions of 3.0:1.0:6.0, 3.0:2.0:5.0, 3.0:3.0:4.0, and 3.0:4.0:3.0. Diltiazem HCl, HPMC or XG, and MCC were blended in a planetary mixer (Kenwood Chef, Havant Hants, UK) for 5 min. Sufficient distilled water as granulating fluid was incorporated, and mixing continued for another 10 min. The wet powder mixture was sieved using a 1.40-mm mesh before being dried in an oven (Memmert, Schwabach, Germany) at 60°C for 1 hr. After drying, the granules were again sieved using a 1.00-mm mesh, and 0.5% magnesium stearate as a lubricant was added before the granules were compressed into tablets. Tablets of approximately 300 mg in weight containing 90 mg of diltiazem HCl were produced using a rotary tableting machine (Chung Yung Industrial, Taiwan) equipped with 10 mm diameter flat-face punches. The tableting machine was adjusted to produce a consistent tablet weight and compaction force for all the different batches of tablets.

In Vitro Drug Dissolution Studies

Drug release was investigated using the basket method of the USP 23 dissolution test apparatus (model AT7

CH4008, Sotax, Basel, Switzerland). The test was conducted in 900 ml of dissolution medium maintained at 37.0°C ± 0.5°C at a basket rotation speed of 100 rpm. Samples of 5 ml were collected at predetermined time intervals over a 12-hr period using an automated fraction collector (model C613, Sotax) equipped with a piston pump (model CY7-50, Sotax). The drug concentrations of the samples were analyzed after appropriate dilution using UV spectroscopy (UV/Vis spectrophotometer, Hitachi, Tokyo, Japan) at 254 nm. One tablet was used in each vessel, and each test was run in sets of six. The mean percentage of drug release over time was then calculated and plotted. Throughout the studies, the dissolution medium employed was distilled water.

To determine the effect of pH on the rate of drug release, different dissolution media (0.1 M HCl, phosphate buffer BP of pH 4 and 7) were used. In addition, the effect of agitation rate on the rate of drug release was also evaluated, and the agitation rates employed were 50, 100, and 150 rpm. The tablets selected for the studies of pH and agitation rate consisted of diltiazem HCl, HPMC or XG, and MCC in proportions of 3.0:3.0:4.0.

Application of Similarity Factor

Dissolution profiles of different batches of tablets were compared with that of the reference product (Herbesser 90 SR) using the similarity factor f_2 as follows:

$$f_2 = 50 \log_{10}\{[1 + (1/T)\sum_{i=1}^{T}(\bar{x}_{ti} - \bar{x}_{ri})^2]^{-1/2} \cdot 100\}$$

$\bar{x}_{ti}$ and $\bar{x}_{ri}$ represent the average percentage of drug dissolved from the 6 tablets measured at the ith time point of the test and reference preparations, respectively, and T is the number of time points tested, which was equivalent to 10 in the present study. Dissolution of the test preparation was considered similar to that of the reference preparation if the f_2 value was above 50.

In the estimation of f_2, bias could occur due to contribution of the variances of percentage drug dissolved measured at a particular time point of the test and reference preparations. As such, unbiased similarity factor f_2^* (14) was also calculated to determine the effect of variances of percentage drug dissolved measured at particular time points of the test and reference preparations on the f_2 · f_2^* is given as follows:

$$f_2^* = 50(\log_{10}\{1 + (1/T)[\sum_{i=1}^{T}(\bar{x}_{ti} - \bar{x}_{ri})^2 - \sum_{i=1}^{T}(s_{ti}^2 - s_{ri}^2)/n]\}^{-1/2} \cdot 100)$$

The term $\sum_{i=1}^{T}(s_{ti}^2 + s_{ri}^2)/n$ was subtracted within the log function of f_2, where s_{ti}^2 and s_{ri}^2 represent the variances of percentage drug dissolved measured at the ith time point of the test and reference preparations, respectively. Since

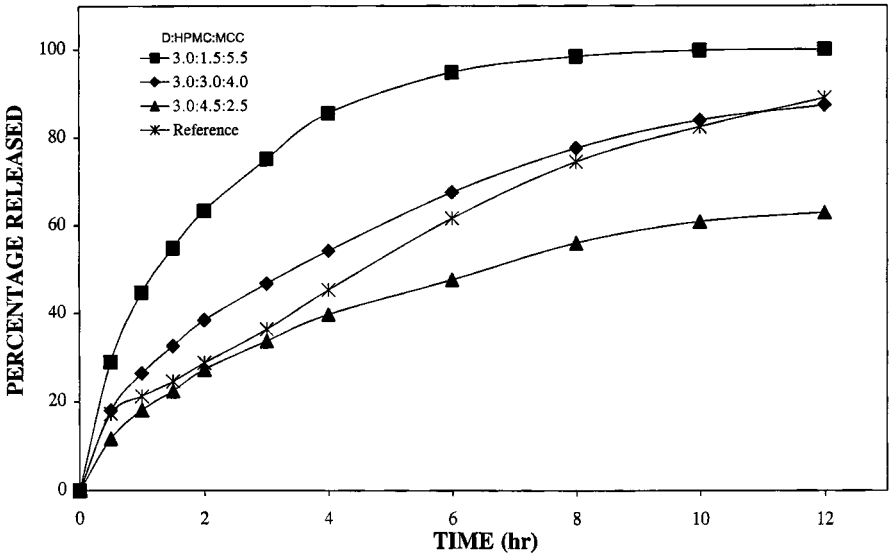

Figure 1. Drug dissolution profiles of tablets containing diltiazem HCl (D), hydroxypropylmethylcellulose (HPMC), and microcrystalline cellulose (MCC) in various proportions.

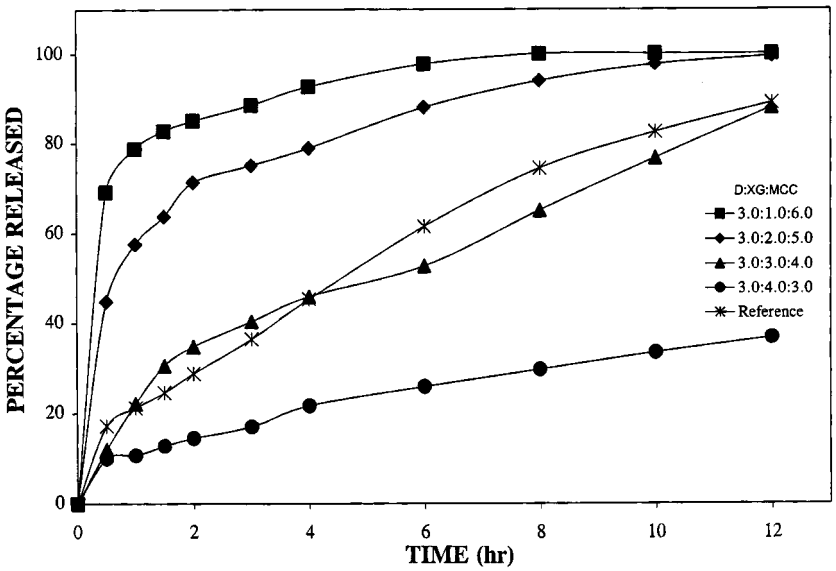

Figure 2. Drug dissolution profiles of tablets containing diltiazem HCl (D), xanthan gum (XG), and microcrystalline cellulose (MCC) in various proportions.

dissolution testing was conducted with 6 units of tablets in the present study, *n* is thus equivalent to 6.

RESULTS AND DISCUSSION

The drug release profiles of tablets containing different proportions of HPMC or XG and MCC are given in Figs. 1 and 2. With the incorporation of HPMC or XG, it can be seen that increasing the polymer content led to a corresponding decrease in the rate of drug release, and the drug release could be sustained up to 12 hr. From the various batches studied, the drug dissolution profiles of tablets containing diltiazem HCl, HPMC or XG, and MCC in proportions of 3.0:3.0:4.0 were noted to be more similar to that of the reference product than the

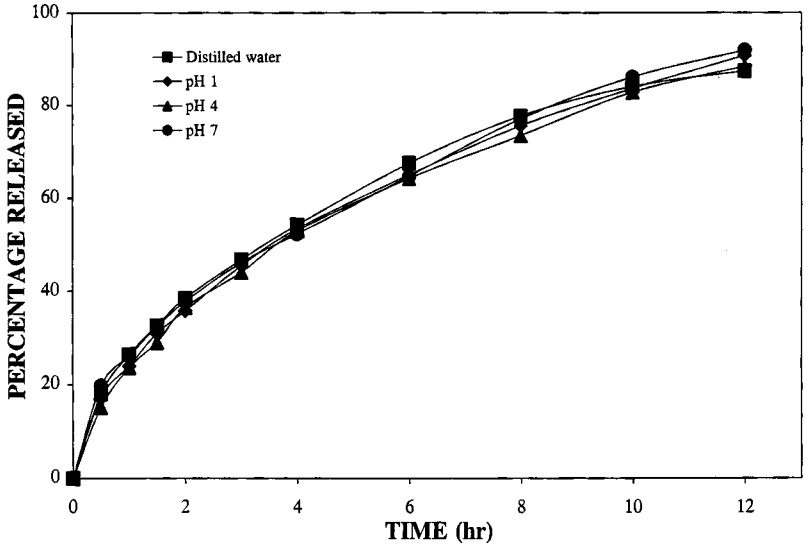

Figure 3. Drug dissolution profiles under different pH of tablets containing diltiazem HCl, hydroxypropylmethylcellulose (HPMC), and microcrystalline cellulose (MCC) in proportions of 3.0:3.0:4.0.

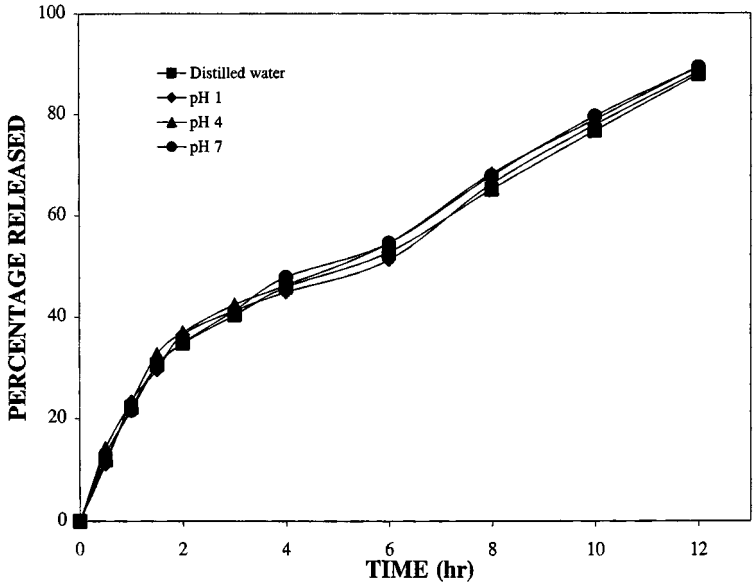

Figure 4. Drug dissolution profiles under different pH of tablets containing diltiazem HCl, xanthan gum (XG), and microcrystalline cellulose (MCC) in proportions of 3.0:3.0:4.0.

other batches. The drug release profiles of tablets containing diltiazem HCl, HPMC or XG, and MCC in proportions of 3.0:3.0:4.0 under different pH as well as agitation rate are depicted in Figs. 3–6. It can be observed that the dissolution profiles of tablets produced using HPMC or XG were closely similar under different pH and agitation rates, demonstrating that the drug release profiles were independent of pH and agitation rate. The independence of agitation rate or stirring speed may suggest that the drug release, which proceeded via a diffusion process, is internalized and occurs within the tablets. This is because, if diffusion occurs in a static layer of

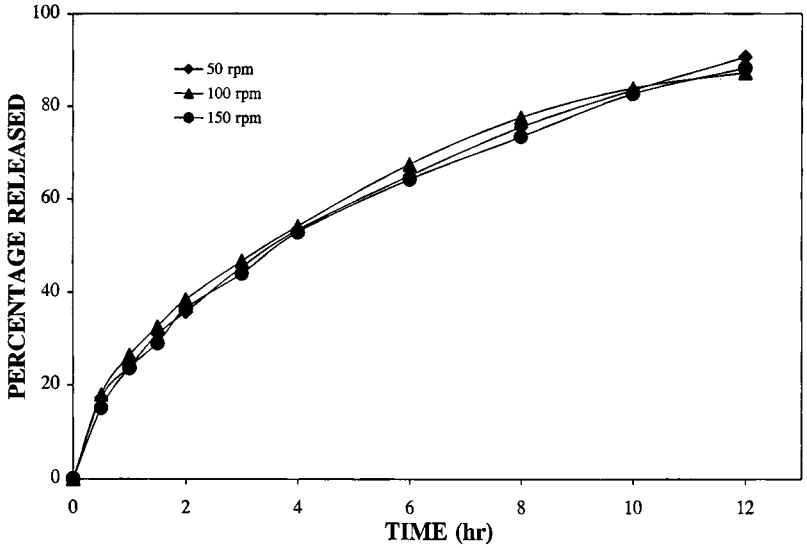

Figure 5. Drug dissolution profiles under different agitation rates of tablets containing diltiazem HCl, hydroxypropylmethylcellulose (HPMC), and microcrystalline cellulose (MCC) in proportions of 3.0:3.0:4.0.

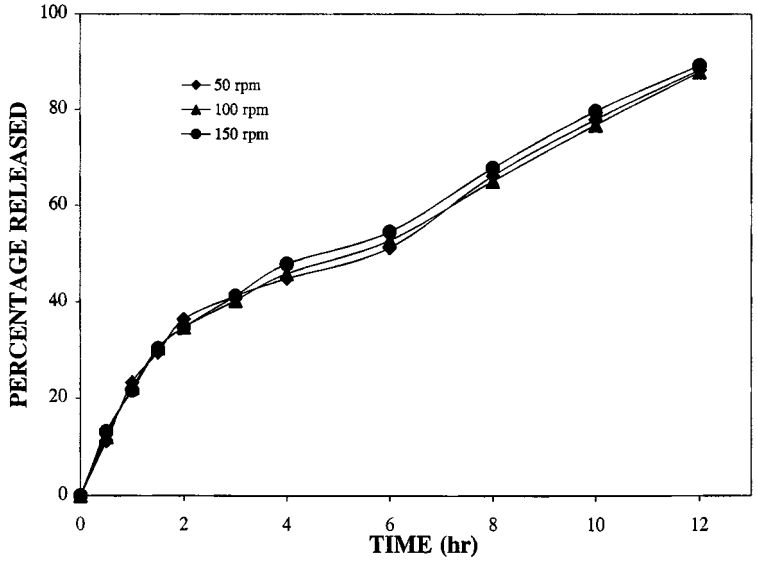

Figure 6. Drug dissolution profiles under different agitation rates of tablets containing diltiazem HCl, xanthan gum (XG), and microcrystalline cellulose (MCC) in proportions of 3.0:3.0:4.0.

fluid surrounding the tablet, changes in agitation rate should have altered the drug release profiles (15).

Table 1 shows the f_2 values of the different batches of tablets evaluated. Only tablets comprised of diltiazem HCl, HPMC or XG, and MCC in proportions of 3.0:3.0:4.0 had f_2 values above 50, while all the other batches of tablets had values less than 50. In this regard, only one of the many batches of tablets investigated was considered to have dissolution similar to that of the reference product. For this particular batch of similar compositions, tablets prepared with XG gave a relatively larger f_2 value than HPMC (62.29 and 59.07, respectively), indicating a more closely similar dissolution profile as that of the reference product. These findings concurred with the dissolution profiles described earlier (Figs. 1 and 2). Hence, f_2 can be used as a screening tool to select batches of tablets produced using different types of polymer with the desired dissolution profile.

The f_2^* values calculated for all the different batches of tablets were not much different from the f_2 values shown in Table 1. These findings could be attributed to the small dissolution variance calculated at particular time points of the test and reference preparations. As a result, it can be concluded that, as long as the dissolution variance was small, estimation of f_2 may be deemed adequate in the dissolution profile comparison. In addi-

Table 1

f_2 and f_2^* Values of the Various Batches of Tablets

Batches	f_2	$\sum (s_{ti}^2 + s_{ri}^2)/6$	$\sum (\bar{x}_{ti} - \bar{x}_{ri})^2$	f_2^*
Diltiazem:HPMC:MCC				
3.0:1.5:5.5	27.39	15.69	8,014.35	27.41
3.0:3.0:4.0	59.07	14.52	423.83	59.44
3.0:4.5:2.5	43.77	51.37	1,764.71	44.09
Diltiazem:XG:MCC				
3.0:1.0:6.0	17.54	15.17	19,876.62	17.54
3.0:2.0:5.0	25.56	26.19	9,488.64	25.59
3.0:3.0:4.0	62.29	62.85	312.37	64.65
3.0:4.0:3.0	25.17	22.25	9,838.17	25.19

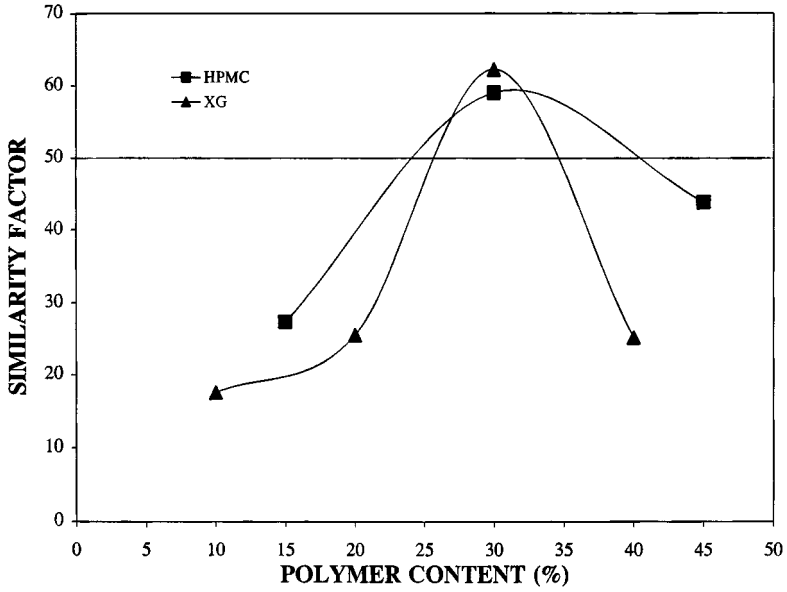

Figure 7. Similarity factor f_2 versus hydroxypropylmethylcellulose (HPMC) or xanthan gum (XG) content curves of different batches of tablets.

tion, f_2^* is also not recommended by the regulatory agencies.

Figure 7 illustrates the profiles of f_2 versus HPMC or XG content in the tablets. It can be observed that, to obtain tablets with a dissolution profile with an f_2 value above 50, the content of HPMC employed should range approximately between 25% and 40%, and XG should range between 25% and 35%. Below or above this range of values, the dissolution profiles would not be similar to that of the reference product. As such, the f_2 values can also be used as an optimization tool in product development.

CONCLUSIONS

In conclusion, controlled-release diltiazem HCl tablets could be prepared using HPMC or XG as matrix materials. Drug release could be modified in a predictable manner via varying the content of HPMC or XG. In addition, drug release of the tablets prepared using these matrix materials was not affected by pH and agitation rate. The f_2 values exhibited that only one batch of tablets, the batch with diltiazem HCl, HPMC or XG, and MCC in proportions of 3.0:3.0:4.0, had a dissolution profile that was considered similar to that of the reference product. The f_2^* values were found not much different from the f_2 values, which could be ascribed to the small dissolution variance of the test and reference preparations. The amount of polymer content required to produce tablets with a dissolution profile similar to that of the reference product could be determined from the profile curves of f_2 versus polymer content. Hence, the similarity factor can be used as screening and optimization tools in product development.

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