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Research paper

Effect of HLB of additives on the properties and drug release from the glyceryl monooleate matrices

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Abstract

Glyceryl monooleate (GMO) is an amphiphilic surfactant, which as such can solubilize hydrophilic, lipophilic and amphiphilic drug molecules in its different polarity regions. Addition of additives with different polarities in GMO leads to change in phase behavior and related properties of GMO. Effect of the additives with different hydrophilic lipophilic balance (HLB; 1.5, 3, 4, 5, 7, 10 and 11) in GMO matrices on its phase transformation, rheological properties, mechanical properties, wetting and release behavior was investigated. Polarizing light microscopy showed that the GMO matrices incorporated with lower HLB additive (1.5, 3, 4 and 5) form cubic phase at higher rate while lamellar phase was prominent for matrices with additive of HLB 7, 10 and 11. The diametrical crushing strength and viscosity was decreased with increased HLB of additive. Lower HLB additives enhanced contact angle as compared to plain matrices and high HLB additives induced change in solid–liquid interface from hydrophobic to hydrophilic leading to decline in contact angle. Percent swelling of matrices was increased linearly with increase in HLB of additives. Tensiometric method was used for determination of bioadhesive strength of hydrated matrices and it was observed that matrices with additives of HLB 10 presented highest bioadhesion due to higher rate of hydration and formation of lamellar phase. As the HLB of additives in matrix increased, release was shifted from anomalous (non-Fickian) diffusion and/or partially erosion-controlled release to Fickian diffusion. Initial lag was observed for drug released from matrices with additive of HLB 1.5, 3, 4 and 5. Thus incorporation of the additives of different HLB changed molecular packing, which significantly affected drug release pattern.

Keywords: Glyceryl monooleate; Glyceryl mono-stearate; Phase transformation; Diametrical crushing strength; Contact angle; Rheological behavior

1. Introduction

Glyceryl monooleate (GMO) is a water insoluble (HLB = 3) synthetic amphiphilic surfactant. Being non-toxic, biocompatible and biodegradable, it has emerged as a potential candidate for various drug delivery systems especially controlled ones [1–5].

Upon contact with water GMO forms different sequential liquid crystalline phases viz. lamellar, cubic and hexagonal phase. These phases are highly ordered microheterogeneous systems, capable of being transformed into each other in definite sequence under certain circumstances [6–8]. Phase transformation was mainly determined by water content, temperature and polarity of additives. With increase in water content, system forms most complex cubic phase via reverse micellar and lamellar phase [9–11]. Cubic phase is most favored for sustained delivery system as it is highly viscous, robust and insensitive to salts and solvents. It is highly stable phase being in equilibrium with excess of water. It is lipid and water continuous phase, where the lipid forms curved, non-intersecting bilayers containing hydrophobic and hydrophilic domains. These bilayers are organized in such a way that two unconnected continuous systems of water channel are formed. Such a 'honeycombed' structure can simultaneously accommodate hydrophilic, lipophilic

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and amphiphilic molecules [12,13]. Incorporation of additives with different polarities may lead to phase transformation due to change in packing parameter resulting from interaction of the additives with curved bicontinuous lipid bilayer. Packing parameter can be used to describe local constraint upon the curvature of the interface that can attribute to the geometric features of the lipid and is given by the following equation [14].

$$v = al \quad (1)$$

where 'v' is the hydrophobic chain volume, 'a' is the group area and 'l' is the chain length.

The phase transformation of GMO can be predicted by the packing parameter as it connects molecular shapes and properties to the favored curvature of the polar–non-polar interface and therefore topology and shape of aggregates [15].

To optimize drug release pattern from GMO based formulation, it is suggested to evaluate the effect of polarity of formulation additives on phase transformation of GMO. Chang and Bodmeier [16] investigated the effect of varying amounts of oleic acid on the release from GMO matrices. It was observed that cubic phase was transformed to reverse hexagonal phase with solubilization of oleic acid in lipophilic domain of matrix system. This inherently increased hydrocarbon chain space and altered molecular packing, presenting different release pattern. Recently, Shah and Paradkar [17] prepared *in situ* cubic phase transforming system of GMO by utilizing hydrophobic nature of magnesium trisilicate and Gelucire® 43/01. Increased drug release was observed due to transformation of cubic phase into hexagonal phase with these hydrophobic additives. Very few researchers have focused on the degree of freedom in cubic phase system with respect to phase transformation, rheological and mechanical properties and their impact on the drug release pattern.

A model study was carried out here to explore the effect of polarities of formulation additives on phase transformation of GMO. This study signifies the importance of additives' polarity for effective and optimum formulation development of the GMO based formulations. Therefore, in the present study, the effect of HLB of additives on phase transformation of GMO, crushing strength, rheological behavior, contact angle, swelling, bioadhesion and drug release of such formulations was studied. As drug properties can affect the formation of mesophases and release from the GMO matrices, the amphiphilic drug melatonin was selected as model drug.

2. Materials and methods

2.1. Materials

Glyceryl monooleate (Rylo™ MG Pharma19) was obtained as a gift sample from Danisco Cultor (Copenhagen, Denmark). Glyceryl mono-stearate and PEG monostearate were gift samples from Nikko Chemical Co. Ltd. (Seoul, Korea) (see Table 1). Melatonin was a gift sample from Aristo Pharma (Bhopal, India). All other chemicals used were of analytical grade.

2.2. Methods

2.2.1. Preparation of matrices

Plain GMO matrices were prepared by melting GMO (300 mg) at 55 °C on a water bath followed by addition of melatonin (5 mg) to it under continuous stirring. This molten mixture was then poured in fabricated stainless steel cylindrical moulds (inner diameter of 8.5 mm, height of 10 mm) and allowed to solidify at −15 °C for 10 min. These matrices were trimmed in order to obtain the uniform cylinders. Matrices with the additives were prepared in a similar manner as described above with an additional step of individual addition of the additives of different HLB (1.5, 3, 4, 5, 7, 10 and 11) (50 mg each) to molten mixture of GMO and melatonin. The matrices thus prepared were kept in desiccator at room temperature over silica gel for 12–24 h before being subjected to further evaluation.

2.2.2. Polarizing light microscopy

The matrices were placed in a dissolution test apparatus (USP 24 type II) (Electrolab TDT-08L, Mumbai, India) containing 0.1 N HCl (900 ml) maintained at 37 ± 0.5 °C and allowed to hydrate under stirring at 100 rpm. The hydrated samples were examined under polarizing light microscope (Nikon, Kanagawa, Japan) using λ 1/4 compensator in order to study the texture of structure indicative anisotropic phases. The phase boundaries were examined at a magnification of 200×. Photomicrographs of these samples were taken at room temperature after hydration of 1 and 8 h.

2.2.3. Diametrical crushing strength

Diametrical crushing strength of the matrix was determined using diametrical crushing tester (Incorp., Hyderabad, India). The force required for diametrical deformation of the matrices was determined. This study was performed in six replicates.

2.2.4. Rheological behavior

The rheological examination was carried out using Brookfield LV-DV III programmable rheometer equipped with spindle CP40 (Brookfield Engineering Laboratories, Inc. Middleboro). A cone and plate sensor having a diameter of 2.4 cm and the cone angle of 0.8° was used. The thickness of sample in the middle of sensor was 0.0127 mm. The matrices were hydrated for 1 h in 0.1 N HCl (900 ml) contained in dissolution vessel (USP 24 type II; Electrolab TDT-08L, Mumbai, India) maintained at 37 ± 0.5 °C under stirring at 100 rpm. The hydrated sample was loaded on rheometer plate at temperature 25 ± 0.3 °C and the initial linear viscoelastic region of the samples was determined and 100 rpm was chosen as a suitable shear rate (corresponding calculated shear rate was 13,333 s^{-1}) for all

Table 1
Different additives used to study the effect on performance and the drug release from the glyceryl mono-oleate matrices (as given in product catalogue)

Sr. No.	Additive	HLB	Melting point (°C)	Comment
1.	MGS-F 75	1.5	64.0	Glyceryl mono-stearate; lipophilic emulsifier containing 75% mono-glycerides
2.	MGS-C	3.0	61.3	Glyceryl mono-stearate; lipophilic emulsifier containing non-ionic surfactant
3.	MGS-A	4.0	57.5	Glyceryl mono-stearate; lipophilic emulsifier
4.	MGS BSE-C	5.0	55.5	Glyceryl mono-stearate; lipophilic emulsifier containing soap
5.	MGS-F 20	7.0	60.0	Glyceryl mono-stearate; emulsifier containing 20% mono-glycerides
6.	MGS-150	10.0	58.3	Glyceryl mono-stearate; emulsifier containing acid stable mono-glycerides
7.	MYS-10	11.0	–	PEG mono-stearate; hydrophilic emulsifier

systems investigated. The data obtained were further analyzed by regression analysis. As the melting point of GMO (36 °C) is very low, rheological measurement at comparatively high temperature may lead to softening of matrices under such high stress applied during rheological measurements. Hence rheological measurements were carried out at 25 ± 0.3 °C, as a precautionary step.

2.2.5. Measurement of water droplet contact angle

The contact angle was determined by method reported by Peh et al. [18] using a stereomicroscope (Carl Zeiss, Oberkochen, Germany) equipped with digital camera (Watec, WAT-202, Japan). The microscope was tilted at 90 °C and the matrix was placed before the objective lens. Sample of distilled water (30 μl) was pipetted and placed on the surface of the matrix. The whole assembly was further covered with a glass container to prevent water evaporation. After a lapse of 10 s the water droplet was photographed. The contact angle between the water droplet and the matrix was measured from the photograph taken. Measurements were performed in six replicates.

2.2.6. Swelling studies

Swelling studies were carried out by equilibrium weight gain method [3]. The studies were carried out using USP 24 type I dissolution test apparatus (Electrolab, TDT-06P, Mumbai, India). The GMO matrices containing different additives were accurately weighed and placed in a dissolution basket. The baskets were immersed in the dissolution vessel containing 900 ml of 0.1 N HCl maintained at 37 ± 0.5 °C and rotated at 100 rpm. At regular time intervals, the basket-matrix systems were removed from the dissolution vessel, blotted with tissue paper to take out excess water and reweighed. Increase in the weight was reported and percent swelling was calculated.

2.2.7. Measurement of bioadhesion

Bioadhesion was determined by tensiometric method [2]. Sheep intestinal tissue was freshly excised and stored in Tyrode solution at 4 °C. Stored sheep intestinal tissue was cut into pieces (3–4 cm) and washed with cold Tyrode solution and blotted with tissue paper to remove the surface associated water. Sheep intestinal tissue was mounted in the bioadhesion cell and the bioadhesion was determined using Advanced Force Gauge (Mecmesin, West Sussex, England) in which the hydrated (1 h in 900 ml of 0.1 N HCl maintained at 37 ± 0.5 °C, and rotated at 100 rpm.) matrix was stacked to the lower side of the moving instrument probe. Probe was then lowered onto the tissue at a test speed of 0.1 mm s^{-1} so as to bring the tissue and sample in contact. The experiments were performed at room temperature. The contact force was 0.2 N and contact time was 5 min. After 5 min, the probe was withdrawn at a rate of 0.1 mm s^{-1}. The peak detachment force was considered as a bioadhesive force. The force per cm^2 required to separate the matrices from biological substrate was recorded using software Dataplot (Mecmesin, West Sussex, England). Fresh sample and mucosa were used for each bioadhesive testing.

2.2.8. Release studies of matrices

Drug release from the matrices was studied by using USP 24 type II dissolution test apparatus (Electrolab TDT-08L, Mumbai, India). The dissolution test for each batch was performed in triplicate. Dissolution medium was 900 ml of 0.1 N HCl maintained at temperature 37 ± 0.5 °C and stirred constantly at 100 rpm. Aliquots (5 ml) were withdrawn at predetermined time intervals and replenished with fresh dissolution medium maintained at 37 ± 0.5 °C. The aliquots were assayed spectrophotometrically (Jasco V500, Tokyo, Japan) at 221 nm.

3. Results and discussion

3.1. Polarizing light microscopy

The liquid crystalline structures under polarizing light of the matrices with additives of different HLB are presented in Table 2. Plain matrices hydrated for 1 h showed existence of lamellar as well as cubic phase, but percentage of lamellar phase in the hydrated layer was high due to incomplete hydration of GMO. After 12 h, plain matrices showed the presence of hexagonal phase (Fig. 1a). This may be due to presence of melatonin in the matrix, which was relatively lipophilic and transformed cubic phase into hexagonal phase. The matrices incorporated with additive of HLB 1.5, 3, 4 and 5 revealed presence of the cubic phase after hydration of 1 h (Fig. 1b). The hydrophobicity of the added additives had transformed the lamellar phase into cubic phase at higher rate by increasing availability of water to mesophases. After 12 h these matrices showed the hexagonal phase. This indicates that the incorporated

Table 2
Microscopic characteristics of liquid crystalline systems of GMO matrices as a function of HLB of additives

HLB of additive	1 h		12 h	
	Structure under polarizing light microscopy	Liquid crystalline phases	Structure under polarizing light microscopy	Liquid crystalline phases
Plain matrix	Birefringent mosaic structure and isotropic dark background	Lamellar phase/cubic phase	Birefringent geometric and striated texture	Hexagonal phase
1.5	Isotropic dark background	Cubic phase	Birefringent geometric and striated texture	Hexagonal phase
3	Isotropic dark background	Cubic phase	Birefringent geometric and striated texture	Hexagonal
4	Isotropic dark background	Cubic phase	Birefringent geometric and striated texture	Hexagonal phase
5	Isotropic dark background	Cubic phase	Birefringent geometric and striated texture	Hexagonal phase
7	Mosaic structure and isotropic dark background	Lamellar phase/cubic phase	Birefringent mosaic structure	Lamellar phase
10	Mosaic structure and isotropic dark background	Lamellar phase/cubic phase	Birefringent mosaic structure	Lamellar phase
11	Birefringent mosaic structure	Lamellar phase	Birefringent mosaic structure	Lamellar phase

hydrophobic additive was dissolved in lipophilic domain of GMO and increased the apparent hydrophobic chain volume of the lipid. Therefore, it might affect topology and shape of the aggregate by increasing the monoglyceride packing parameter and transformed mesophase from the cubic phase into hexagonal phase [19,16,17]. The matrices with high HLB (7 and 10) presented higher extent of lamellar phase and lower extent of cubic phase after 1 h of hydration (Fig. 1c). Interestingly after 12 h of hydration, these matrices exhibited complete transformation into the lamellar phase (Fig. 1d). The matrices with additives of HLB 11 shown presence of lamellar phase throughout the study. Decrease in availability of water to mesophases may be responsible for such transformation with these hydrophilic additives.

3.2. Diametrical crushing strength

The diametrical crushing strength of GMO matrices with the additives of different HLB is shown in Fig. 2. All matrices subjected to diametrical crushing strength had shown deformation rather than physical breaking. The diametrical crushing strength value of the matrices was governed by nature of additive in the matrices. It was observed that as the HLB of the additive in the matrices increased, the diametrical crushing strength decreased. However, the diametrical crushing strength of the matrices having additive of HLB 11 was comparable with that of plain matrices. No change in diametrical crushing strength was observed for PEG stearate as that of glyceryl monostearate matrices. It may be attributed to comparatively high glyceride content in glyceryl monostearate.

There was some correlation between chemical structure and change in diametrical crushing strength, although clearly the mechanisms involved are complex.

3.3. Rheological behavior

From the literature, it was focused that viscosity of GMO matrices has strong influence on drug release pattern. Therefore the effect of HLB of the additives on the viscosity of GMO matrices was studied and is shown in Fig. 3. Viscosity was found to be the function of HLB of the additives in matrices as shown in the following equation derived by regression analysis

$$\text{Viscosity} = 2.04 - 0.095\ (\text{HLB of the additives in matrices})\ (p = 0.015) \quad (2)$$

Above equation is fit and valid for applied shear of 100 rpm during rheological measurements. (Corresponding shear rate 13,333 s^{-1}.)

It was noted that as the HLB of additive in the matrices increased, viscosity was found to be decreased ($r^2 = 0.72$). The additive of HLB 1.5 has the highest viscosity owing to quick transformation of low viscosity lamellar phase

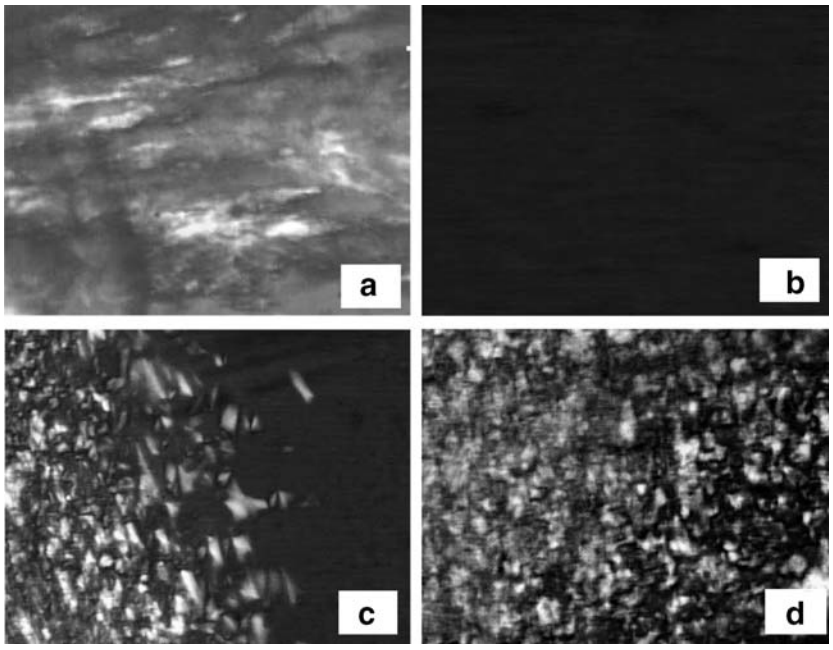

Fig. 1. Polarizing light microphotographs of GMO matrices showing different phases of liquid crystalline system: (a) hexagonal phase; (b) cubic phase; (c) lamellar phase and cubic phase; (d) lamellar phase.

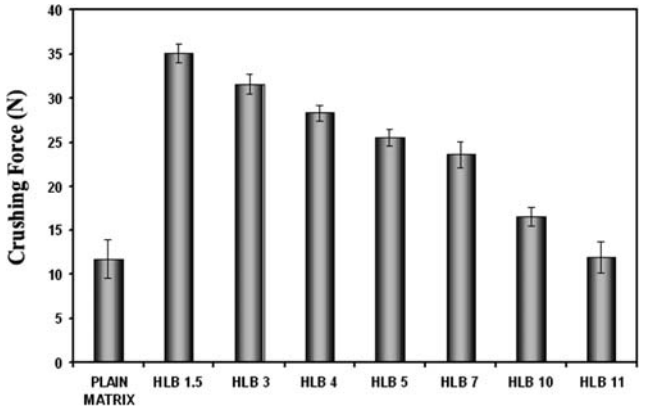

Fig. 2. Effect of HLB of additives on the diametrical crushing strength of GMO matrices. Mean ± SD, $N = 6$.

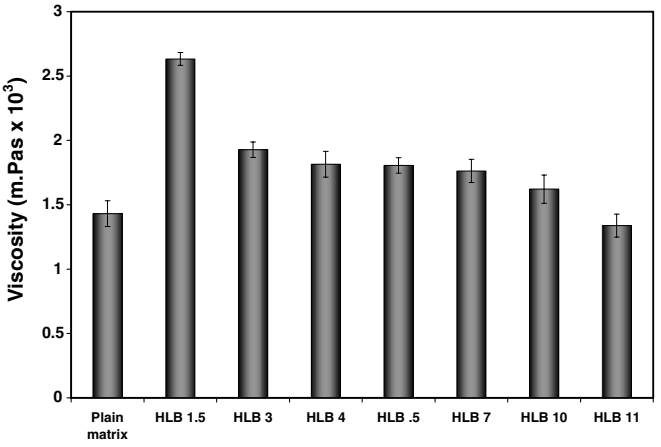

Fig. 3. Effect of HLB of additives on viscosity of GMO matrices at 100 rpm (shear rate 13,333 s^{-1}). Mean ± SD, $N = 6$.

into highly viscous cubic phase. The matrices with the additive of HLB 11 had lower viscosity than the plain matrices. This effect may be due to hydrophilic nature of additive, which contributed to formation of porous and less viscous lamellar phase by decreasing availability of water to mesophases.

3.4. Measurement of contact angle

The hydrophobicity or hydrophilicity of a surface is usually expressed in terms of wettability that can be quantified by contact angle. It was observed in Fig. 4 that contact angle had inverse relationship with HLB of additives. As the HLB of the additive increased, the contact angle of water droplet was found to decrease. The contact angle of water droplet of matrices with the additives of HLB 1.5, 3 and 4 was greater while that of HLB 7, 10 and 11 was lower than the plain matrices. The contact angle of the matrices with the additive of HLB 5 was similar to that of the plain matrices.

The contact angle between water droplet and surface of matrices with the additive of HLB 1.5, 3 and 4 was higher due to the incomplete wetting of the surface. Furthermore these additives decreased wetting of matrices owing to high surface free energy and high surface tension. The high HLB additives (7, 10 and 11) had less surface free energy than free energy at interface of matrices and water droplet; consequently it reduced the surface tension and provided the spreading of water droplet and therefore decreasing the contact angle.

GMO systems strongly respond to changes in their microenvironment. Small changes in lipid composition

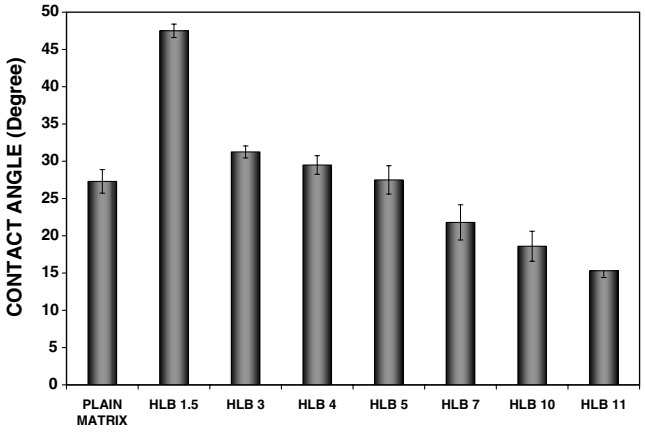

Fig. 4. Contact angle of water droplet as a function of HLB of additives. Mean ± SD, $N = 6$.

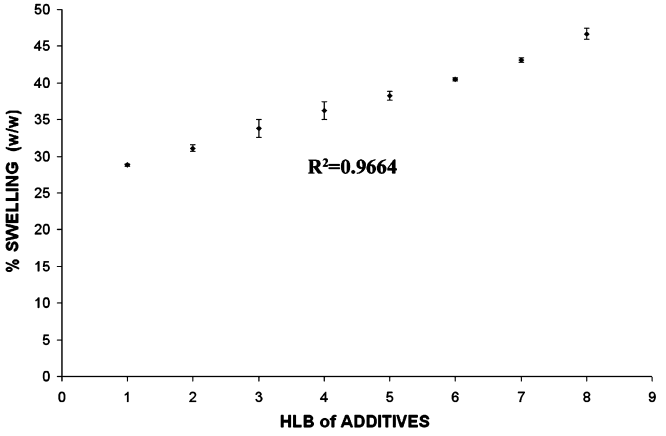

Fig. 6. Effect of HLB of additives on the swelling of GMO matrices at 720 min.

had affected the arrangement of fluid and solid domains [20]. Therefore as HLB of additives was increased, the physicochemical state of solid–liquid interface was transformed from hydrophobic to hydrophilic, consequently the contact angle decreased with increased spreading.

3.5. Swelling studies

Swelling of matrices is an important parameter to influence drug release pattern. Percent swelling of matrices with additives of different HLB is presented in Fig. 5.

Percent swelling increased linearly with increase in HLB (Fig. 6). In case of matrices with low HLB additives, swelling was higher in initial stage due to partial hydration of lamellar phase. But with time, swelling was significantly decreased owing to complete transformation into the cubic phase. Cubic phase was induced by hydrophobicity of additives and is in equilibrium with excess of water, hence showing very low swelling tendency. The photograph of hydrated matrices after 1 and 6 h in the dissolution is shown in Fig. 7. A straightforward consequence of the gradient in swelling is that the total thickness of the system varies with changes in boundary condition. The swelling

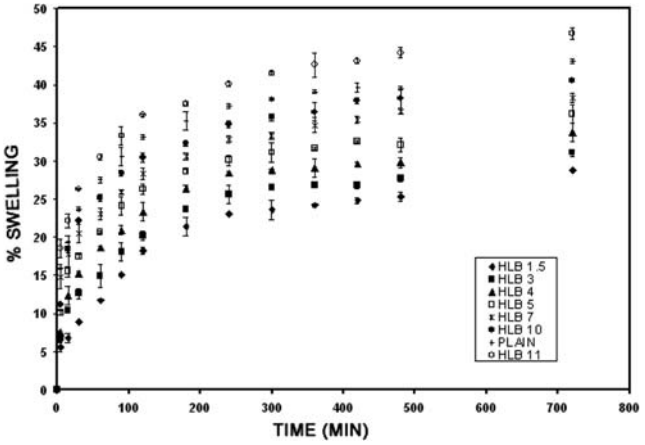

Fig. 5. Effect of HLB of additives on swelling of GMO matrices. $N = 3$.

was most pronounced for high HLB additives, whereas for lower HLB additive matrices, swelling was almost similar.

From phase behavior studies, it was observed that cubic phase was favored with lipophilic additives whereas lamellar phase was dominating with hydrophilic additives (Table 2). Therefore it can be correlated with swelling rate, which increased with increase in HLB of additives owing to transformation into less viscous lamellar phase.

3.6. Measurement of bioadhesion

Engstrom et al. [21] focused on GMO based bioadhesive-controlled release delivery system especially for rectal and vaginal route. Hence, additives must be selected cautiously with preference to those which have ability to enhance the bioadhesive strength of GMO. The influence additive of various HLB on the bioadhesion of GMO matrices is shown in Fig. 8. The matrices with additive of HLB 10 showed the greatest bioadhesion followed by the matrices with additive of HLB 7 and the plain GMO matrix. However, the matrices with additive of HLB 1.5, 3, 4, 5 and 11 showed less adhesion to intestinal mucosa. Lamellar phase was dominant in case of plain matrices and matrices with additives of HLB 7, 10 whereas cubic phase was dominant with low HLB (1.5, 3, 4 and 5) matrices (Table 2). Thus the matrices in the lamellar phases showed greater bioadhesion as compared to matrices that formed the cubic phase. These results were in affirmation with early reports by Engstrom et al. [21] and Nielsen et al. [2] where they observed that the lamellar phase of GMO had greater bioadhesion as compared to the cubic phase. Nielsen et al. [2] have explained mechanism of bioadhesion and according to that the liquid crystalline phases take up water from mucosa and induce bioadhesion. Therefore bioadhesion increases with increase in the ability of liquid crystalline phases to absorb water from mucosa and hence partially hydrated lamellar phase showed higher bioadhesion than fully hydrated cubic phase. Swelling

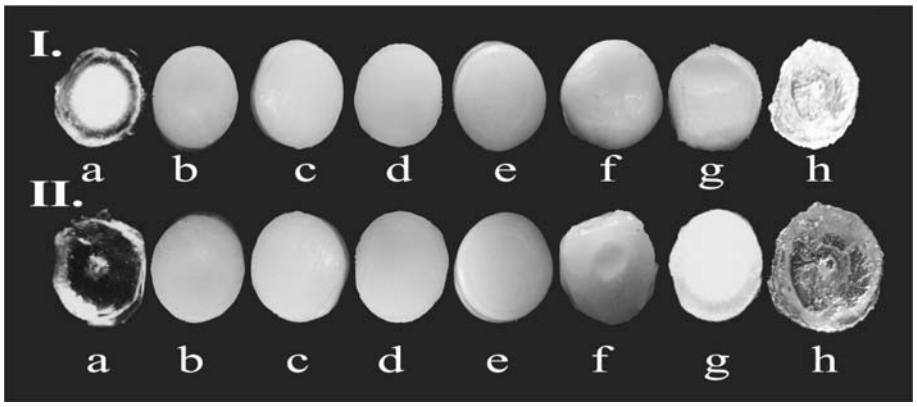

Fig. 7. Photograph showing GMO matrices after hydration (I) 1 h, (II) 6 h in 900 ml of 0.1 N HCl: (a) plain matrices; (b) HLB 1.5; (c) HLB 3; (d) HLB 4; (e) HLB 5; (f) HLB 7; (g) HLB10; (h) HLB11.

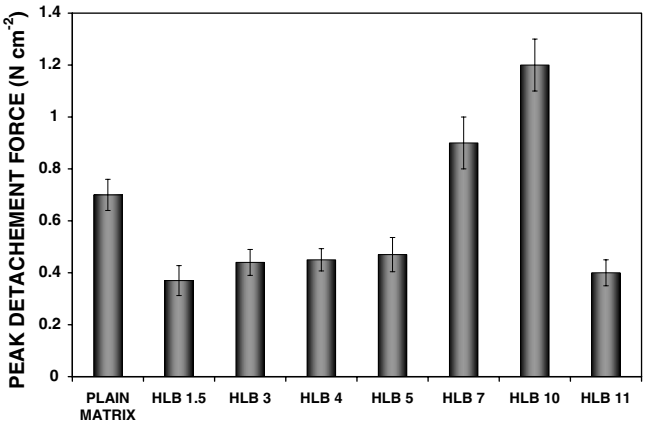

Fig. 8. Effect of HLB of additives on the bioadhesion of GMO matrices.

study showed that the plain matrix and the matrices with additive of HLB 7 and 10 have superior ability to take up water as compared to matrices with additive of HLB 1.5, 3, 4 and 5 and hence showed greater bioadhesion.

The plain matrices presented lower adhesion as compared to matrices with additive of HLB 7 and 10. This effect was due to partial transformation of the plain matrices into lamellar phase whereas the matrices with additive of HLB 7 and 10 had higher amount of lamellar phases. Furthermore the matrices with additive of HLB 7 and 10 have lower contact angle as compared to the plain matrices. This signifies that the matrices of additive of HLB 7 and 10 hydrate at faster rate as compared to the plain matrices and hence dehydrate mucosa at faster rate resulting in greater bioadhesion.

Bioadhesion of the matrix with the additive of HLB 11 was not satisfactory though it was in lamellar phase. As appeared from percent swelling and contact angle studies, this matrix takes up water at higher rate and resists further swelling after hydration. It forms less viscous porous mass, which does not have enough ability to take water from mucosa and therefore does not have significant high bioadhesion, which can be claimed due to lamellar phase.

3.7. Release studies of matrices

The quantity of drug released from matrix system is often analyzed as a function of the square root of time. This is typical for systems where drug release is governed by pure diffusion. However, the use of this relationship in swellable systems is not completely justified. Therefore, analysis of drug release from swellable matrices must be performed with a flexible model that has ability to identify the different contributory factors affecting overall drug release kinetics. An empirical equation Eq. (3), proposed by Ritger and Peppas [22], rapidly gained popularity for the analysis of release data in these systems. The equation is a power law in which the fraction of drug released is linearly related to the time raised to an exponent 'n'. The n exponent is used to characterize the drug transport mechanism. For example, $n = 0.43$ for Case I and $0.45 < n < 0.89$ for anomalous behavior or non-Fickian transport, whereas for $n = 1$, which suggest that drug is released predominantly by erosion mechanism. Therefore the data obtained from the dissolution profiles were fitted in Ritger and Peppas Eq. (3) [22].

$$M_t/M_\infty = kt^n \tag{3}$$

where 'k' is a constant incorporating structural and geometric characteristics of the drug dosage form; 'n' is the release exponent indicative of the drug release mechanism; M_t is the drug released at time t and M_∞ is the quantity of drug released at infinite time ('M_t/M_∞' is the fraction of drug released). The values obtained after subjecting dissolution profiles to Ritger and Peppas equation are shown in Table 3. The 'n' value of the low HLB additives (1.5, 3, 4, and 5) decreased from 0.93 to 0.90 and at higher HLB (7 and 10) the 'n' value further decreased from 0.81 to 0.60. This showed that as the HLB of additive in matrix increased the release was shifted from anomalous (non-Fickian) diffusion and/or partially erosion-controlled release to Fickian diffusion revealing the characteristics of Higuchi matrix in which the initial drug release is faster. For the matrices with HLB 11 additive, the value of exponent n

Table 3
Effect of HLB of additives on the drug release from the GMO matrices

HLB of additive	Drug released		
	n	*k*	*r*
Plain	0.37	0.347	0.9696
HLB 1.5	0.93	−0.950	0.7894
HLB 3	0.93	−0.957	0.8356
HLB 4	0.91	−0.809	0.8634
HLB 5	0.90	−0.756	0.8902
HLB 7	0.81	−0.358	0.9784
HLB 10	0.60	0.299	0.9795
HLB 11	0.30	0.475	0.9336

was below 0.45 and release mechanism followed was Fickian diffusion with a burst effect as seen in Fig. 9. These swellable matrix systems are activated by water and drug release is controlled by the interaction between water, lipid, drug and additive. The release profiles of GMO matrices with the additives of different HLB are shown in Fig. 9. The release profiles of matrices with additives of HLB 1.5, 3, 4 and 5 were characterized by initial lag. These matrices had larger contact angle and higher surface tension, therefore delayed wetting of matrices. Further the extent of swelling of these matrices was very slow owing to the hydrophobic nature of incorporated additive resulting in faster and higher formation of the cubic phase, as confirmed by polarizing microscopy (Table 2). Release of drug from these matrices in sustained manner was inherent to formation of the viscous cubic phase.

Melatonin is an amphiphilic drug, hence it gets located partly in lipid bilayer and partly in the aqueous channels. Therefore, the release is controlled by both, partition to aqueous channels and diffusion. Being large molecule its diffusivity through the water channel in the swollen matrix has also significantly affected drug release. These matrices did not show any erosion (Fig. 7).

In case of matrices incorporated with high HLB additives (HLB 7, 10 and 11), the drug release was faster. Time required for 50% drug release in case of matrices with additive of HLB 1.5 was higher than that for matrices containing additives of HLB 7, 10 and 11 (Fig. 10). These high HLB matrices had small contact angle (Fig. 4) and greater spreadabiliy of water droplet and therefore provided faster wetting of matrix surface. Furthermore, these matrices had higher swelling and their hydrophilic nature decreased the availability of water to the mesophases and therefore transforms the cubic phase into less viscous lamellar phase resulting in faster release of drug. Polarizing light microscopy (Table 2) supported the formation of the lamellar phases in these matrices. In case of HLB 7 and 10 additives, the release was slower than plain matrix due to increase in viscosity of phases thereby providing resistance to movement of drug molecule. The additive with HLB 7 and 10 followed anomalous transport kinetics whereas the plain matrices and matrices with additive of HLB 11 followed Higuchi model. The matrices of HLB 7 and 10 showed very little erosion. The plain matrices had not shown erosion and formed the transparent matrix while the matrices with additive of HLB 11 formed low-density porous matrix with formation of low viscosity lamellar phase providing faster drug release (Fig. 7).

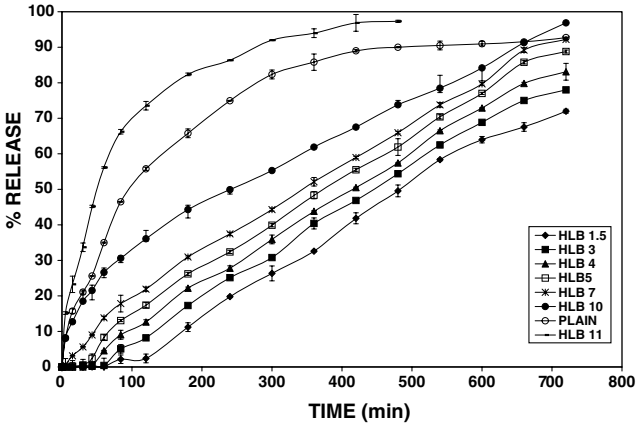

Fig. 9. Effect of HLB of additives on the release of melatonin from GMO matrices.

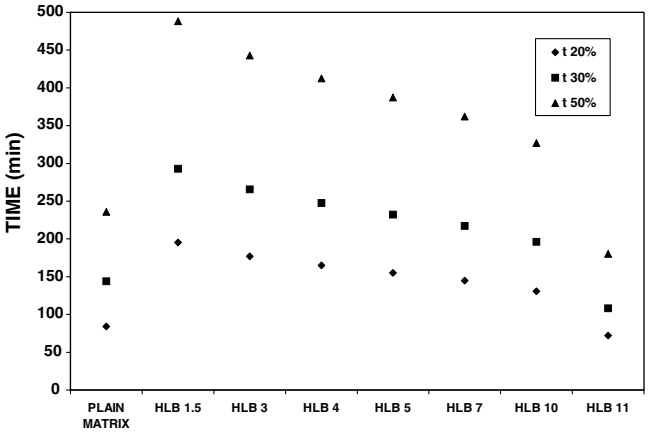

Fig. 10. Effect of HLB of additives on the release of melatonin from GMO matrices showing $t_{20\%}$, $t_{30\%}$, $t_{50\%}$.

Although diffusion was principal mechanism for drug release, the incorporation of additives of different HLB had also caused a gradient in swelling and phase transformation, which significantly affected molecular microenvironment and thus the local diffusional properties and drug release.

4. Conclusion

Phase behavior of GMO mainly depends on its degree of hydration as well as polarity of the additives, which ultimately affects the drug release pattern of the incorporated drug molecules. Our study demonstrates that efficiency of GMO based-controlled release formulations can be enhanced with addition of low HLB additives, which upon hydration promote higher and faster transformation into the viscous cubic phase. However, high HLB additives that promote lamellar phase formation of GMO are

appropriate for bioadhesive formulations. Rheological studies also substantiate these findings. Selection of the additives for optimal performance of the GMO based drug delivery system is critical in formulation development due to differential HLB values of the additives. We provide trends for selection of the additives based on their HLB.

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