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Study of In-Vitro Release Characteristics of Carbamazepine Extended Release Semisolid Matrix Filled Capsules Based on Gelucires

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ABSTRACT

Various extended release carbamazepine (CBZ) formulations have been developed previously, in order to reduce the frequency of dosing in chronic therapy and to decrease the variability in drug plasma concentration. In the present study, the suitability of different grades of Gelucires (G, glyceride based excipients) to formulate CBZ extended release capsules by the application of semisolid matrix (SSM) filling capsule technology was investigated. The possible modification of CBZ release kinetics by using Gelucire blends or inclusion of hydrophilic additives in the SSM was studied. The effect of ageing on some selected formulations was also evaluated, using scanning electron microscopy and differential thermal analysis. Twenty-one capsule formulations were prepared and assessed for their release characteristics. The mechanism of drug release from the test formulations was studied. The following results were obtained: a) Release data could not be correlated to the melting point (mp) of Gelucires used, pointing to relative lipophilicity of the base as a more important determinant of drug release. Among Gelucire grades having melting points higher than 37°C, the release rate proved to be highly dependent on the HLB value and matrix composition. b) CBZ release occurred by different mechanisms, including matrix disintegration, diffusion and or erosion depending on the vehicle employed. c) Zero order release profiles of CBZ were obtained from SSM-based on G50/13, G53/10 and their blends in ratios higher than 1:1 and G53/10 containing croscarmellose sodium. d) The ageing study revealed that these latter formulations, except those based on G50/13, also showed high dissolution stability during one year of shelf ageing. e) PVP, as a polymorphic transformation inhibitor, can be used to reduce the storage-induced changes of some grades of Gelucires. From the above data, it can be

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concluded that different grades of Gelucires and their blends as well as hydrophilic additives could be successfully used to formulate CBZ extended release SSM filled capsules with various release kinetics.

Key Words: Carbamazepine; Semisolid matrix; Formulations; Gelucires; Hydrophilic additives; Release kinetics; Ageing.

INTRODUCTION

Carbamazepine (CBZ) is considered as the drug of choice for the control of most forms of epilepsy, trigeminal neuralgia and excited psychosis. CBZ shows a relatively short half-life, in chronic treatment, due to autoinduction of the drug metabolism.[1] Frequently, its half-life may be further shortened by coadministration of other enzyme inducer drugs. Moreover, CBZ has a narrow therapeutic range and shows bioavailability differences.[2] In an effort to reduce the frequency of dosing required for chronic CBZ therapy and to decrease variability in plasma concentration, various extended release formulations have been developed by many authors. Modified release CBZ granules, prepared by loading cross-linked sodium carboxymethylcellulose with the drug were compressed into tablets using hydroxypropyl-methylcellulose.[1,3] In another study, extended release CBZ capsules containing immediate, extended and enteric release beads have been designed.[4] Further, an osmotic-release delivery system (Oros) has been utilized to control the release of CBZ.[5] Most of the above techniques are complicated and require several steps. By contrast, filling hard gelatin capsules with semi-solid matrices (SSM) is a simple technique that has been used to extend the release of many drugs and obviates the need for additional excipients, granulation and/or compression steps. For instance, prolonged release phenylpropanolamine SSM capsules were formulated by suspending the drug in oily vehicles to which thixotropic characters was imparted by addition of silicon dioxide.[6] The release of oxprenolol hydrochloride was also retarded by incorporation into thixotropic formulation prepared with liquid parafin and cutina HR.[7] On the other hand, monolithic systems such as lipid systems were easily prepared and directly filled in the molten state into hard gelatin capsules.[8]

Glycerides are naturally occuring substances that have been used for a number of years as suppository bases. More recently, glyceride based materials, particularly Gelucires,[9–12] have been used as extended release matrices for encapsulation. Gelucires (G) are a group of essentially inert excipients derived from natural hydrogenated food grade fats and oils. Chemically, Gelucires may contain pure glycerides (mono-, di-and tri-glycerides of saturated fatty acids), mixtures of glycerides and fatty acid esters of polyethylene glycols (mono-and di-fatty acid esters) in varying proportions or, in the case of G55/18, pure PEG esters with no glycerides present. The various grades of Gelucires are characterized by their hydrophile-lipophile-balance value and melting point which lead to a specific behaviour when placed in the gastrointestinal fluids in respect of hydrodispersibility, melting and floatability. As for the in-vitro sustained-release characteristics, the Gelucire grade and its proportion in the matrix can influence the mechanism of drug release from the controlled matrix formulations. For instance, a diffusion controlled system was obtained with G46/07, 48/09 or 62/05 containing lithium sulfate. On the contrary, erosion was proved to control indomethacin release when G33/01was added to G46/07.[13]

A number of studies have also demonstrated that Gelucire products may exhibit a change in drug release characteristics during storage. It has been reported that upon ageing, a decrease in the release rate of nifedipine,[14] the antiviral agent UC-781[15] and salbutamol[16] has occurred from sustained release formulations based on G53/10, G44/14 and G35/10 respectively. In contrast, Sutananta et al.[17] noted an increase in the release of theophylline anhydrous from dispersions in G50/13 and G55/18 after storage for up to 180 days. These changes have been attributed to either the conversion of triglycerides to more stable polymorphic forms or conversion from the amorphous to the crystalline state of the fat bases.[18]

Therefore, the aim of the present study was to investigate the suitability of different grades of Gelucires for the preparation of CBZ extended release capsules, by utilization of SSM filling capsule technology as a simple and relatively inexpensive technique. Further, the effect of using Gelucire blends as well as the inclusion of hydrophilic additives in the SSM on CBZ release kinetics was studied. The effect of shelf ageing on some selected formulations was also evaluated.

MATERIALS AND METHODS

Materials

The following materials were used as received: Anhydrous CBZ (Novartis Pharma, Egypt), Gelucire (G) grades 33/01, 39/01, 50/13, 53/10, and 44/14 (Gelucire is a saturated polyglycolyzed glyceride consisting of mono-, di-and triglycerides and of mono-and di-fatty acid esters of polyethylene glycol.-Gattefossé Etablissement, France), polyvinyl pyrrolidone MW 24000, K25 (BASF Ludwigshafen, Germany), croscarmellose sodium, methyl cellulose and Aerosil 200 (Courtesy of Pharco pharmaceuticals, Egypt), sodium lauryl sulphate (El-Nasr Pharmaceutical Chemical Co., Egypt). Tegretol® 200 CR tablets (Novartis Pharma, Egypt. BN: 116) were also used. Hard gelatin capsules, size 3 transparent, yellow cap-colourless body (shell contains quinoline as colourant and is preservative free) were kindly supplied by Arab-Caps. Pharmaceuticals, Egypt.

Formulation of Capsule Fills

Twenty-one CBZ extended release formulations were prepared using Gelucire bases, Gelucire blends, and hydrophilic additives (Table 1). Semi-solid matrices were prepared by heating the respective base to 10°C above its melting point. CBZ powder (p.s.0–125 μ) and the additive, if any, were dispersed in the molten base with constant stirring. The molten mixtures were then filled, with a syringe, into size 3 transparent hard gelatin capsules, to a weight of 200±2 mg equivalent to 100 mg CBZ and allowed to set at 25°C for 24 h.

Release Rate Studies

In-vitro release of CBZ from the prepared formulations and commercial tablets was determined according to the CBZ dissolution procedure reported by EL-Massik et al.[19] The dissolution medium consisted of 900 mL 0.5%w/v sodium lauryl sulphate solution containing 0.01%w/v methylcellulose kept at 37°C and stirred at 75 rpm using USP apparatus 2. Samples were withdrawn at 1-hour interval for 8 hours. They were filtered through 0.45-μm cellulose nitrate membrane filters and assayed spectrophotometrically at 286 nm. Presented results are the means of three determinations. Standard error bars are shown in the release profiles.

Table 1. Composition of SSM capsule formulations, each containing 100 mg CBZ.

Formulation ingredients (%)							
G33/01	G39/01	G50/13	G53/10	G44/14	PVP	Croscarmellose	Aerosil 200
100	–	–	–	–	–	–	–
–	100	–	–	–	–	–	–
–	–	100	–	–	–	–	–
–	–	–	100	–	–	–	–
–	–	–	–	100	–	–	–
–	–	80	–	20	–	–	–
–	–	70	–	30	–	–	–
–	–	60	–	40	–	–	–
–	–	80	20	–	–	–	–
–	–	50	50	–	–	–	–
–	–	20	80	–	–	–	–
–	–	–	80	20	–	–	–
–	–	–	60	40	–	–	–
98	–	–	–	–	–	–	2
90	–	–	–	–	10	–	–
80	–	–	–	–	20	–	–
–	–	–	90	–	10	–	–
–	–	–	80	–	20	–	–
–	–	–	99	–	–	1	–
–	–	–	96	–	–	4	–
–	–	–	90	–	–	10	–

Analysis of the Release Kinetics

The mechanism of drug release from the SSM capsule formulations under study was investigated using the following mathematical models:

a) Langer–Peppas model: $M_t/M_\infty = kt^n$ (1)
where M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant and n is the so-called diffusion exponent, indicative of the mechanism of the drug release. The equation generally holds for $M_t/M_\infty \leq 70\%$ of drug release. n=0.45 or $0.45<n<0.89$ or $n>0.89$, indicates Fickian diffusion or anomalous transport or Case ''II'' transport kinetics respectively.[20]

b) Peppas–Sahlin model:
$M_t/M_\infty = k_1t^m + k_2t^{2m}$ (2)
Where k_1 and k_2 are constants describing the diffusion and erosion-controlled release mechanisms respectively. k_2 includes the effect of polymer relaxation. If this process is the rate limiting step, the release of the drug from the matrix will be zero order and is called relaxation-controlled, swelling-controlled or Case ''II'' transport process.[21] Drug release data were fitted to equation 2 by using computer software (RELS-FIT program). This program is based on the least square curve fitting methodology.

c) Higuchi square root of time equation: $Q=k_3\ t^{1/2}$

d) Zero- order Kinetics: $Q=k_4\ t$

e) First- order Kinetics: $\text{Ln}\,(100-Q) = \text{Ln}\,100 - k_5\,t$

f) Hixson- Crowell Kinetics: $W_o^{1/3} - W^{1/3} = k_6\ t$
Where Q is the percent drug released at time t, W_o is the initial drug loading, W is the amount remaining in matrix at time t, k_3–k_6 are release rate constants.

Hixson Crowell relationship applies to matrices where dissolution takes place normal to matrix surface, and, if the matrix dimensions decrease in proportion to one another, the exact initial geometric shape of the matrix is maintained at all times. The model is applied to release data from disintegrating lipophilic matrices.[22]

Study of the Effect of Ageing on CBZ Release from Some Selected Formulations

Selected SSM capsule formulations were stored in closed glass containers over the shelf, at room temperature (25°C). After a storage period of one year, the release of CBZ from these formulations was tested using the above mentioned dissolution conditions. Scanning electron photomicrographs were used to illustrate the effect of ageing on the surface characteristics. The samples were coated with a 40-nm layer of pure gold, using a current sputter technique, before viewing under the scanning electron microscope (JEOL JSM-5300 Japan). Differential thermal analysis of the fresh and aged formulations was performed using DTA, DT-30 analyser, Shimadzu Corp., Japan. The instrument was calibrated with indium standard after adjustment of the base. The heating rate was 1°C/min. over a temperature range of 25–100°C. The chart speed was 2.5 mm/min.

RESULTS AND DISCUSSION

Study of CBZ Release Kinetics

An earlier study[19] showed that polymorphic transformation of CBZ from anhydrous to dihydrate form occurs during the dissolution of CBZ in water, simulated gastric or intestinal fluid and 1% sodium lauryl sulphate solution (USP dissolution medium). Such transformation results in dynamic changes in saturation solubility of the drug in the diffusion layer as well as changes in particle size due to crystal growth. These two effects cause a continuous change in the rate of drug dissolution through the dissolution run which might affect the validity of the dissolution system. Therefore the authors developed a new dissolution system for CBZ consisting of 0.01% w/v methylcellulose in 0.5%w/v sodium lauryl sulphate (SLS) solution. The system offers the following advantages: a) protection against CBZ polymorphic transformation by the use of methylcellulose, as inhibitor b) minimization of the wetting effect of surfactant due to reduction of SLS concentration to 0.5% w/v, as compared to USP dissolution medium composed of 1% w/v SLS solution and c) sink conditions for up to 400 mg CBZ with 4.6 folds of saturation volume, as the equilibrium solubility was that of the more soluble anhydrous form, rather than the less soluble dihydrate form.

Effect of Gelucire Bases

Lipophilic (G33/01 and G39/01), amphiphilic (G50/13 and G53/10) and water dispersible (G44/14) Gelucire bases were selected as sustained release matrices for CBZ, on the basis of high melting point and/or low HLB values. Figure 1 illustrates the release profiles of CBZ from SSM based on different grades of Gelucires, as compared to that of commercial tablets.

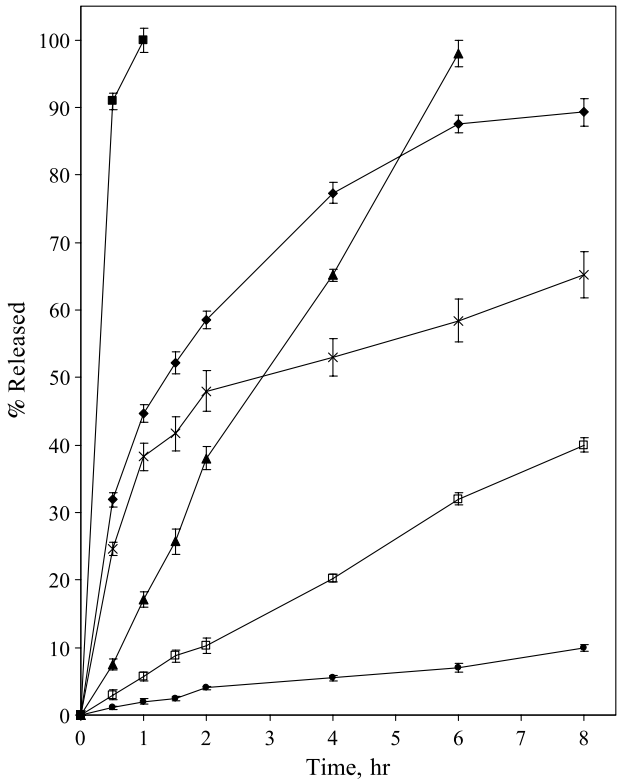

Figure 1. Release profiles of CBZ from different Gelucires: (■) G44/14, (▲) G50/13 (x) G33/01, (□) G53/10, (●) G39/01 and (◆) commercial tablets.

Gelucires exhibited various effects on CBZ release, $t_{50\%}$ was 15 min. for G44/14, 2.8 h in case of G50/13 and G33/01 and more than 8 h for G53/10 and G39/01 SSM, in comparison to 1.3 h for commercial tablets. This diversity in CBZ release profiles suggests the implication of matrix composition, HLB and melting point of the base in drug release. Obtained release data could not be correlated to the mp of Gelucires used, pointing to relative lipophilicity of the base as a more important determinant of drug release. Among Gelucire grades having melting points higher than 37°C the release rate proved to be highly dependent on the HLB value and matrix composition.

Lipophilic Gelucire Bases

G33/01 and G39/01 consist of pure glycerides. They are extremely hydrophobic and may be expected to release CBZ at a very slow rate. The amount of drug released by the end of 8 hr was 10% and 65% for G39/01 and G33/01 respectively (Fig. 1). For G39/01, the matrix remained unaltered and showed no signs of swelling or erosion throughout the dissolution run. Table 2 shows that release of CBZ from G39/01 was best fitted by Higuchi diffusion model ($r = 0.999$). It is likely that the dissolution of drug particles at the surface of the matrix allowed the establishment of channels, from which the drug was slowly released. On the other hand, the release profile of G33/01 formulation, having low mp, was biphasic with high release rate for the first 2 hours (Fig. 1). This may be due, in part, to surface release of the drug and the large available surface area provided by the high dispersibility of G33/01 base after melting. The slower drug release observed after 2 hours can be attributed to melting of Gelucires, probably resulting in collapse of the pores created by dissolution of the dispersed drug particles and reduction in matrix permeability.[23] In both phases, square root time dependence was shown, indicating a Higuchi diffusion-controlled release mechanism (Table 2). Such biphasic release profile from G33/01 was previously observed with both water-soluble and water insoluble drugs.[24]

Amphiphilic Gelucire Bases

G50/13 and G53/10 are made of the same glyceride and PEG ester components but in different

Table 2. Release mechanisms of CBZ from different SSM capsule formulations under study.

	$Q=K\,t^n$ (eq.1)			$Q=K_1\,t^{0.5}+K_2\,t$ (eq.2)			Higuchi	Zero order	1st order	Hixon Crowell
Matrix composition	r	K	n	K_1	K_2	K_1/K_2	r	r	r	r
G39/01	–	–	–	–	–	–	0.999	–	–	–
G33/01	–	–	–	–	–	–	0.940	–	–	–
G50/13	0.996	16.734	1.039	0.47	15.82	0.03	–	0.998	–	–
G53/10	0.998	5.690	0.936	–	5.11	–	–	0.998	–	–
G50/13–G53/10										
80 : 20	0.998	16.05	1.02	2.78	12.66	0.21		0.987		
50 :50	0.998	11.20	1.067	0.84	10.50	0.08		0.992		
20 : 80	0.994	7.345	0.999	0.37	8.22	0.05		0.990		
G53/10–G44/14										
60:40	–	–	–	–	–	–	–	–	0.983	–
80:20	–	–	–	–	–	–	–	–	0.988	–
G50/13–G44/14										
80:20	–	–	–	–	–	–	–	–	–	0.992
70:30	–	–	–	–	–	–	–	–	–	0.988
60:40	–	–	–	–	–	–	–	–	–	0.971
G53/10+10% PVP	0.987	6.153	0.913	–	8.536	–	–	–	–	–
G53/10+20% PVP	0.990	7.948	1.038	0.250	9.244	0.027	–	–	–	–
G53/10+10%croscar.	0.994	5.263	0.85	–	5.965	–	–	–	–	–
G33/01+10% PVP	0.982	27.630	0.364	33.184	–	–	–	–	–	–
G33/01+20% PVP	0.985	13.605	0.379	15.997	–	–	–	–	–	–
G33/01+2% Aerosil	0.998	9.51	0.825	3.19	7.02	0.454	–	–	–	–

proportions. Figure 1 shows that the amount of CBZ released from G53/10 was 40% by the end of 8 hr, while 100% drug release was observed at 6 hr in case of G50/13. In dissolution medium, G50/13 matrix swelled and exhibited surface erosion. No transparent gel layer could be seen, instead, the erosion occurred through the disintegration of the masses at the surface of the matrix. This is possibly due to inability of the matrix to accommodate water uptake. Similar matrix characteristics were observed during a release study of theophylline from G50/13.[25] On the other hand, G53/10 matrix hydrates and slowly erodes during dissolution. Matrix erosion was not as extensive as in case of G50/13. This could explain the relatively slow release of CBZ from G53/10 as compared to G50/13. Table 2 shows the parameters describing the mechanism of CBZ release from the latter formulations. The data indicate a super Case ''II'' swelling/relaxation (erosion) controlled release mechanism. As expected for such release mechanism, drug release from both G50/13 and G53/10 fitted Zero order kinetics.

Water Dispersible Gelucire Base

As expected, formulation with G44/14, water dispersible and soluble base resulted in rapid release of CBZ with 90% drug released within 30 min (Fig. 1). This grade would be used to modify the release from other grades of slower release rates.

Effect of Gelucire Blends

Possible modification of CBZ release kinetics by using Gelucire blends was investigated. Choice of Gelucire grades to be blended and blending ratios was based on a preliminary miscibility study.

G53/10-G50/13 Blends

Figure 2 and Table 2 show the release profiles and mechanism of drug release from G53/10-G50/13 blends respectively. In general, as the level of the more hydrophilic G50/13 increased, the overall release rate increased (Fig. 2). Table 2 shows that the corresponding values of n ranged from 0.999 to 1.02, indicating relaxation/erosion controlled release mechanism in all the tested blends. Analysis of release profiles by equation 2 showed that increasing the level of G50/13 increased the values of both k_1 and k_2, indicating enhancement of both release mechanisms. The relative importance of the two mechanisms is illustrated by k_1/k_2 ratio, which increased from 0.05 to

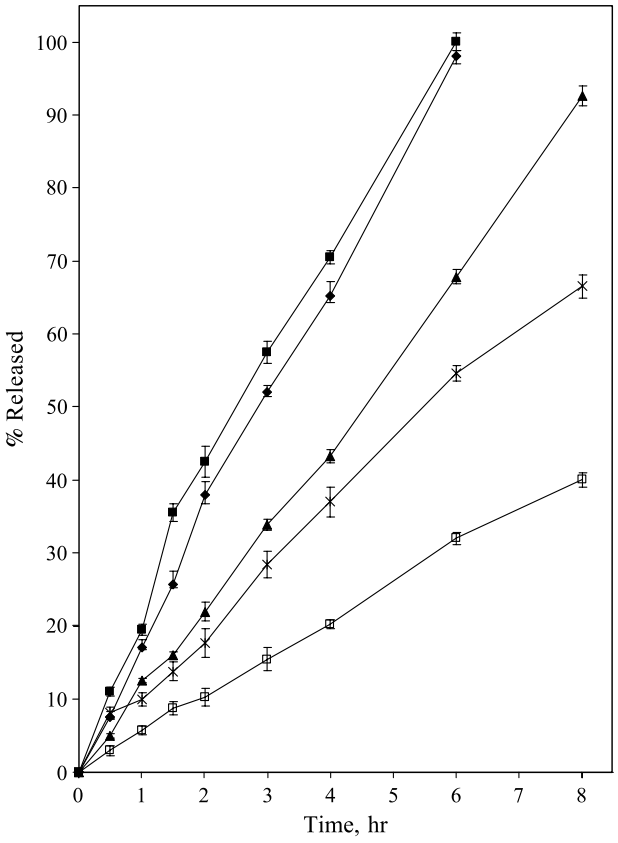

Figure 2. Release profiles of CBZ from G53/10–G50/13 blends containing: (□) 0%, (x) 20%, (▲) 50%, (■) 80% and (◆) 100% G50/13.

0.21 pointing to increased diffusion contribution with increasing percentage of G50/13. A deviation from zero order kinetics is expected in swellable matrix systems exhibiting diffusion release mechanism. This is due to increase in the diffusional pathlength leading to decreased diffusion rate with time. However, for G50/13 and G53/10 blends showing coupled diffusion/erosion, the increase in the diffusion path length is probably compensated by the erosion process leading to constant pathlength and constant diffusion rate.[26] Hence, apparent zero order kinetics were observed in all the tried blends (Table 2).

G53/10-G44/14 Blends

Figure 3 illustrates the release profiles of the CBZ/G blends and commercial tablets. Addition of G44/14 increased the rate and extent of drug release. G44/14 altered the slowly hydrating nature of G53/10 into a disintegrating matrix. Release pattern from a matrix containing 40% G44/14 nearly simulated that of the commercial product. Release from these blends was biphasic and followed first order kinetics (Table 2). The higher initial release rate may be attributed to leaching of the hydrophilic G44/14 with concomitant rapid drug release followed by a slower drug release from the remaining G53/10 flakes. Similar observation was reported for the release of propranolol hydrochloride from matrices made of G50/13- precirol blend.[10]

G50/13-G44/14 Blends

The initial drug release rate from G50/13 based formulation was relatively slow as compared to that of the commercial product ($t_{50\%}$ were 2.8 h and 1.3 h respectively). To increase the initial release from this matrix, it was blended with G44/14. Figure 4 shows that addition of 20% G44/14 slightly increased the initial release rate and reduced the $t_{50\%}$ to 2.5 h. Matrices containing 30% and 40% w/w G44/14 disintegrated rapidly and released 100% CBZ at 3 h and 2 h respectively. Release of CBZ from the different

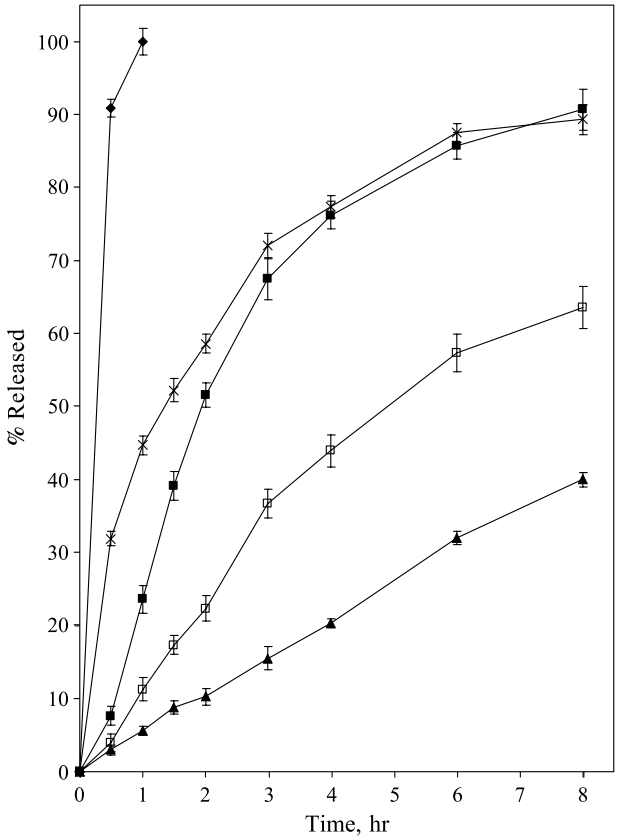

Figure 3. Release profiles of CBZ from G53/10–G44/14 blends containing: (▲) 0%, (□) 20%, (■) 40%, (◆) 100% G44/14 and from (x) commercial tablets.

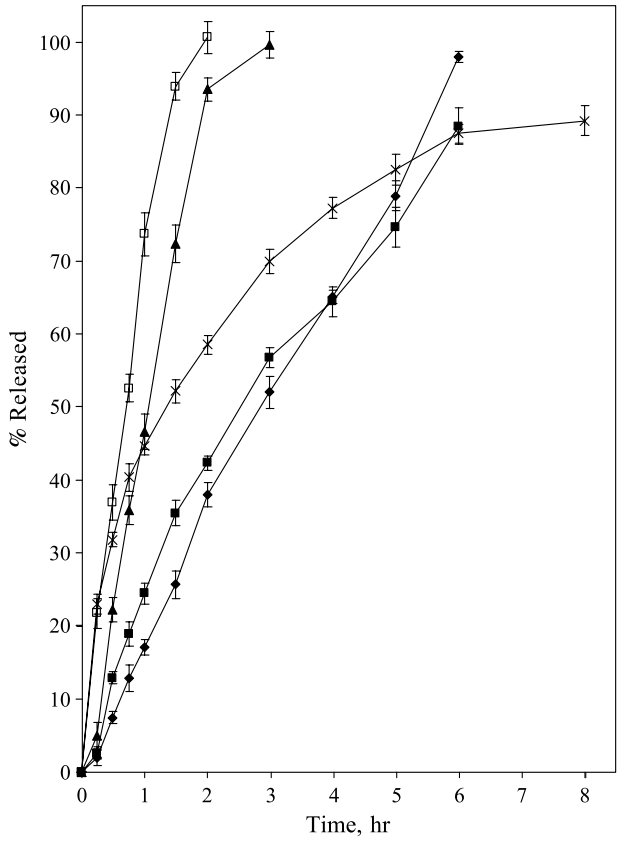

Figure 4. Release profiles of CBZ from G50/13–G44/14 blends containing: (◆) 0%, (■) 20%, (▲) 30%, (□) 40% G44/14 and from (x) commercial tablets.

G50/13–G44/14 blends followed Hixson-Crowell Kinetics (Table 2). Furthermore, a linear relationship between the percent G44/14 and Hixson-Crowell kinetic constant was found ($y=0.1047\times -1.7165$; $R^2=0.9978$). Hixson-Crowell model was previously applied to release data from disintegrating lipophilic matrices.[27,28]

Effect of Inclusion of Hydrophilic Additives

The possibility of drug release modification from Gelucire matrices by addition of some hydrophilic additives was studied. Two Gelucire grades were selected, G33/01, a matrix with biphasic release pattern similar to the commercial product but with slower rate, and G53/10, a matrix showing a relatively slow zero order release pattern.

Three groups of additives were tried: a) channeling agent eg. PVP. b) swelling and disintegrating additive eg. croscarmellose sodium and c) thixotropic gel forming agent eg. Aerosil 200. This latter was added to G33/01 to improve the matrix stability at temperatures higher than 30°C, since leakage of this matrix from capsules was observed at this temperature.

G33/01-Hydrophilic Additives

Figure 5 shows the release profiles of CBZ commercial tablets and G33/01 based formulations containing PVP or Aerosil 200. Unexpectedly, addition of 10% and 20% PVP resulted in dissolution retardation and loss of the dispersible nature of the matrix. This could be explained by the low water uptake capacity of this lipophilic base which led to the formation of PVP gel through the matrix. This resulted in a dramatic decrease in the available surface area and retardation of further penetration of the dissolution medium. Fitting to equations 1 and 2 shows that the drug release from this matrix is diffusion-controlled (Table 2). The release of CBZ from G33/01 was also retarded by inclusion of 2% Aerosil 200 in the matrix. This may be explained by the formation of a gel matrix

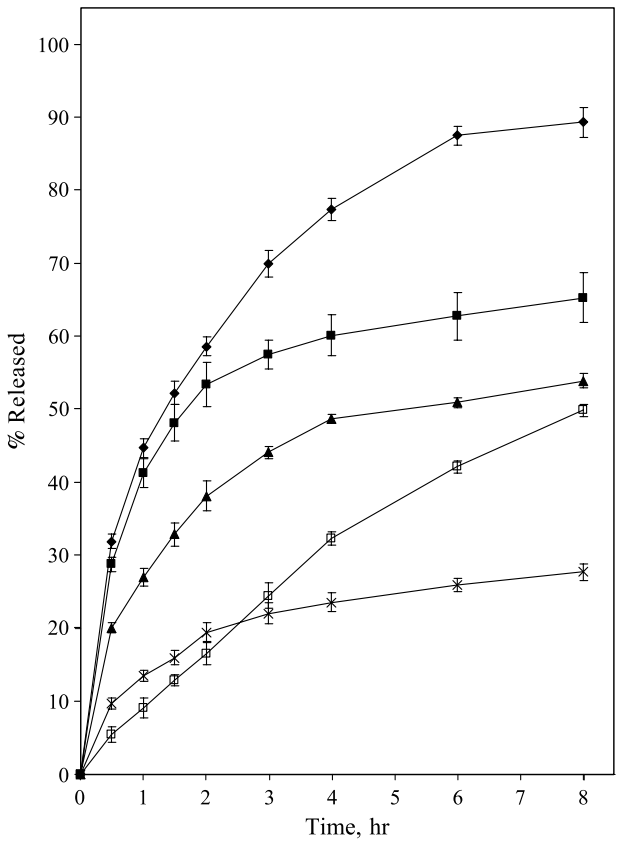

Figure 5. Release profiles of CBZ from G33/01 SSM capsules containing: (■) 0%, (▲) 10% and (x) 20% PVP, (□) 2% Aerosil and from (◆) commercial tablets.

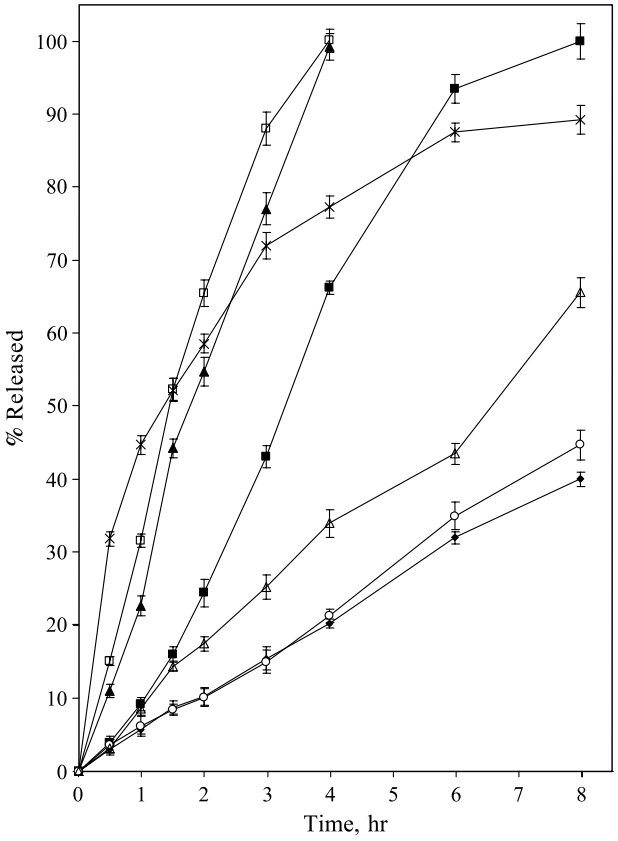

Figure 6. Release profiles of CBZ from G53/10 SSM capsules containing: (◆) 0%, (■) 1%, (▲) 4%, and (□) 10% croscarmellose sodium and (○) 10%, (△) 20% PVP and from (x) commercial tablets.

structure observed during the dissolution run. Similar dissolution retarding effect was observed upon addition of Aerosil to lipophilic suppository bases.[29]

G53/10-Hydrophilic Additives

Figure 6 shows the release profiles of CBZ from G53/10 matrices containing PVP. Addition of 10% PVP to G53/10 did not affect the release pattern or mechanism (Table 2). The release was still dominated by erosion of the matrix. Increasing the concentration to 20% relatively increased the drug release rate. The matrix appeared to have fissures as dissolution proceeds, suggesting a concomitant increase in the porosity of the matrix. Complete disintegration of the matrix observed after 6 hours, may explain the inflection in the release profile occurring at this time interval. In addition to erosion, diffusion contributed to the release of CBZ from the matrix containing 20% PVP. This is probably due to diffusion of the drug through pores and channels created by dissolved PVP. In contrast to G33/01, the effect of PVP as a channeling agent could be observed with G53/10 since the relatively high HLB allows imbibition of water into the matrix and consequent channel formation by dissolved PVP.

Figure 6 also shows that addition of croscarmellose (1–10%) to G53/10 markedly increased CBZ release rate. Croscarmellose is a superdisintegrant characterized by high particle swelling and disintegrating power. This allows further penetration of dissolution medium, resulting in a rapid disruption and erosion of the matrices. A matrix containing 1% croscarmellose exhibited controlled release of CBZ over

Table 3. Calculated values of dissolution efficiency at 8 h (D.E.8 h) and the time for 50% CBZ release ($t_{50\%}$) of fresh and aged CBZ SSM capsules.

	D.E.8 h (%)		t50% (h)	
Matrix composition	Fresh	Aged	Fresh	Aged
G50/13	62.44	87.87	2.85	0.86
G53/10	20.79	21.75	–	–
G50/13+G53/10				
80:20	66.01	80.03	2.43	1.26
50:50	45.03	47.98	4.43	3.93
20:80	33.95	36.12	5.66	5.4
G53/10+G44/14				
60:40	64.73	75.62	1.9	1.9
G53/10+1% Cros	57.80	57.48	3.13	3.13
G53/10+4% Cros	75.74	76.39	2.73	2.67
G33/01	54.69	20.24	2.96	–
G33/01+10% PVP	29.15	17.84	–	

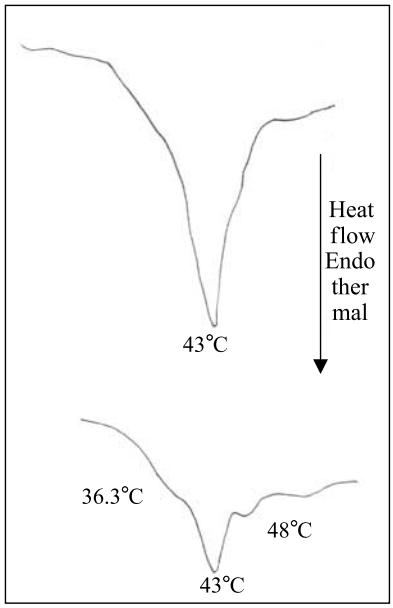

Figure 7. DTA thermograms of fresh (above) and aged (below) G50/13 based formulations.

8 hours, while increasing the concentration to 4% resulted in 100% drug release within 4 hours. Further increase to 10% slightly affected the release pattern. Zero order release was obtained from all matrices containing croscarmellose (Table 2).

EFFECT OF AGEING ON THE RELEASE OF SOME SELECTED CBZ EXTENDED RELEASE FORMULATIONS

A number of studies[14–17] have demonstrated that the drug release from Gelucire matrices may change with storage. Therefore, the effect of one-year shelf ageing on the release of CBZ from ten SSM capsule formulations was studied. Formulations based on G50/13, G53/10, and their blends, in addition to G53/10 containing croscarmellose sodium, were chosen for ageing study since they exhibited zero order release kinetics. G53/10-G44/14 (60: 40) based formulation was also chosen since it represents a matrix exhibiting first order release kinetics and showing release profile comparable to that of the commercial product. Finally, the effect of PVP as a polymorphic transformation inhibitor on the well known storage-induced changes of synthetic glyceride bases was evaluated by testing formulations based on G33/01 in absence and presence of 10% PVP. The efficiency of dissolution at 8 hours (DE.8 h) and $t_{50\%}$ were chosen as parameters to compare the dissolution profiles of both fresh and aged formulations. The results are given in Table 3.

Effect of Ageing on Formulations Based on G50/13 and/or G53/10

Table 3 shows the effect of ageing on the release characteristics of CBZ from G50/13 and G53/10 SSM based formulations. A remarkable increase in the drug release rate from G50/13 occurred upon storage (D.E.8 h were 62.44% and 87.87% for fresh and aged formulations respectively). During the dissolution run, the stored matrices showed a very rapid erosion and complete disintegration within 4 h, compared to 6 h with fresh formulations. This observation implies some weakening in tensile strength of the matrix[30] or possible fissure formation with time. DTA thermogram of freshly prepared CBZ/G50/13 matrix shows a main endothermic peak at 43°C, whereas that of aged sample shows a similar peak in addition to a shoulder at 36.3°C and a small broad endothermic peak at 48–52°C (Fig. 7). The greater number of peaks observed with aged matrix implies a solid state fractionation i.e. phase separation, involving different chemical entities within the matrix rearranging over time to form further microsegregated regions.[17] This view is supported by SEM of aged

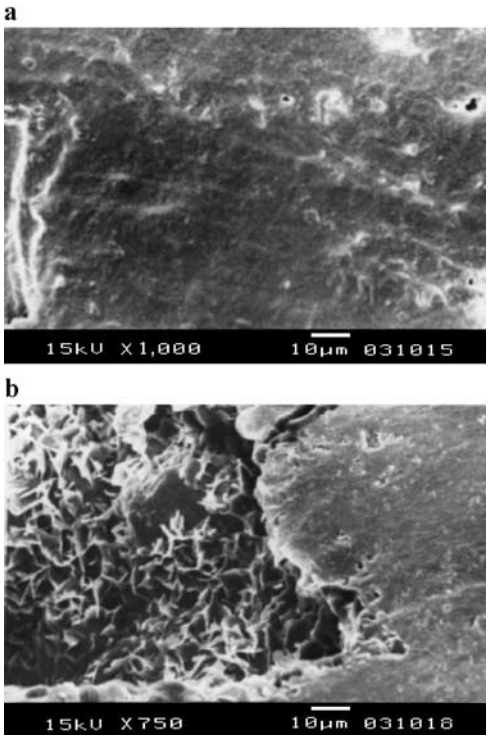

Figure 8. (a): SEM of fresh G50/13 based formulation. (b): SEM of aged G50/13 based formulation.

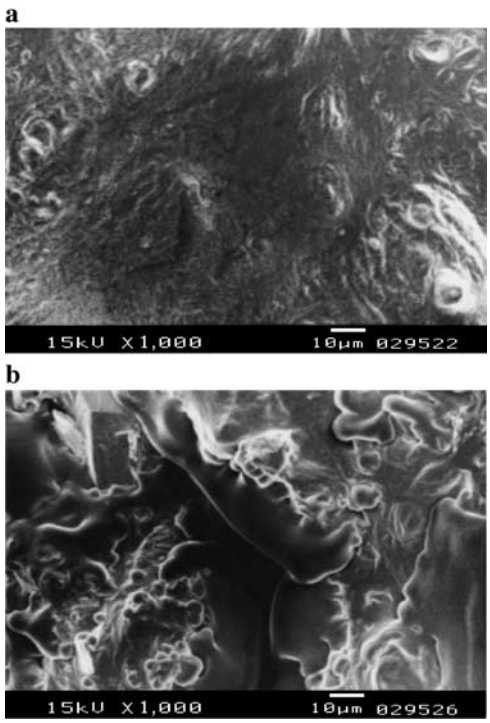

Figure 9. (a): SEM of fresh G53/10:G44/14 (60:40) based formulations. (b): SEM of aged G53/10:G44/14 (60:40) based formulations.

SSM showing formation of cracks and fissures on the surface of the matrix (Fig. 8b), whereas SEM of the freshly prepared G50/13 matrix indicates a smooth rather homogeneous surface (Fig. 8a). These changes would allow easier penetration of the dissolution medium and subsequent faster dissolution of the drug from aged samples. Similar surface changes were reported in a study of theophylline/ G50/13 matrix.[31]

On the other hand, release pattern of CBZ from G53/10, having the same nominal components of G50/13 but in different proportions, did not alter on storage (Table 3). This may be due to the lack of changes in matrix integrity or surface characters, as revealed from SEM, where no change in surface characteristics of G53/10 SSM was observed upon ageing. So blending G50/13 with G53/10 seemed to produce formulations with improved dissolution stability. Table 3 shows a decrease in the storage-induced change in drug release characteristics as the amount of G53/10 in the blend increases. This may be explained by the possible action of G53/10 as a bridge former between G50/13 micro crystals, which prevent phase separation and keep the matrix homogeneity and surface integrity.

In addition, the inclusion of 1% or 4% croscarmellose sodium, as a hydrophilic additive in G53/10 SSM, did not alter CBZ release characteristics, upon storage.

Table 3 shows that the D.E.8 h and $t_{50\%}$ values of both fresh and aged formulations were nearly identical, indicating dissolution stability of these formulations

Effect of Ageing on Formulations Based on G53/10–G44/14 Blend (60:40)

Table 3 indicates that the release rate of CBZ from the aged G53/10–G44/14 blend was unaltered over the first 2 hours ($t_{50\%}$ was 1.9 h for both fresh and aged matrices), after which the matrix disintegrated and released 100% CBZ in 6h compared to 8 h for fresh formula. This change in release pattern may be associated with a kind of phase separation during storage. SEM (Figs. 9a and b) show a smooth uniform surface of the freshly prepared blend and non uniform surface of the aged sample involving both gap formation and crystal growth on the surface. DTA thermograms of fresh and aged blend were identical, and showed two separate endothermic peaks at 39°C and 53–55°C, which most probably represent the two blended gelucires (Fig. 10). The blend therefore is a solid dispersion of one gelucire in the other, rather than a single homogenous phase i.e. a solid solution. Aggregation of dispersed gelucire during ageing may account for the crack formation observed in SEM of this blend.

Effect of Ageing on Formulations Based on G33/01

Table 3 shows that release rate of CBZ from G33/01 was largely decreased upon ageing. This observation is quite common among glyceride bases and has

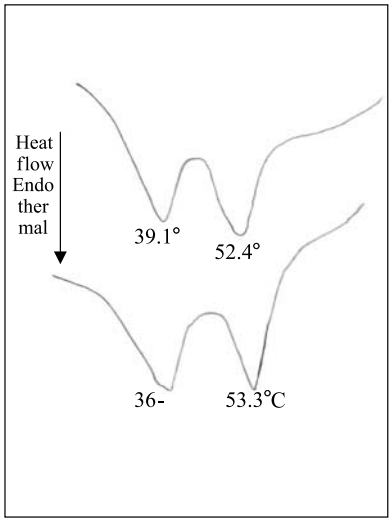

Figure 10. DTA thermograms of fresh (above) and aged (below) G53/10: G44/14 (60:40) based formulations.

been detected in our previous work with phenytoin sodium/G33/01 SSM.[32] The mechanism involved may include the conversion of the base into a more stable polymorphic form, the conversion of the amorphous form to the crystalline state of the fat form and/ or the formation of network structure. Inclusion of 10% PVP, a well known polymorphic transformation inhibitor, into G33/01 clearly reduced the physical changes occurring in the matrix during ageing as shown by D.E.8 h values of both fresh and aged formulations (Table 3).

CONCLUSION

From the above results, it can be concluded that:

a) Different grades of Gelucire bases (G50/13, 53/10 and 33/01) could be successfully used to prepare extended release CBZ capsules by the application of SSM filling capsule technology.
b) The use of Gelucire blends or inclusion of hydrophilic additives as channeling agents (PVP), swellable polymers (croscarmellose sodium) or thixotropic gel forming agents (Aerosil) enabled the preparation of CBZ extended release capsules with various release kinetics.
c) CBZ release occurred by different mechanisms, including matrix disintegration, diffusion and or erosion depending on the vehicle employed.
d) Zero order release profiles of CBZ were obtained from SSM-based on G50/13, G53/10 and their blends in ratios higher than 1:1 and G53/10 containing croscarmellose sodium.
e) The ageing study revealed that these latter formulations, except those based on G50/13, showed high dissolution stability during one year of shelf ageing.
f) PVP, as a polymorphic transformation inhibitor, could be used to reduce the well known storage-induced changes of some grades of Gelucires.

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