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Effect of drug solubility and different excipients on floating behaviour and release from glyceryl monooleate matrices

Kiran Kumar M., Manish H. Shah, Anant Ketkar, K.R. Mahadik, Anant Paradkar*

Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandawane, Pune 411038, Maharashtra State, India

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Abstract

Glycerol monooleate (GMO) matrix was found to be a gastro-retentive carrier system suitable for both polar and as well as non-polar drugs. Chlorpheniramine maleate (CPM) and diazepam (DZP) were used as model drugs. Effect of PEG 4000, PEG 10000, and stearic acid on floatability and release profile was studied.

Water uptake increased with increase in the loading of polar drug (CPM) and decreased with non-polar drug (DZP). Similar effect was found to occur in case of drug release. PEGs increased the release up to certain concentration and decreased thereafter. Drug release decreased linearly with concentration of stearic acid. The type and extent of mesophases formed were significantly affected by the nature of drug, excipients and their concentration. Thus the selection of suitable excipients depending on polarity of drug, could help to modulate the floatability and release profile from GMO matrices.

Keywords: Glyceryl monooleate; Diazepam; Chlorpheniramine maleate; Liquid crystalline phases; Floating matrices

1. Introduction

Recently, much attention has been focused on the use of fats and fatty acids as carriers in drug delivery systems. Lipids have received considerable attention in the development of drug delivery systems due to the advantages, which lipids offer (Porter and Charman, 2001; Wyatt and Dorschel, 1992). At the same time, the technological advances have made it feasible to process lipids and thermo-softening agents for their use in the oral drug delivery systems.

Glycerol esters of fatty acids have been recently thought as carrier systems for sustained delivery of drugs (Chang and Bodmeier, 1997; Geraghty et al., 1996; Burrows et al., 1994). These polar amphiphilic lipids such as glyceryl monooleate (GMO) belong to a class of water insoluble lipids, which swell in water and form various kinds of lyotropic liquid crystals (Tardieu and Luzzata, 1970; Larsson, 1989). A sample of GMO take up about 80% of its own weight of water at room temperature, going through three different one phase regions. At low water content, a reversed micellar phase (L_2) is formed followed by lamellar liquid crystalline phases (L_α). At higher water content, the system enters into the cubic phase region (C). This region consists of two cubic phases belonging to different cubic space group. At higher temperature, a reversed hexagonal liquid crystalline phase (H_{II}) is formed (see Fig. 1). The cubic phase of GMO can coexist in equilibrium with excess

* Corresponding author. Tel.: +91-20-5437237; fax: +91-20-5439383.
E-mail address: arparadkar@rediffmail.com (A. Paradkar).

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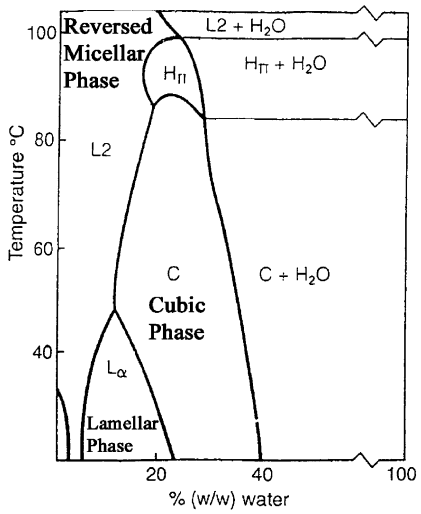

Fig. 1. Phase diagram of GMO–water system (adapted with modification from references: Shah et al., 2001; Larsson, 1989; Nielsen et al., 1998).

of water and the monomer solubility in water is about 10^{-6} M.

The cubic phase formed consists of a curve bilayer extending in three dimensionally and separating two congruent networks of water channels, as shown in Fig. 2. Thus, this cubic phase is both lipid- and water-continuous, and the pore size of fully swelled phases is about 5 nm. The interfacial area is about 400 m^2/g cubic phase (Shah et al., 2001; Engstrom and Engstrom, 1992).

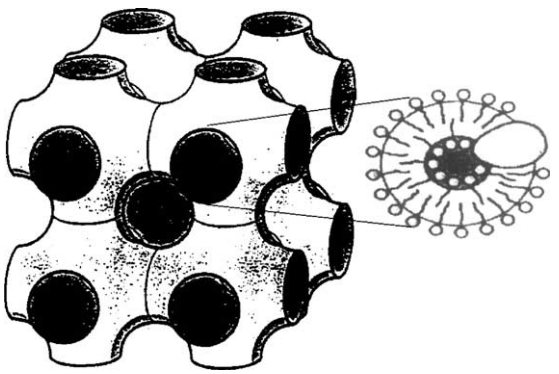

Fig. 2. Structure of GMO–water cubic phase in three dimension with inset showing the lipid bilayer (adapted with modification from references: Shah et al., 2001; Wyatt and Dorschel, 1992).

Gastroretentivity of drug delivery system is desired in the formulation of many drugs. Numbers of technique have been reported for the design of gastro-retentive drug delivery system (Ponche and Irache, 1998; Singh and Kim, 2000). Swelling of GMO matrix system due to water uptake reduces its density and will float if it is less than unity. Physiochemical properties of drug and additives will significantly affect floatability. The mesophases of GMO are also reported to exhibit bioadhesive property (Nielsen et al., 1998). Residence of drug in the cubic phase provides protection from gastric degradation. In floating system, duration of floating is significantly affected by number of factor such as particle size, food, etc. (Singh and Kim, 2000). Bioadhesive nature of GMO improves chances of gastroretention of the matrices. But studies on GMO matrices reported till now have been carried out with restriction to the movement of the matrix system. Therefore, GMO matrices may be considered as potential drug delivery system with gastroretentivity.

The present work was undertaken to study the effect of drug solubility and different additives viz. PEG 4000, PEG 10000, and stearic acid on the integrity, floatability, and release properties of GMO matrices. Diazepam (DZP; sparingly soluble in water, log P = 3.18) and chlorpheniramine maleate (CPM; freely soluble in water) were selected as the lipophilic and hydrophilic model drugs, respectively.

2. Materials and methods

2.1. Chemicals

GMO (Rylo MG19 Pharma) was obtained as a gift sample from Danisco Cultor, Denmark. DZP and CPM were obtained as gift samples from Ranbaxy Laboratories Ltd., India and Emcure Ltd., India, respectively. PEG 4000, PEG 10000, and stearic acid were obtained from Merck, India. All other chemicals were of analytical grade.

2.2. Preparation of GMO matrices

2.2.1. Plain matrices

GMO was taken in a beaker and melted at 55 °C on a water bath. The molten mass was poured in fabricated

cylindrical moulds (inner diameter of 8.5 mm, height of 10 mm) and frozen at −15 °C. The matrices were equilibrated to room temperature for 24 h before evaluation.

2.2.2. Drug-loaded matrices

Matrices containing 8, 10, 12, and 15 mg of drug (per 300 mg of GMO) were prepared. GMO was melted at 55 °C on a water bath and drug was added with stirring and the matrices were prepared by the procedure described above.

2.2.3. Matrices for studying effect of additives

GMO was melted at 55 °C on water bath, to which additives viz. PEG 4000, PEG 10000, and stearic acid were added separately with stirring and the matrices were prepared by the procedure described above. For matrix integrity and buoyancy lag-time studies, amount of PEG 4000 and PEG 10000 was varied between 25 and 300 mg and that of stearic acid between 25 and 150 mg. Effect of additives on drug release was studied in matrices containing 10 mg drug.

2.3. Evaluation of matrices

2.3.1. Buoyancy lag-time

The matrices were tested for buoyancy lag-time, matrix integrity, and duration of floating by using USP 24 type II dissolution test apparatus (Electrolab TDT-06P, India). Matrices were added to 900 ml of 0.1N HCl maintained at 37 ± 0.5 °C and stirred at 100 rpm. Time required to float was reported as buoyancy lag-time. Matrix integrity and duration of floating were inspected visually.

2.3.2. Gamma scintigraphy

The plain GMO matrices were studied for in vivo gastric retention test by gamma scintigraphy. Six healthy volunteers were selected between age 23 and 30 years having weight in the range of 50–60 kg. ^{99m}Tc 0.1 mCi was uniformly mixed with the molten monoglyceride and the mass was poured into capsules and frozen at −15 °C. The volunteers were asked to swallow these capsules with water after taking light breakfast in the morning. Images were recorded at different time intervals up to 5–6 h using millennium MPR Gamma camera (low-energy high-resolution collimeter integrated to ENTEGRA work station).

2.3.3. Water uptake studies

Water uptake studies were carried out by equilibrium weight gain method (Roy and Rohera, 2002). The studies were carried out using USP 24 Type II dissolution test apparatus (Electrolab, TDT-06P, India). The GMO matrices were accurately weighed and placed in a dissolution basket. The baskets were immersed in dissolution vessel containing 900 ml of 0.1N HCl maintained at 37 ± 0.5 °C, and rotated at 100 rpm. At regular intervals, the basket-matrix systems were removed from the dissolution vessels, blotted with tissue paper to remove excess water and reweighed. The increase in the weight was reported as percent water uptake.

2.3.4. Release studies

Drug release from the matrices was studied by using USP 24 type II dissolution test apparatus (Electrolab TDT-06P, India). The matrices were placed in 900 ml of 0.1N HCl (at 37 ± 0.5 °C) and speed was kept at 100 rpm. Sample (5 ml) was withdrawn at predetermined time intervals and replenished with fresh dissolution medium maintained at 37 ± 0.5 °C and

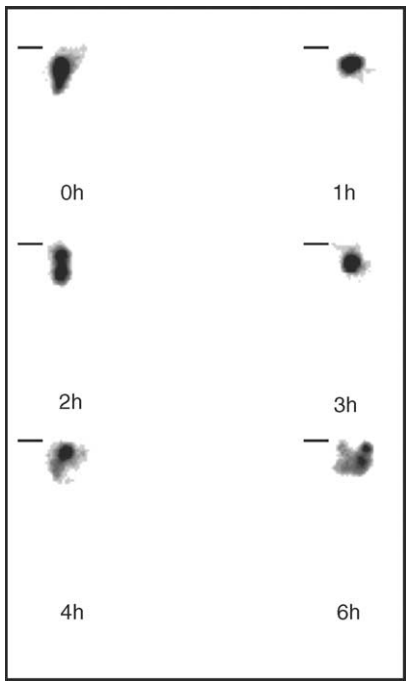

Fig. 3. Gamma scintigraphs of GMO matrix.

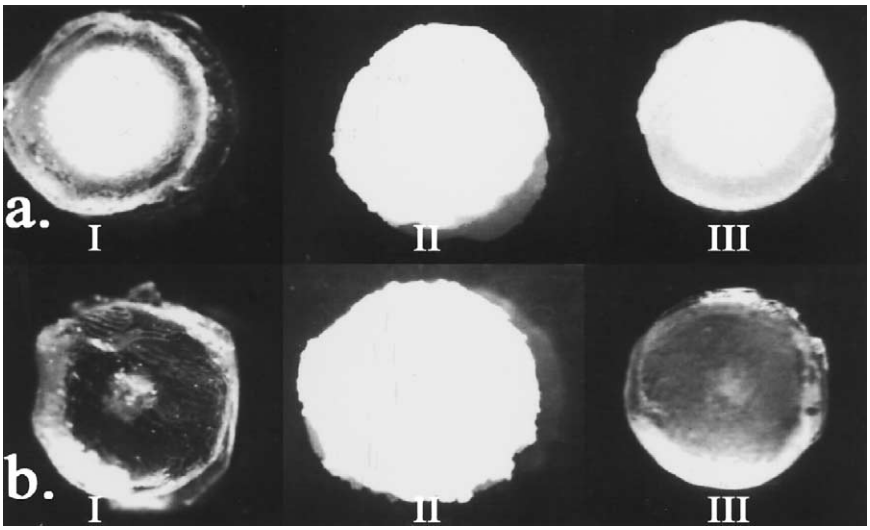

Fig. 4. Photograph showing GMO matrix after hydration. (a) 1 h, (b) 6 h. I: plain matrices; II: containing 50 mg PEG 4000; III: containing 50 mg stearic acid.

assayed spectrophotometrically at 284 and 264.4 nm, for DZP and CPM, respectively.

3. Results and discussion

During preliminary studies, it was observed that GMO matrix swells in water and the swollen mass floats on the surface for a prolonged period of time. The gastro-retentivity of the formulation was confirmed by gamma scintigraphy (Fig. 3). The matrix remained intact and was retained in stomach for 5–6 h. The photograph of swollen matrices, after 1 and 6 h, in the dissolution medium are shown in Fig. 4.

Buoyancy lag-time (BLT; Table 1) was found to increase with increase in PEG and stearic acid amount above 50 mg of each. Molecular weight of PEG did not significantly affect the BLT. The increase in BLT was more in case of stearic acid due to reduction in water uptake caused by hydrophobic nature of stearic acid. It was also observed that above 75 mg, all the additives showed erosion of the matrix from the surface, and even breaking of the matrix into small aggregates in case of PEG. Thus, further study was carried out with up to 75 mg of each additive.

Water uptake data was subjected to Vergnaud equation (Vergnaud, 1993) to determine the rate of water uptake (Eq. (1)).

$$M_t = kt^n \quad (1)$$

where M_t represent the amount of liquid transferred at time t and k is swelling constant which depends upon

Table 1
Effect of different amounts of PEG and stearic acid on buoyancy lag-time of GMO matrices

PEG 4000 (mg)	Buoyancy lag-time (min)	PEG 10000 (mg)	Buoyancy lag-time (min)	Stearic acid (mg)	Buoyancy lag-time (min)
0	1.1 ± 0.1	0	1.2 ± 0.2	0	1 ± 0.2
25	2.3 ± 0.2	25	2.1 ± 0.3	25	1 ± 0.2
30	2.2 ± 0.1	30	2.3 ± 0.2	50	9 ± 0.5
40	2.2 ± 0.3	40	2.1 ± 0.4	75	24 ± 0.9
50	3.9 ± 0.5	50	3.8 ± 0.8	100	37 ± 1.4
75	12.6 ± 0.7	75	13.3 ± 0.6	125	42 ± 2.3
100	27.2 ± 2.6	100	26.3 ± 1.9	150	53 ± 2.9

Table 2
Effect of amount of CPM and DZP on water uptake

Amount of drug (mg)	Diazepam			CPM		
	n	*k*	*r*[a]	*n*	*k*	*r*
0	0.2694	7.202	0.9958	0.2694	7.191	0.9959
8	0.2472	7.423	0.9915	0.2768	4.921	0.9993
10	0.2333	7.714	0.9916	0.3107	4.454	0.99986
12	0.2231	7.809	0.9808	0.3165	4.616	0.9975
15	0.1672	9.15	0.9694	0.3296	4.477	0.9976

[a] Correlation coefficient.

the amount of liquid transferred after infinite time, porosity of matrix and diffusivity. The exponent indicates the mechanism of water uptake. The regression analysis of water uptake data is summarized in the Table 2.

Effect of amount of drug on water uptake and drug release is shown in Figs. 5–8. It was observed that the water uptake increases with increase in the loading of polar drug (CPM; Fig. 5) and decreases with non-polar drug (DZP; Fig. 6). Similar effect was found to occur in case of drug release. Initial water uptake rates were found to be independent of amount of drug. The inflection in the water uptake profile after 15–20% water uptake may be attributed to formation of cubic phase, which is highly viscous and acts as a rate-limiting factor in further absorption of water. It is reported that, generally hydrophilic drugs favor transformation of cubic phase into lamellar phase while lipophilic drug transforms cubic phase into reverse hexagonal phase. Therefore, due to the presence of lipophilic drug DZP, the cubic and hexagonal phases are favored and lamellar phase fastly transforms into cubic phase with increasing amounts of DZP. Similarly hydrophilic drug CPM, exhibits concentration dependent formation of lamellar phases, which have low viscosity and causes increase in the water uptake with increase in concentrations of CPM. Thus, above discussion regarding water uptake suggests that DZP fervors cubic phase, i.e. proportion of cubic phase in the hydrated layer is expected to increase with increase in DZP concentration. Whereas CPM favors lamellar phase, i.e. percentage of lamellar phase in the hydrated layer will increase with increase in concentration of CPM, thereby correspondingly affecting the water uptake.

Though water uptake in presence of drug has shown inflections in the profiles especially at higher drug concentrations, which may be attributed to phase transformations. The inflections at later stage may be due to slight erosion at the surface.

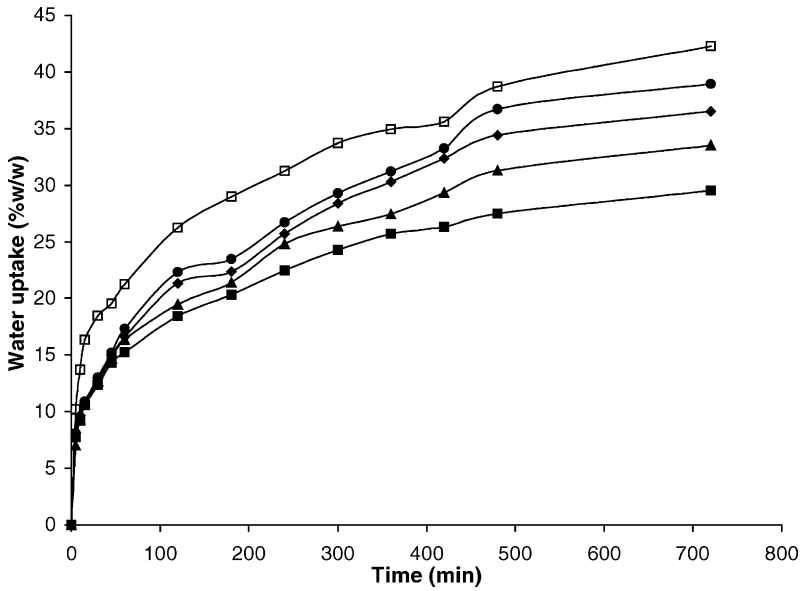

Fig. 5. Effect of amount of chlorpheniramine maleate on water uptake of GMO matrices: blank (□); 8 mg (■); 10 mg (▲); 12 mg (◆); 15 mg (●).

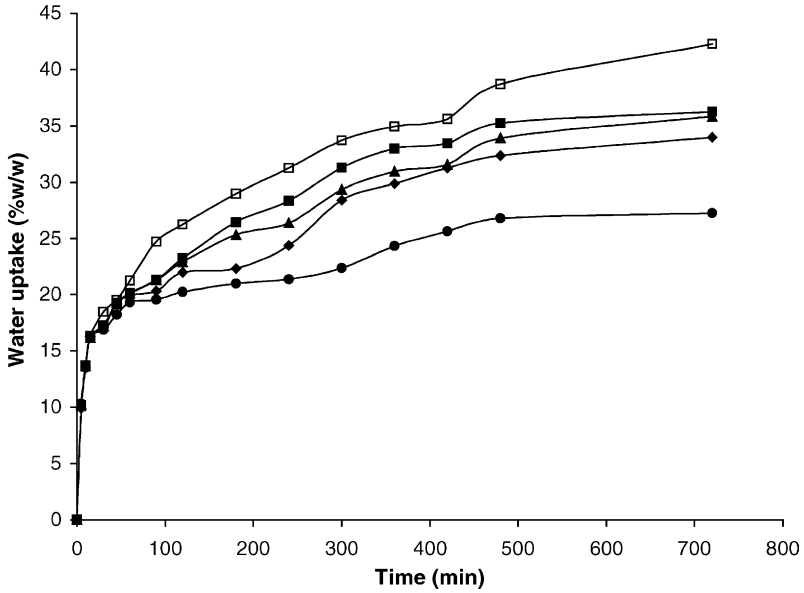

Fig. 6. Effect of amount of diazepam on water uptake of GMO matrices: blank (□); 8 mg (■); 10 mg (▲); 12 mg (◆); 15 mg (●).

The results of drug release from the matrices were in good correlation with the water uptake studies. The dissolution profiles were fitted in Eq. (2) (Korsmeyer et al., 1980).

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

where 'k' is a constant incorporating structural and geometric characteristics of the drug dosage form; 'n'

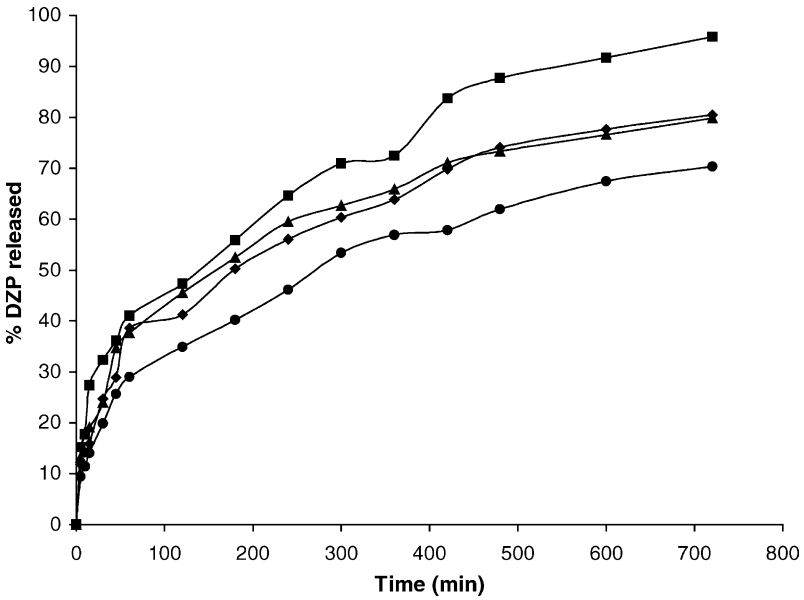

Fig. 7. Effect of amount of diazepam on release from GMO matrices: 8 mg (■); 10 mg (▲); 12 mg (◆); 15 mg (●).

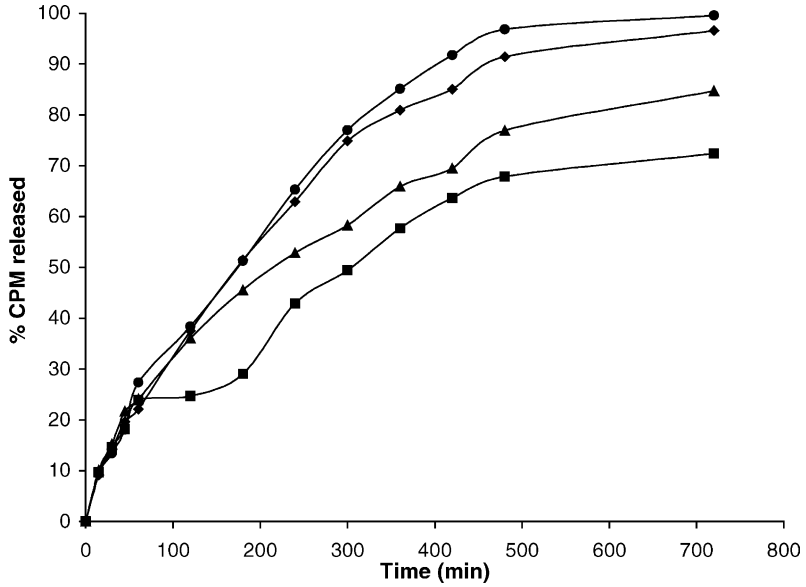

Fig. 8. Effect of amount of chlorpheniramine maleate on release from GMO matrices: 8 mg (■); 10 mg (▲); 12 mg (◆); 15 mg (●).

is the release exponent indicative of the drug release mechanism; and 'M_t/M_∞' (fraction of drug released) is the function of time '*t*.' The release of DZP from the matrix, correlated well with its effect on water uptake. As shown in Table 3 with increasing amount of DZP, the '*n*' value increased from 0.37 to 0.41. As DZP favors formation of cubic phases, the release shift towards Fickian diffusion due to swelling of matrix. In contrast to DZP, with increasing amount of CPM the '*n*' value decreases from 0.37 to 0.18, as CPM favors formation of lamellar phases, which are less viscous than cubic phases.

Location of the drug is an important parameter, which affects release rate and kinetics. DZP, due to its lipophilicity gets incorporated into the lipid bilayers, thus its partition into the aqueous channels becomes the rate-limiting step. Therefore, partitioning into the aqueous channels and the resistance offered by different mesophases formed in the swollen matrix, control the release of DZP.

Table 3
Effect of drug loading on release kinetics of DZP and CPM from GMO matrices

Amount of drug (mg)	Diazepam			CPM		
	n	*k*	*r*[a]	*n*	*k*	*r*
8	0.3669	8.735	0.994	0.3766	2.380	0.995
10	0.3698	7.516	0.995	0.3637	2.310	0.997
12	0.4046	6.013	0.994	0.1999	1.584	0.995
15	0.4169	4.754	0.997	0.1855	1.532	0.993

[a] Correlation coefficient.

Effects of PEG 4000 and PEG 10000 on drug release are shown in Figs. 9 and 10. The effect could be attributed to following reasons: (1) PEG increases water uptake and forms a porous, non-transparent, low-density matrix. (2) It favors partitioning of the drug to the aqueous phase by its co-solvent effect. (3) Due to its hydrophilic nature, it decreases the availability of water to the lipid and thereby favors lamellar phases, which causes faster release of drug. (4) At higher concentration, it may increase the viscosity of aqueous phase and retard the movement of drug molecules.

In presence of PEG 4000, the release of DZP, which is expected to be dependent on the partitioning and the mesophase concentration was found to increase significantly. The drug release from matrices initially increased up to 25 mg and decreased afterwards. The release is favored by increase in the porosity and formation of lamellar phase, whereas opposed by the viscosity of aqueous filled channels and the extent of mesophases formed. After critical concentration (25 mg) PEG 4000, the release opposing factors dominate the favoring ones. Similar effect was observed

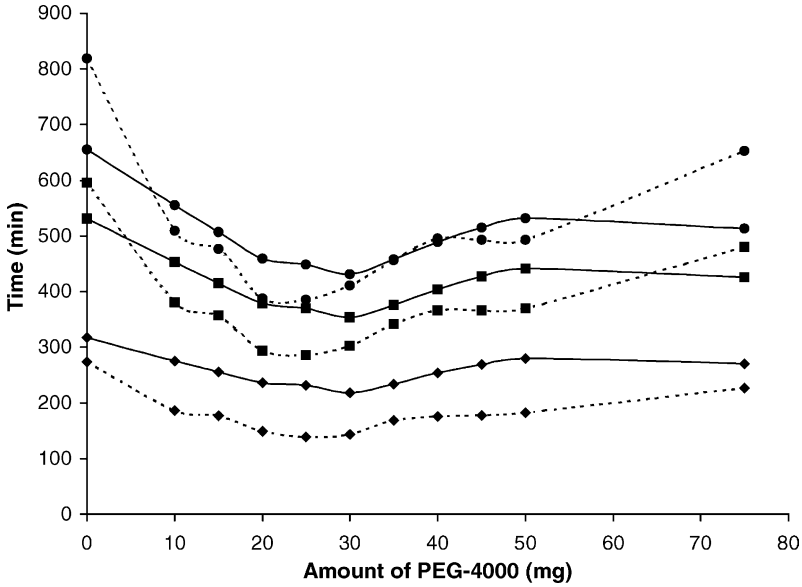

Fig. 9. Effect of PEG 4000 on the release of diazepam (10 mg; dotted lines) and chlorpheniramine maleate (10 mg; bold lines) from GMO matrices: $t_{60\%}$ (◆); $t_{80\%}$ (■); $t_{90\%}$ (●).

with incorporation of PEG 10000. But the extent of release enhancement at lower concentrations was comparatively less. It might be attributed to the high molecular weight and less polarity of PEG 10000, which reduces formation of mesophases yielding less spongy matrices.

PEGs were found to show less pronounced effect on release of CPM as compared to DZP. Faster water

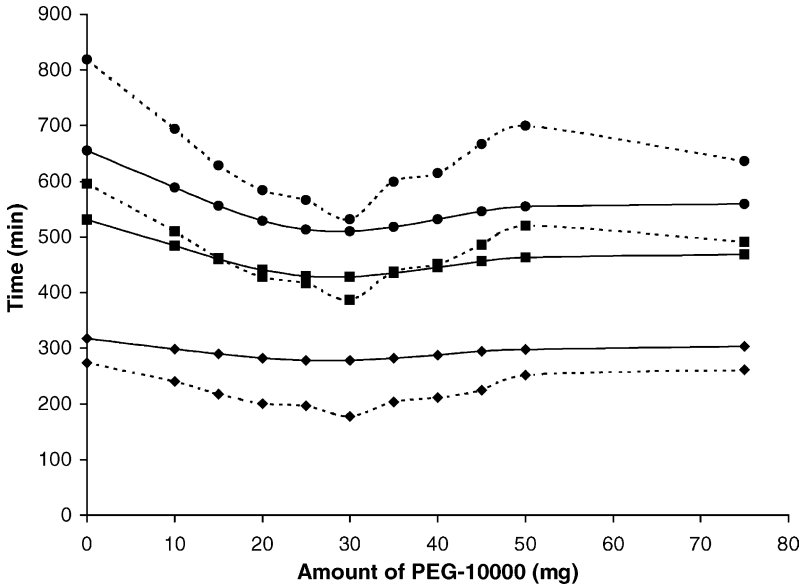

Fig. 10. Effect of PEG 10000 on the release of diazepam (10 mg; dotted lines) and chlorpheniramine maleate (10 mg; bold lines) from GMO matrices: $t_{60\%}$ (◆); $t_{80\%}$ (■); $t_{90\%}$ (●).

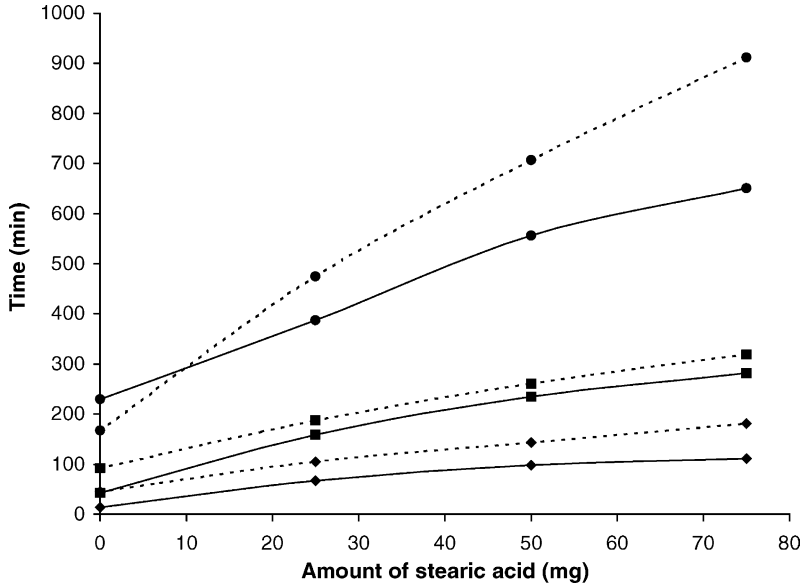

Fig. 11. Effect of stearic acid on the release of diazepam (10 mg; dotted lines) and chlorpheniramine maleate (10 mg; bold lines) from GMO matrices: $t_{20\%}$ (◆); $t_{30\%}$ (■); $t_{50\%}$ (●).

uptake in presence of PEGs enhances rate of solution of dispersed CPM up to 30 mg of PEG 4000. At higher PEG concentrations, the release opposing factors dominate as discussed in case of DZP.

Though PEG 10000 increases release rate at lower concentrations up to 25 mg, the release favoring effects are completely nullified by the retarding effects, exhibiting no significant change in the release of CPM from the matrix.

Effect of stearic acid (SA) on drug release is shown in Fig. 11. It was found to retard the release of both the drugs. Formation of slimy layer at the surfaces of matrices containing 50 and 75 mg of stearic acid indicated significant erosion from the SA-containing matrices. The release retardant effect of SA was found to be more pronounced in case of DZP as compared to CPM. SA gets incorporated in the lipid bilayer structure, thereby causing more resistance for the movement of lipophilic molecule from the lipid bilayers to the aqueous channel. The hydrophobic nature of SA favors formation of cubic phase at faster rate. In case of matrices containing lipophilic drugs, this effect was more pronounced exerting higher retarding effect on lipopihilic drugs. Incorporation of SA in the lipid bilayers reduces the volume of water in the aqueous channels. As the release of lipophilic drug is controlled by its partitioning to the aqueous phase, it will be retarded to a greater extent.

Thus, the nature and extent of mesophases formed in GMO matrices is governed by water uptake, which depends on the nature of the drug and excipients used.

4. Conclusions

GMO matrix is a thermo-softening system suitable for oral controlled release floating gastro-retentive systems of hydrophilic as well as lipophilic drugs. Incorporation of excipients such as high molecular weight PEGs and stearic acid, depending on the solubility of the drug, could help to modulate the floatability and drug-elution profiles from GMO matrices.

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