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Original scientific paper

Application of experimental design in the examination of the dissolution rate of carbamazepine from formulations. Characterization of the optimal formulation by DSC, TGA, FT-IR and PXRD analysis

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Abstract: Poor solubility is one of the key reasons for the poor bioavailability of carbamazepine drugs. This study considers formulation of solid surfactant systems with carbamazepine, in order to increase its dissolution rate. Solid-state surfactant systems were formed by application of fractional experimental design. Poloxamer 237 and Poloxamer 338 were used as the surfactants and Brij® 35 was used as the co-surfactant. The ratios of the excipients and carbamazepine were varied and their effects on the dissolution rate of carbamazepine were examined. Moreover, the effects of the addition of natural (diatomite) and a synthetic adsorbent carrier (Neusilin® UFL2) on the dissolution rate of carbamazepine were also tested. The prepared surfactant systems were characterized and the influences of the excipients on possible changes of the polymorphous form of carbamazepine examined by application of analytical techniques (DSC, TGA, FT-IR and PXRD). It was determined that an appropriate selection of the excipient type and ratio could provide a significant increase in the carbamazepine dissolution rate. By application of analytical techniques, it was found that the employed excipients induce a transition of carbamazepine into the amorphous form and that the selected sample was stable for three months, when kept under ambient conditions.

Keywords: poloxamer; neusilin; diatomite; solid surfactant drug delivery systems; polymorphous transition.

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INTRODUCTION

According to Ku and Dulin, the number of new drug candidates that exhibit poor aqueous solubility has increased by up to 70 %.[1] The dissolution of poorly soluble drugs is the rate-limiting step for drug absorption and bioavailability. Therefore, formulation of drug delivery systems that promote drug release could be a useful approach to improve absorption and oral bioavailability.[2] A number of alternative technologies have been developed to overcome the drawbacks associated with poor aqueous solubility, for example, decreases in the particle size, the use of the amorphous form of the active pharmaceutical ingredient, solid dispersions, lipid-based formulations, surfactant application, cyclodextrin complexation, *etc*.[3–8]

In recent years, the application of surfactants has been widely used in the formulation of self-emulsifying drug delivery systems (SEDDS),[9] self-nanoemulsifying drug delivery systems (SNEDDS)[10] and self-microemulsifying drug delivery systems (SMEDDS),[11] as well as in the formulation of surfactant systems.[12] According to the Plouton classification system of lipid formulations, a lipid formulation type IV consists of systems containing only surfactants without the addition of lipid excipients (*e.g.*, surfactant systems).[2] Such surfactant systems (consisting of drug, surfactants and co-surfactants), in contact with gastrointestinal fluids, allow drug solubilization and subsequent absorption.[2]

Poloxamers are non-ionic polyoxyethylene–polyoxypropylene block copolymers widely used in pharmaceutical technologies as gelling, emulsifying or solubilizing agents.[13–15] They are also frequently used in the formulation of solid dispersions.[16] Due to their good solubilization capacities, poloxamers are commonly used in the creation of SEDDS.[17] Brij® 35 is commonly used as a surfactant or co-surfactant in oral drug delivery systems with demonstrated improved drug solubility and bioavailability.[18–20]

Nowadays, porous carriers with a large surface area are used in order to improve dissolution and bioavailability of poorly soluble drugs.[11,21] Most frequently, such carriers are of synthetic origin (for example magnesium aluminometasilicate or porous silica). However, carriers of natural origin, such as diatomite (natural silica) are playing the leading role. Diatomites, as a new potential drug carrier, have several advantages in comparison to synthetic silicas: biocompatibility arising from their natural origin, thermal stability, chemical inertness and low cost. Additionally, the complex 3-dimensional (3-D) architecture of silica walls, called frustules, with highly ordered porous structures and high specific surface areas, provide for potential diffusion and controlled drug release.[22,23] Like many complex silicates, the surface of Neusilin has different types of silanol groups, which make it a potential proton donor as well as an acceptor. The hydrogen bonding potential of silanols in the local environment on silica surfaces is well documented.[24–26]

Carbamazepine (CBZ) is a substance with poor water solubility (0.17 mg mL^{-1} at 24 °C) and high permeability.[27,28] Based on its characteristics, it is classified into class II of the Biopharmaceutics Classification System (BCS).[29] After oral administration, its gastrointestinal absorption is slow and irregular due to poor solubility in water, leading to incomplete bioavailability.[27,28] CBZ is interesting as a model substance not only because of its poor solubility, but also because it exists in multiple polymorphous forms, *i.e.*, 4 crystalline forms, 1 hydrate and an amorphous form. Transition from one to another form during the formulation process in the presence of certain excipients is possible without changes in its stability.[27,30,31]

The objective of this study was the formulation of a solid surfactant system with increased dissolution rate of CBZ. Fractional factorial design was applied in order to evaluate the influence of the following variables on the drug release: a) the type of poloxamer as surfactant (Poloxamer 237 and Poloxamer 338), b) the ratio of Brij® 35 as a co-surfactant, c) the type and ratio of the adsorption carrier (Neusilin UFL2 or Diatomite) and d) the ratio of the drug.

Analysis of potential polymorphous transitions of CBZ was conducted by application of several analytical techniques, *i.e.*, differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), powder X-ray diffraction analysis (PXRD) and Fourier transform infrared (FT-IR) spectroscopy.

EXPERIMENTAL

Materials

Poloxamer 237 (Kolliphor™ P 237) and poloxamer 338 (Kolliphor™ P 338) were kindly donated by BASF ChemTrade GmbH (Burgbernheim, Germany). Polyoxyethylene(23)lauryl ether (Brij® 35) was obtained from Sigma–Aldrich, Germany. Magnesium aluminometasilicate (Neusilin® UFL2) was gifted by Fuji Chemical Industry (Toyama, Japan). Diatom porous silica particles of different particle size: 1–2 μm (10 %), 10 μm (60 %) and 30–50 μm (30 %) were obtained from Mount Sylvia, Pty. Ltd., Australia. CBZ (Ph. Eur. 8.0) was used as a model of a poorly soluble active ingredient. Double-distilled water was used in all experiments.

Methods

Preparation of solid surfactant systems. All formulations were prepared by melting a mixture of surfactant and co-surfactant at 60 °C. CBZ was then added to the molten mass under vigorous stirring until a homogenous dispersion was obtained. The dispersion was then rapidly cooled on an ice bath to solidify and subsequently pulverized with a pestle and mortar, before being sieved through a 300-μm sieve. The sieved mixtures were mixed with an adsorbent carrier (Neusilin® UFL2 or diatomites) and the final formulations were thus obtained. These formulations were tested with regard to the CBZ dissolution rate, which provided dissolution rate profiles for each formulation.

Two sets of experiments were conducted. In the first set of experiments, the individual effects of the excipients on the CBZ dissolution rate were investigated through a screening study. The following binary and ternary mixtures were prepared: Poloxamer 338/CBZ (80/20); Poloxamer 338/CBZ/Neusilin® UFL2 (40/10/50); Brij® 35/CBZ (80/20); Brij®

35/CBZ/Neusilin® UFL2 (40/10/50), in order to determine the individual effect of the excipients on the CBZ dissolution rate.

In the second set of experiments, fractional factorial experimental design was applied (2^{5-2}) for testing the influence of the formulation factors on the CBZ dissolution rate from the solid surfactant systems. The input parameters and the levels at which they were varied are given in Table I. The experimental plan (according to 2^{5-2} factorial design) is given in Table S-I of the Supplementary material to this paper. According to the experimental plan, a mixture of CBZ, Brij® 35 and poloxamer (comprising the surfactant system) was first created, in the appropriate mass ratio, their individual ratios adding up to 100 %. The adsorbent carrier was added to this mixture at a later stage. The prepared surfactant system/adsorption carrier ratio was varied at two levels: 66.67/33.33 and 33.33/66.67 (Table I). The percentages of released CBZ were followed as output parameters after 10, 20, 30, 45, 60 and 120 min ($Y1$–$Y6$). The influence of the investigated input parameters on the output parameters (*i.e.*, factor effects), according to the 2^{5-2} factorial design, was calculated by fitting the results into the linear model:

$$y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 4X4 + \beta 5X5 + \varepsilon \quad (1)$$

where y is the output parameter, $X1$–$X5$ are the input parameters, $\beta 1$–$\beta 5$ are the effects of individual input parameters on the output parameter (factor effects) and ε is the experimental error.

TABLE I. Varied input parameters in the second set of experiments

Parameter	Low level (–1)	High level (+1)
Type of Poloxamer ($X1$)	P237	P338
Brij® 35 ratio ($X2$), %	10	20
CBZ ratio ($X3$), %	10	20
Type of adsorption carrier ($X4$)	Neusilin UFL2	Diatomites
Adsorption carrier ratio ($X5$), %	33.33	66.67

Design Expert software (version 7.0.0; Stat-Ease, Inc., Minneapolis, MN, U.S.A.) was applied.

After performing the second set of experiments, the solid surfactant system with the fastest CBZ release was selected. In the selected formulation, the percentage of CBZ was varied at three levels: 10, 15 and 20 %. Dissolution rate profiles of the selected optimal formulation were compared with pure CBZ and commercially available immediate release CBZ tablets (Galepsin®, Galenika a.d, Serbia).

In vitro *drug release studies*

The dissolution profiles of the different solid surfactant systems and pure CBZ were determined using a rotating paddle apparatus (Erweka DT70, Germany). The dissolution conditions were: water as medium; 37±0.5 °C; 900 mL and 50 rpm. Aliquots of 4 mL were withdrawn from the medium at fixed times (10, 20, 30, 45, 60 and 120 min). Sink conditions were maintained at all times. All samples were filtered through a 0.45-μm MF-Millipore® membrane filter (Millipore Corporation, Bedford, NY, USA). The CBZ concentration was determined spectrophotometrically at λ = 287 nm (Evolution 300 spectrophotometer, Thermo Fisher Scientific, UK). The dissolution experiments were performed in triplicate and the data are expressed as the mean value.

The release profiles of CBZ from solid surfactant systems were compared with the dissolution profiles of pure CBZ by calculating the difference (*f*1) and the similarity (*f*2) factors.[32]

Characterization of the solid phase

In order to determine the polymorphous form of CBZ in the final formulation and the influence of individual excipients on the change in the polymorphous form, DSC and TGA analyses were conducted in the first set of experiments. DSC, TGA, X-ray and FT-IR analyses were performed on the optimal formulation and pure CBZ.

The optimal formulation was kept under room conditions (*T* 25 °C and *RH* 40 %) for three months in order to assess its stability, after which the DSC, TGA, X-ray and FT-IR analyses were repeated.

Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA)

Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) were applied in order to determine thermal properties of the compounds. Thermal properties were examined at temperatures ranging from room temperature up to 250 °C on a SDT Q600 TGA/ /DSC instrument (TA Instruments) under a dynamic dry nitrogen atmosphere (flow rate: 100 cm^3 min^{-1}) at a heating rate of 20 °C min^{-1}. The sample masses were between 7.3 and 11.5 mg.

Fourier transform infrared (FT-IR) studies

FT-IR spectra in the region of 600–4000 cm^{-1} for both starting materials and the solid formulations were obtained using a Shimadzu IR-Prestige-21 FT-IR spectrometer coupled with a horizontal Golden Gate MKII single-reflection ATR system (Specac, Orpington, UK) equipped with a ZnSe lens, after appropriate background subtraction. Sixteen scans over the selected wave number range at a resolution of 4 cm^{-1} were averaged for each sample.

Powder X-ray diffraction analysis (PXRD)

The X-Ray diffraction (PXRD) patterns of the powders were recorded on an Ital Structure APD2000 X-ray diffractometer with Bragg–Brentano geometry using CuK_α radiation (λ =1.5418 Å) in the 2θ range from 4 to 45°.

RESULTS AND DISCUSSION

CBZ release profiles from the binary and ternary mixtures prepared in the first set of experiments, as well as the release profile of the pure drug, are presented in Fig. S-1 of the Supplementary material. The CBZ release was increased in all mixtures compared to that of the pure drug. Similarity and difference factors were calculated for all mixtures (Table II).

TABLE II. The difference (*f*1) and the similarity (*f*2) factors for the mixtures and pure CBZ (from the first set of experiments). The percentage mass loss in the temperature range 100––200 °C for the mixtures prepared in the first set of experiments

Mixtures	*f*1	*f*2	Mass loss, % 100 °C < *T* < 200 °C
CBZ & CBZ+Brij® 35	8.32	62.15	7.31
CBZ & CBZ+Brij® 35+ Neusilin® UFL2	23.14	36.41	4.34
CBZ & CBZ+P338	51.41	9.15	0.19
CBZ & CBZ+P338+ Neusilin® UFL2	57.98	3.38	4.31

Based on the results presented in Table II, it could be concluded that the CBZ dissolution rate was statistically significantly increased in following mixtures: Brij® 35/CBZ/Neusilin® UFL2 (40/10/50), Poloxamer 338/CBZ (80/20) and Poloxamer 338 /CBZ /Neusilin® UFL2 (40/10/50). The CBZ dissolution rate in the mixture Brij® 35/CBZ (80/20) was similar to that of pure CBZ dissolution.

The increase in the CBZ dissolution rate with the addition of Poloxamer 338 was expected because of its high hydrophilic–lipophilic balance (HLB) value (HLB-27) and solubility characteristics.[33] The adsorbent carrier with its large specific surface leads to better soaking of the substance and more contact with the medium, which also increases the CBZ dissolution rate.[34] The addition of Poloxamer 338 had more effect individually than the addition of Brij® 35, which was expected due to its lower *HLB* value of 16 in comparison to 27 for Poloxamer 338.[33] Therefore, Brij® 35 was used as a co-surfactant in the second set of experiments.

The CBZ dissolution rate profiles obtained from the second set of experiments are given in Fig. 1. Significant increases in the dissolution rate were registered compared to that of pure CBZ.

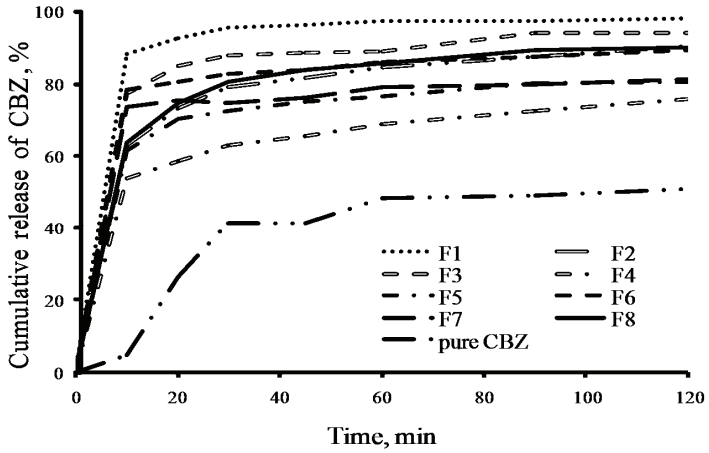

Fig. 1. Dissolution profiles of the CBZ formulation prepared in the second set of experiments and pure CBZ.

The calculated factor effects (Eq. (1)) are given in Table III. The sign of the coefficient shows whether the effect is positive or negative, *i.e.*, whether the CBZ dissolution rate increases (positive effect) or decreases (negative effect) with a change in the parameter value.

The CBZ ratio (*X*3) had the most pronounced influence on the drug release in the first 10 min of the drug release study. This parameter had a negative effect

because of the poor solubility of CBZ. The percentage of released CBZ decreased with increasing of its ratio in the formulation (from 10 to 20 %).

TABLE III. Analysis of the influence of the input parameters on the output parameter, released CBZ, %, in the second set of experiments

Factor effect	τ / min					
	10 (*Y*1)	20 (*Y*2)	30 (*Y*3)	45 (*Y*4)	60 (*Y*5)	120 (*Y*6)
*X*1 (type of Poloxamer)	+1.09	+0.31	+1	+1.01	+1.15	0.9
*X*2 (Brij® 35 ratio)	–1.8	–2.02	–1.31	–1.47	–1.23	0.037
*X*3 (CBZ ratio)	–6.45	–5.8	–5.12	–4.6	–3.86	–3.02
*X*4 (type of adsorption carrier)	–3.17	–5.13	–6.26	–6.15	–5.77	–5.72
*X*5 (adsorption carrier ratio)	–5.87	–4.16	–3.53	–3.15	–3.55	–2.33
*X*2 and *X*3 interaction	–3.23	–2.57	–1.99	–1.81	–1.62	–1.26
*X*2 and *X*5 interaction	+3.31	+1.55	+0.8	+0.24	+0.16	–0.14

After 30 min of the drug release study, the type of carrier had more influence. Initially, CBZ was released from the surfaces of both carriers. Due to the larger specific surface area of Neusilin® UFL2 (300 m^2 g^{-1}) compared to diatomites (211 m^2 g^{-1}), a higher CBZ release rate was achieved [22,35,36] and the significance of this factor increased with time. In solid surfactant systems with diatomites, due to their specific structure, the substance is absorbed into the interior of the diatomite, from where it is gradually released;[37,38] hence, the CBZ release was delayed as the release had to occur from the interior of the system.

It was shown that the higher carrier ratio had a negative impact on drug release. A higher release rate was achieved when the carrier ratio was at its lower level (33.33 %). According to Agarwal *et al.*,[35] the adsorbent magnesium aluminometasilicate, with a large specific active surface (300 m^2 g^{-1}) and small particle size (2−8 μm), has pores in which an adsorbed substance could enter by means of capillary forces. Inside the pores, potential crystallization is disabled. It could be presumed that the decrease in the dissolution rate after adsorption derives from the precipitation of the drug on the surface of the adsorbent and the capturing of the drug inside the carrier. This was particularly evident after 10 and 20 min, when the percentage of the substance to be released was low, due to the poor availability of CBZ to the medium.

The type of employed Poloxamer had the least pronounced influence on the CBZ release rate. The systems created with Poloxamer 338 (HLB 27) showed a slightly higher CBZ release rate compared to those of the Poloxamer 237 systems (HLB 24), which, was expected, due to the higher HLB value of the former.[33] Poloxamer 338 also has a lower value of the critical micellar concentration (*CMC*) compared to Poloxamer 237 and is, therefore, a more efficient solubilizer, which corresponds to the obtained result (the *CMC* of Poloxamer 338 is 2.2×10^{-5} mol L^{-1} while that of Poloxamer 237 is 9.1×10^{-5} mol L^{-1}).[39,40]

Comparing the obtained factor effects from Eq. (1), it is evident that the Brij® 35 ratio had less influence on the CBZ release rate. The formulation with the higher Brij® 35 ratio had a lower Poloxamer ratio. In the first set of experiments, it was shown that the Poloxamer had a greater influence on the increase in the CBZ dissolution rate compared to Brij® 35. However, there was a significant interaction between the CBZ ratio and the ratio of Brij® 35. Formulations with a higher level of the CBZ ratio and a lower level of Brij® 35 showed the highest percentages of released CBZ.

The analysis revealed another significant interaction, *i.e.*, that of the ratios of Brij® 35 and the carrier ratio. When the carrier ratio was at the lowest level, a change of the Brij® 35 ratio from 10 to 20 % decreased the percentage of released substance. From the previous interaction, it could be concluded that higher release rates were achieved with 10 % of Brij® 35 in the formulation. In this case, a higher substance release rate was achieved when the carrier ratio was at the lower level, *i.e.*, 33.33 %.

From second set of experiments, the selected: Poloxamer 338, Brij® 35 10 %, Neusilin UFL2 33.33 % formulation exhibited the highest CBZ release rate. In such a solid surfactant system, the CBZ ratio was set at 10, 15 and 20 %. The results of drug release study from these formulations are shown in Fig. S-2A of the Supplementary material.

The highest percentage of released CBZ was obtained from the formulation with 15 % of CBZ. The CBZ drug release profile from this formulation is compared with the profiles of pure CBZ and commercially available immediate release CBZ tablets in Fig. S-2B of the Supplementary material.

The results of the TGA analysis (Fig. 2A) showed that in the temperature range of 100 to 200 °C, Neusilin® UFL2 exhibited a mass loss of about 8.5 %, whereas the optimal formulation lost 4.31 % of its mass. The mass loss for samples prepared in the first set of experiments in the temperature range of 100 to 200 °C are presented in Table II. CBZ exhibited a small mass loss within the temperature range of 100 to 200 °C, while in the range of 200 to 250 °C, an immediate mass loss of 2.5 % was registered, probably indicating the commencement of its degradation. A somewhat higher loss of mass was registered in the samples in which Brij® 35 was used as the surfactant. Moreover, a significant decrease in mass of all samples was registered in the temperature range of 200 to 250 °C, which correlates with the result obtained for pure CBZ (Fig. 2B).

The DSC curves of the tested samples and pure CBZ showed an endothermic peak at about 60 °C (Fig. 2C). Bearing in mind the very broad range over which the device was calibrated (60–800 °C), this peak could derive from measurement uncertainty, *i.e.*, the imprecision of the instrument. With formulations containing Poloxamer, this peak was somewhat more distinct, because their peak derives from the melting of Poloxamer.[41] This led to an overlapping of the peaks in these

formulations. Based on the two endothermic peaks at 178 and 195.6 °C, it could be concluded that the pure CBZ was in the polymorphous form III.[31,42] The reason for these peaks occurring at higher temperatures than those given in the literature[31] could be explained by the higher heating rate employed in the present study (20 °C min^{-1}) than the rate used in the literature study (10 °C min^{-1}), *i.e.*, the difference in the temperature lag of the two systems. The balance of the system was achieved slightly later and, therefore, the changes identified by the peaks were delayed by a few °C. In addition, because of the difference in the experimental conditions, no distinct recrystallization peak corresponding to the transition of the sample into the polymorphous form I was visible on the DSC curve of pure CBZ recorded in the present study. Furthermore, on the DSC curves of the samples, a broad endothermic peak was registered in the temperature range 230–240 °C. It is assumed that this peak corresponded to the beginning of CBZ degradation, which is in accordance with the results of the TGA analysis. From this point of view, an analysis of the degradation products and the further clarification of this peak could be a part of further investigations. In all

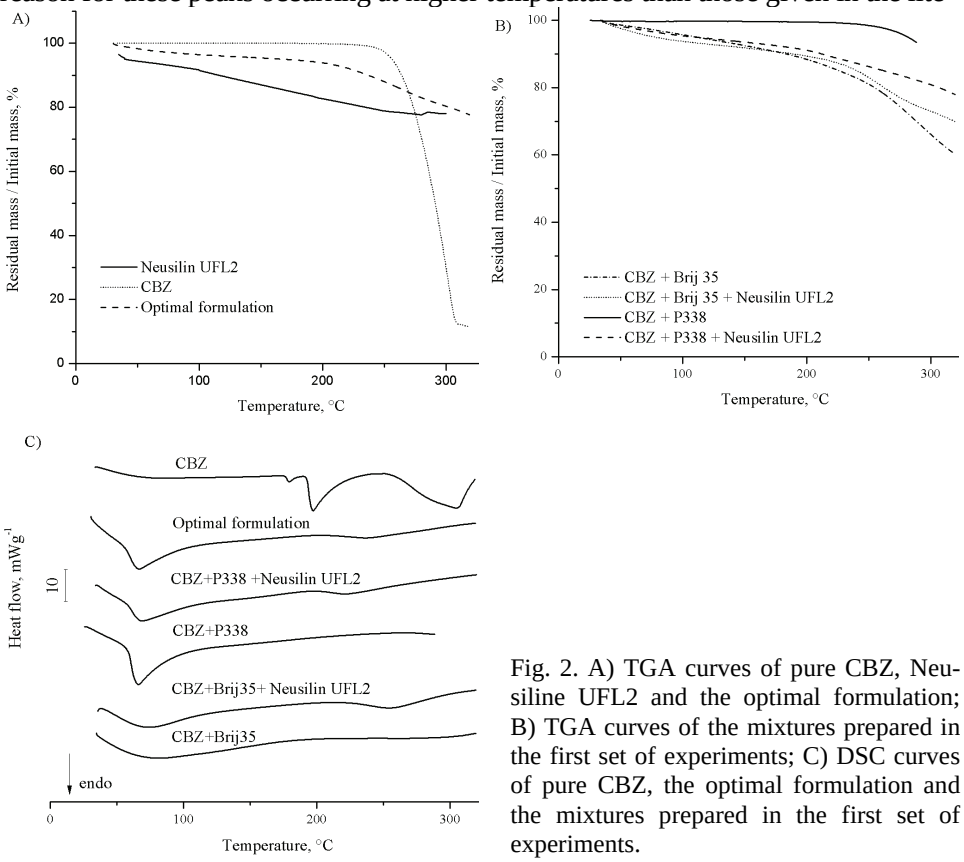

Fig. 2. A) TGA curves of pure CBZ, Neusiline UFL2 and the optimal formulation; B) TGA curves of the mixtures prepared in the first set of experiments; C) DSC curves of pure CBZ, the optimal formulation and the mixtures prepared in the first set of experiments.

four tested mixtures, no characteristic melting peaks from polymorphous form III were evidences in the temperature range of 150 to 175.8 °C.[31,42] In addition, no peaks characteristic for other polymorphous forms were registered. Thus, it could be assumed that a transition of CBZ from the crystal polymorphous form III into amorphous form had occurred. It is notable that the application of the individual surfactants (Poloxamer 338 and Brij® 35, with or without the addition of Neusilin® UFL2) led to the transition of CBZ into the amorphous form. Although DSC is a commonly used technique for the determination of crystalline state of drugs and the absence of a melting peak might suggest the formation of an amorphous phase,[43] care should be taken in the interpretation of the results of DSC analysis, particularly when the formulations contain a Poloxamer. Since poloxamers melt at significantly lower temperatures than CBZ, there is a possibility that crystalline CBZ gradually dissolves into a molten polymer during the DSC scan. As the temperature reaches the melting point of CBZ, there may not be sufficient crystalline drug remaining to give a detectable melting endotherm on the DSC curve.[44] Therefore, further characterization of the optimal formulation was performed by application of PXRD and FT-IR analysis in order to confirm the transition of the drug into the amorphous form.

The FT-IR spectra of CBZ and the optimal formulation are given in Fig. 3A and B, respectively. The CBZ spectrum corresponds to those previously reported for the polymorph form III. Characteristic peaks were observed at 3462 (−NH valence vibration), 1674 (−CO−R vibration), 1593 and 1605 cm^{-1} (in the range of −C=C− and −C=O vibration and −NH deformation).[31] Deformation of bands characteristic for the CBZ form III at 1605 and 1593 cm^{-1} (−C=O vibration and −NH deformation) (Fig. 3B.) in FT-IR spectra of the optimal formulation may suggest that a hydrogen bond between the carbonyl group of CBZ and silanol group of adsorbent participate in the formation of the amorphous state of CBZ. There have been reports of drug amorphization by co-grinding with porous silica or magnesium aluminometasilicate.[24–26] Drug amorphization was accompanied by improvement in the drug release rate. CBZ amorphization is a consequence of disruption of the crystalline structure due to hydrogen bonds formation between the drug and adsorbent.

The PXRD patterns of pure CBZ and the optimal formulation are illustrated in Fig. 4. The PXRD pattern of CBZ exhibits characteristic high-intensity diffraction peaks at 2θ 13.02, 15.22, 15.78, 19.40, 24.92, 27.50 and 31.86°, which is in accordance with diffractograms previously reported for the crystal form III.[31,45] These characteristic peaks cannot be seen on the diffractogram of the optimal formulation, which confirms the results obtained by DSC and FT-IR analysis that the carbamazepine had transformed into the amorphous form. The two broad peaks appearing on the diffractogram of the optimal formulation arose from Poloxamer 338.[46]

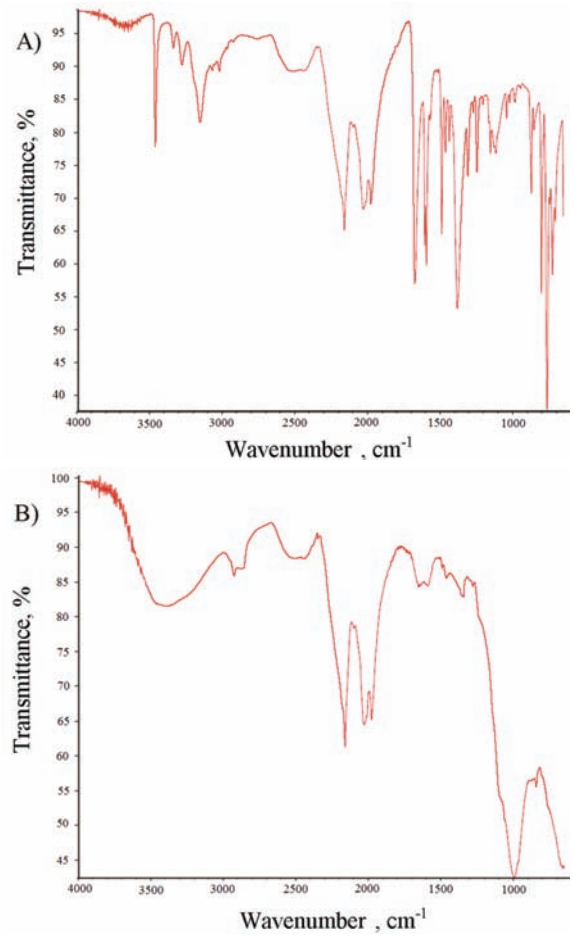

Fig. 3. FT-IR spectra of A) pure CBZ and B) the optimal formulation.

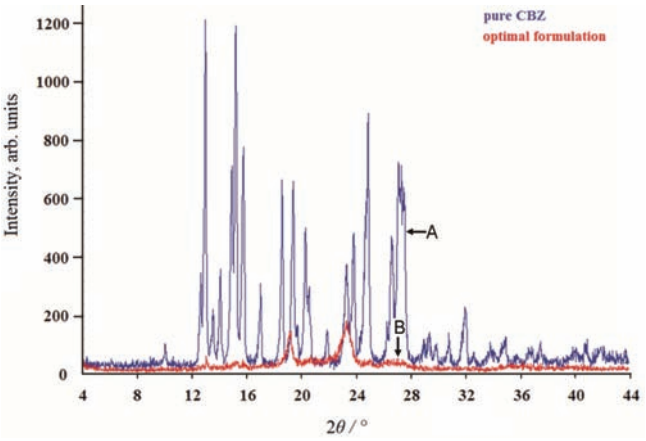

Fig. 4. PXRD patterns of A) pure CBZ and B) the optimal formulation.

DSC, TGA, FT-IR and PXRD analyses of the optimal formulation that had been kept under ambient conditions for three months showed no significant changes in the formulation had occurred. The CBZ remained in the amorphous state and the stability of the formulation was thus confirmed.

CONCLUSIONS

Formulation of solid surfactant drug delivery systems with CBZ as a model drug showed that the addition of Poloxamer (237 or 338), Brij® 35 and an adsorbent (Neusilin UFL2 or diatomite) led to the transition of CBZ into the amorphous state and an increase in its release rate. Poloxamers, as surfactants, had the most significant effect on the increase of the drug release rate. The addition of the adsorbent carrier further increased the CBZ release rate, due to its large specific surface.

The highest carbamazepine release rate was obtained from the optimal formulation in which the surfactant mixture had the following components: 75 % Poloxamer 338; 10 % Brij® 35; 15 % CBZ, while the surfactant mixture and Neusilin® UFL2 as carrier were in 2:1 ratio. This formulation was stable for at least three months.

From all the presented results, it could be concluded that the release rate of poorly soluble CBZ could be increased by solid surfactant systems.

SUPPLEMENTARY MATERIAL

Experimental plan for the second set of experiments, Table S-I, and dissolution profiles of the mixture and CBZ formulation, Figs. S-1 and S-2, are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ЕКСПЕРИМЕНТАЛНИ ДИЗАЈН ИСПИТИВАЊА БРЗИНЕ РАСТВАРАЊА КАРБАМАЗЕПИНА ИЗ ФОРМУЛАЦИЈА. КАРАКТЕРИЗАЦИЈА ОПТИМАЛНЕ ФОРМУЛАЦИЈЕ ПОМОЋУ DSC, TGA, FT-IR И PXRD МЕТОДА

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Слаба растворљивост јесте један од кључних разлога за лошу биолошку расположивост карбамазепина. У овом раду је приказана формулација чврстих површински активних система са карбамазепином, ради повећања његове брзине растварања. Чврсти површински активни системи су формулисани применом фракционог факторског експерименталног дизајна. Као површински активни системи коришћени су Poloxamer 237 и Poloxamer 338, а као ко-површински активни Brij® 35. Варирани су удели ексципијенаса и карбамазепина и испитиван је њихов утицај на брзину растварања карбамазепина. Такође, испитан је и утицај додатка природних (дијатомита) и синтетичких адс-

орпционих носача (Neusilin UFL2) на брзину ослобађања карбамазепина. Извршена је карактеризација израђених површински активних система и испитан је утицај ексципијенаса на могућу промену полиморфног облика карбамазепина применом аналитичких техника (DSC, TGA, FT-IR и PXRD). Утврђено је да се правилним одабиром врсте и удела ексципијенаса може постићи значајно повећање брзине ослобађања карбамазепина. Аналитичким техникама је утврђено да коришћени ексципијенси доводе до преласка карбамазепина у аморфни облик и да је одабрани узорак стабилан 3 месеца, чувањем под собним условима.

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