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COMMUNICATION

Possible Mechanism for Drug Retardation from Glyceryl Monostearate Matrix System

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ABSTRACT

Lipophilicity was evaluated as a possible mechanism for drug retardation from a glyceryl monostearate matrix system. Lipophilicity of the glyceryl monostearate matrix system was studied using contact angle measurement of water droplets on the surface of compressed disks, extrudate ascension of water, and movement of water through a powder mixture packed in a high-performance liquid chromatographic (HPLC) column. Increase in glyceryl monostearate content resulted in an increase in water droplet contact angle, decrease in the rate of water ascending the extrudate, and increase in the pressure values as a function of flow rate of water moving through the powder mixture. These could be due to the increase in lipophilicity of the matrix, rendering the matrix less wettable. As a result, the rate of water penetration into the matrix decreased, and the drug release could be sustained.

INTRODUCTION

In a previous study (1), we described the development and in vitro evaluation of a multiparticulate matrix controlled-release theophylline formulation. Drug release could be sustained and modified in a predictable pattern by varying glyceryl monostearate content. Since glyceryl monostearate is a lipophilic substance, its incorporation could render the matrix system more lipophilic. Increase in the lipophilicity could reduce the rate of water penetration, resulting in a slower rate of drug release. In view of these considerations, lipophilicity could be the possible mechanism for drug retardation from the glyceryl monostearate matrix system.

Hence, the aim of the present study was to demonstrate, using various methods, that lipophilicity may be

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the possible mechanism for drug retardation from the glyceryl monostearate matrix system.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Avicel PH-101) was obtained from FMC Corporation (Philadelphia, PA). Glyceryl monostearate was purchased from Euro-Chemo Pharma (Penang, Malaysia). Anhydrous theophylline BP was purchased from Xiamen Chemical Industrial Corporation (Xiamen, China).

Measurement of Water Droplet Contact Angle

Theophylline, microcrystalline cellulose, and glyceryl monostearate in proportions of 10:10:0, 10:8:2, 10:6:4, and 10:4:6, were mixed. A 0.5-g sample of the powder mixture was weighed and compressed using a hydraulic press (model P16, Beckman, Glenrothes, UK) at 8000 kg for 30 sec to form a disk with a 1.3 cm diameter and 2.1 mm thick. A 20-µl sample of distilled water was pipetted and placed on the surface of the disk. The whole assembly was further covered with a glass container to prevent water evaporation. After a lapse of 10 sec, the water droplet was photographed using an autofocus Minolta 7000AF camera equipped with a Minolta 50 mm macrolens, which was placed along the plane of the disk (Fig. 1). The contact angle between the water droplet and the disk was measured from the photograph taken. Also, the ratio of the height over the length of the water droplet was measured and calculated. Measurements were performed in six replicates.

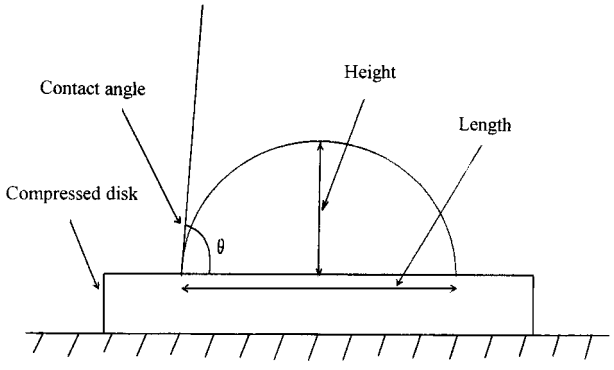

Figure 1. Measurement of water droplet contact angle on the surface of compressed disk.

Extrudate Ascension of Water

Extrudates 1 mm in diameter and approximately 4 cm in length of theophylline, microcrystalline cellulose, and glyceryl monostearate in proportions of 10:10:0, 10:8:2, 10:6:4, and 10:4:6 were prepared using a Ram Extruder (Georgetown, Penang, Malaysia) fitted with a single-hole die with a hole size of 1 mm diameter and 4 mm length as described earlier (1). Extrusion was performed at a constant displacement rate of 30 cm/min. After drying at 40°C until the weight became constant (approximately 24 hr), the extrudates were placed vertically with one end dipped into a small container filled with distilled water in which a few drops of methylene blue were added, while the other end was held in place by a clip holder. The whole assembly was further covered with a glass container to promote water saturation of the enclosed space. The experimental setup is illustrated in Fig. 2. The principle is similar to that applied in thin-layer chromatography. The rate of water ascending the extrudates was determined by measuring the height of extrudates wetted at predetermined time intervals using a magnifying glass (×4). The study was replicated six times.

Water Movement Through Powder Mixture

Microcrystalline cellulose and glyceryl monostearate mixtures in proportions of 10:0, 8:2, 6:4, 4:6, and 0:10 were packed by tapping into an empty high-performance liquid chromatographic (HPLC) column (125 × 4 mm internal diameter, Merck, Darmstadt, Germany). The principle is similar to packing an HPLC column using

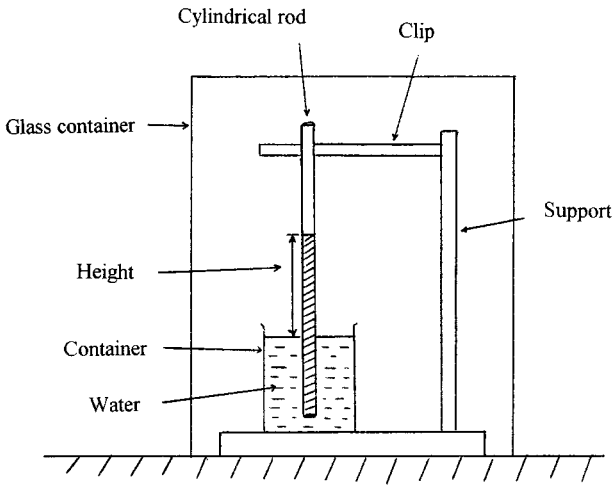

Figure 2. Extrudate ascension of water.

the tapping method. The column was connected to a Jasco PU980 Intelligent HPLC pump (Jasco, Tokyo, Japan). Distilled water, as the mobile phase, was delivered through the column at preset flow rates of 0.2, 0.5, 1.0, 1.5, and 2 ml/min. The corresponding pressure for each flow rate was recorded. Measurement was performed in triplicate.

RESULTS AND DISCUSSION

Figure 3 shows the contact angle and the ratio of height over length of water droplets as a function of glyceryl monostearate content. The two profiles were similar and nearly superimposable. The values of both contact angle and the ratio of height over length of water droplets were observed to increase with an increase in the glyceryl monostearate content. These results indicated that glyceryl monostearate increased the lipophilicity or decreased the wettability of the compressed disk. The present method is relatively more simple compared to other reported methods, such as the goniometric technique (2), reflected light of laser beam technique (3), and captive bubble technique with the sample immersed in water (4,5), which appeared rather sophisticated and complex. Although hysteresis has been reported for the present method (6), this was not observed in the present study, which could have been circumvented by using a small volume water droplet (20 μl) and measuring the water droplet contact angle from photographs taken within a short time interval of 10 sec.

The rate of water (dissolution medium) penetration into the matrix plays a crucial role in controlling the rate of drug release. Decrease in the rate of water penetration is associated with a slower rate of drug release. Therefore, two experiments (extrudate ascension of water and penetration of water through a powder mixture packed in an HPLC column) were designed to study the effect of glyceryl monostearate on the water penetration into the matrix. The rate of water ascension of the extrudate was found inversely proportional to the amount of glyceryl monostearate (Fig. 4). An increase in the glyceryl monostearate content led to a slower rate of water ascending the extrudate, suggesting more lipophilic and less wettable extrudates.

Figure 5 shows the values of pressure obtained for various matrix materials as a function of flow rate. In all cases, an increase in the flow pressure was observed when there was an increase in the flow rate. At a particular flow rate, glyceryl monostearate alone was found to have the highest flow pressure, followed by the mixtures of microcrystalline cellulose and glyceryl monostearate in proportions of 4:6, 6:4, and 8:2, and followed last by microcrystalline cellulose alone. It can be noted that the flow pressure required to achieve a particular flow rate was directly proportional to the glyceryl monostearate content. Although porosity and tortuosity parameters could have affected water movement through the powder mixture, and hence influenced drug release, these factors might not play any significant role. This is because the average particle size of glyceryl monostearate used in our formulations was 300 μm, and that of microcrystalline cellulose is 50 μm. When the proportion of glyceryl monostearate in the powder mixture was increased, it fol-

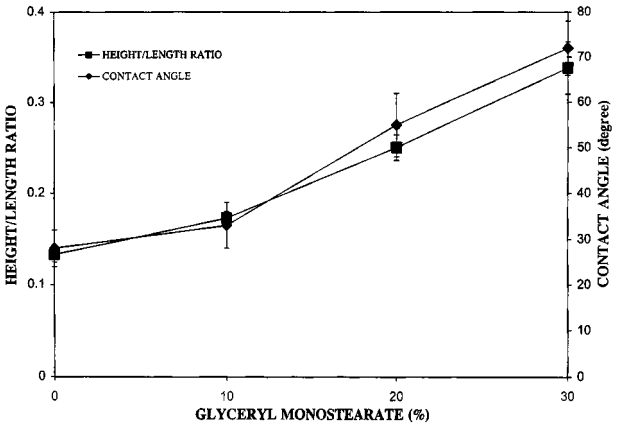

Figure 3. Contact angle and height-over-length ratio of water as a function of glyceryl monostearate content. Mean ± SD, $N = 6$.

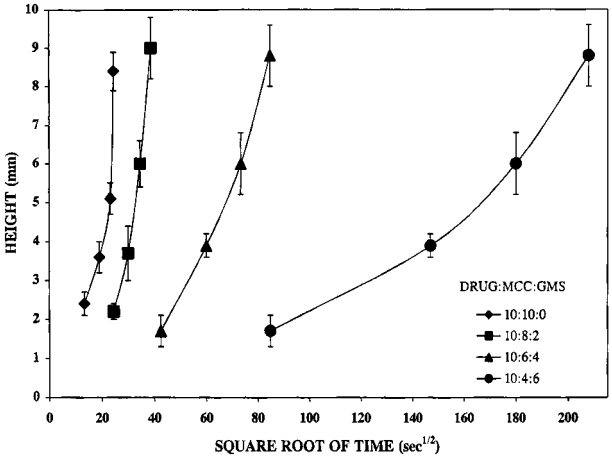

Figure 4. Movement of water through extrudates containing theophylline (drug), microcrystalline cellulose (MCC), and glyceryl monostearate (GMS). Mean ± SD, $N = 6$.

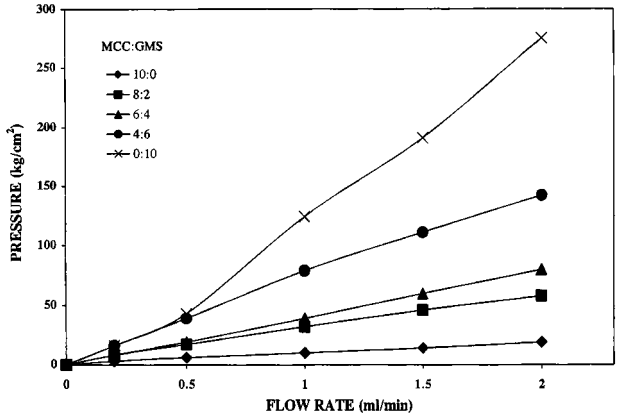

Figure 5. Flow pressure as a function of flow rate for various compositions of matrix materials containing glyceryl monostearate (GMS) and microcrystalline cellulose (MCC). Mean ± SD, $N = 3$.

lowed that a more porous and less compact powder bed should be produced, leading to a lower flow pressure. In contrast, a higher flow pressure was obtained with an increase in the amount of glyceryl monostearate. Therefore, it can be implied that the retarding effect of glyceryl monostearate on the rate of drug release was due mainly to its effect on the lipophilicity, but not the porosity/tortuosity, of the matrix materials. This finding is consistent with those of the two methods described earlier.

CONCLUSIONS

In conclusion, an increase in lipophilicity, and hence a decrease in wettability, could be the possible mechanism for drug retardation from a glyceryl monostearate matrix system. This can be shown from the results obtained from the studies of water droplet contact angle, extrudate ascension of water, and penetration of water through a powder mixture packed in an HPLC column.

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