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Hyperbranched poly(esteramides) as solubility enhancers for poorly water-soluble drug glimepiride

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ABSTRACT

The aim of this work was to study the feasibility of using hyperbranched polymers with highly branched structure and a large number of functional groups as solubilization enhancers for poorly water-soluble drugs. Antidiabetic drug glimepiride was used as a model drug and commercially available hyperbranched poly(esteramide)s as drug carriers.

The results of *in vitro* dissolution studies showed significantly enhanced aqueous-solubility of glimepiride in the form of solid dispersions with hyperbranched poly(esteramide)s as compared to pure glimepiride in crystalline or amorphous form. The results of IR spectroscopic measurements revealed that improved solubility is a consequence of a complex formation between glimepiride and hyperbranched polymer. HB poly(esteramide)s with carbonyls of ester (O)–C=O and amide (N)–C=O groups serve mainly as a source of proton acceptor groups to which NH groups of glimepiride establish hydrogen bonds. Due to complex formation, glimepiride is within solid dispersions with HB polymers amorphous up to concentration of 5% (w/w) as revealed by X-ray powder diffraction measurements. Above this limit, glimepiride crystallizes as a separate phase during solvent evaporation.

1. Introduction

The use of oral antidiabetic drugs for management of type 2 diabetes increases rapidly. It has expanded with the discovery and approval of several new types of oral antidiabetic drugs with different mechanism of pharmacological action (Wysowski et al., 2003; Luna and Feinglos, 2001). Many of these drugs belong to class II of the biopharmaceutical classification system showing poor solubility and high permeability (Seedher and Kanojia, 2009). These drugs provide challenges to deliver them in an active and absorbable form to the desired absorption site using physiologically safe excipients. Therefore, one of the most important steps in the development of dosage forms for poorly soluble drugs is to improve their solubility and/or dissolution rate.

Several approaches to improve water solubility include prodrugs, complexation, cosolvency, solid state modifications, surfactants, and hydrotropy. Among these the addition of cosolvents (Seedher and Kanojia, 2009; Seedher and Bhatia, 2003; Yalkowsky and Roseman, 1981), the formation of cyclodextrins or micellar inclusions (Ammar et al., 2006a,b, 2007) and the preparation of solid dispersions (Kerč et al., 1998; Fini et al., 2005; Serajudin, 1999; Liu and Deasi, 2005; Narang and Srivastava, 2002; Okonogi and Puttipipatkhachorn, 2006), are the most commonly used. Many of these solubilization techniques have their own limitations. For instance, high cosolvent concentration leads to toxicity, use of cyclodextrins is associated with nephrotoxicity (Narendra and Gupta, 2008; Palmieri et al., 1998), whereas in the surfactant-based solubilization strict requirement of maintaining critical micellar concentration is necessary (Palmieri et al., 1998). Solid state modifications using particle size reduction or polymorph modifications are widely employed. The transformation of drug to its amorphous form is often desirable since the solubility increases from a few- to many-fold. However, high enthalpy and molecular mobility of amorphous solid also reflects in thermodynamical and kinetical instability that often necessitate the incorporation of polymeric stabilizers to form solid dispersions (Hilden and Morris, 2004; Gao, 2008). The solid dispersions are preferably prepared by dissolving or dispersing the drug substance and the stabilizing polymer in a suitable solvent to form a feed solution, which is then spray dried to obtain the amorphous solid dispersion as a powder. The presence of hydrophilic compounds in close contact with the drug molecules increases the solubility by maintaining the drug in a molecular state and maximizing the surface area of the compound (Bansal et al., 2007). The polymeric molecules also act as crystallization inhibitors and preserve the drug in its amorphous state. The materials commonly used in the solid dispersion technology

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are sugars, polar lipids, and polymers, such as poly(ethylene glycol), poly(vinylpyrrolidone), poly(methacrylate), etc. The effect of linear polymers on drug solubility has been widely investigated, but only few products using this technology are commercially successful. In the past decade the developed dendritic polymers brought a new challenge in this field.

Dendritic polymers with unique highly branched molecular architecture and a large number of functional groups, i.e., dendrimers and hyperbranched (HB) polymers have attracted in recent years considerable and increasing interest in the field of drug delivery (Gillies and Frechet, 2005; Žagar and Žigon, 2002; Žagar et al., 2007; Florence, 2005; Kolhe et al., 2003). The properties of dendritic polymers are different from those of linear polymers of the same molar mass (less flexibility, lower entanglement degree, a significant chain-end effect, lower viscosity in solution and in the molten state, high solubility in common solvents, a different relationship between hydrodynamic volume and molar mass) (Tomalia et al., 1984; Brabender and Meijer, 1993; Newkome et al., 1992; Buhlein et al., 1978; Mishra and Kobayashi, 1999; Fréchet, 1994). The distinctive mechanical, chemical and physical properties of dendritic polymers make them ideal candidates for use in a wide variety of application, also as drug delivery carriers. Dendrimers have well defined monodisperse perfectly branched structures, which consist of fully branched, i.e., dendritic repeat units, and unreacted terminal repeat units. They are synthesized tedious with many protection and deprotection synthetic and purification steps, which make their large-scale production difficult and expensive (Tomalia et al., 1984; Brabender and Meijer, 1993; Newkome et al., 1992; Buhlein et al., 1978; Mishra and Kobayashi, 1999). On the other hand, HB polymers are simpler to produce on a large scale via one-pot synthesis. However, this simplified procedure yields fewer regular structures and broad molar mass distributions. HB polymers consist not only of dendritic and terminal repeat units but also of linear ones with one unreacted functional group, which are regarded as defects in their branched structures (Mishra and Kobayashi, 1999; Fréchet, 1994; Hult et al., 1999; Sunder et al., 2000; Malmström and Hult, 1997).

A particular class of hyperbranched molecules, which belong to the poly(ester amide) family, are now produced on an industrial scale at a very competitive cost bearing the commercial name Hybrane. These molecules are already being utilized as key components in several high-added-value applications (e.g., in nanolithography, as dispersion agents, surface modifiers), and they also appear as promising candidates for pharmaceutical formulations. For example, the feasibility of using the commercially available hyperbranched polymers, i.e., polyesteramides (Hybranes, DSM) and polyesters (Boltorn, Perstorp), as drug carriers have been intensely studied by Suttiriuengwong et al. (2006). They employed different microencapsulation methods for the drug acetaminophen as well as different microparticle formation methods to study their influence on the release kinetics of acetaminophen.

The present work aims at assessing the influence of hyperbranched polymers as possible solubilization enhancers, affecting glimepiride solubility and dissolution rate. Glimepiride is one of the third generation sulfonylurea drugs useful for control of diabetes mellitus, type 2 (Ammar et al., 2006a). It has a poor solubility and a slow dissolution rate in water and a pH-dependent solubility as well. This may lead to irreproducible clinical response or therapeutic failure in some cases due to subtherapeutic plasma drug levels (Ammar et al., 2007; Frick et al., 1998). From the economical point of view, low oral bioavailability results in wasting of a large portion of an oral dose and adds to the cost of drug therapy, especially in the case of expensive drugs. All these problems necessitate the development and use of alternative materials for improved drug solubility. Until now, the published results on glimepiride solubility improvement have involved inclusion complexation of glimepiride using cyclodextrins in the presence of water soluble polymers (Ammar et al., 2006a,b, 2007), use of cosolvents (Seedher and Kanojia, 2009) and microencapsulation of glimepiride by spray congealing technology using hydrophilic meltable carriers (Ilić et al., 2009).

The hypothesis of this study was that solubility and dissolution rate of glimepiride could be improved by selecting carriers capable of solubilizing it molecularly within the solid dispersion. Solid dispersions of glimepiride with commercially available poly(ester amide) hyperbranched polymers (Hybrane S1200 and Hybrane HA1690), linear polymer poly(ethylene glycol) and stearoyl polyethylene glycerides (Gelucire® 50/13) were prepared by solvent evaporation method. Under the study design, preformulation characterization of drug, excipients and solid dispersions were conducted using X-ray powder diffraction analysis. Following identification of appropriate carrier material, an *in vitro* dissolution studies were conducted in phosphate buffer solution (pH = 6.8) and the dissolution rate of crystalline and amorphous glimepiride alone, as well as in solid dispersions, were compared. To determine the loading capacity of glimepiride in particular HB polymer, solid dispersions with Hybrane in different ratios were prepared. Additionally, the nature of molecular interactions between glimepiride and hyperbranched polymers was studied by infrared spectroscopy (FTIR).

2. Materials and methods

2.1. Materials

Glimepiride, (1-[4.[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamide)ethyl] phenyl sulphonyl]-3-trans-4-methylcyclohexyl) urea (Fig. 1A) in crystalline form was supplied by Glenmark, India. Amorphous form of glimepiride was prepared by lyophilization technique (Lio 5P, 5 Pascal, Italy) and was confirmed using DSC method, the results are not shown.

Poly(ethylene glycol) PEG 6000 (average molar mass 6000–7500 g/mol, Clariant GmbH, Germany) and lipid-based amphiphilic carrier with solubilizing properties Gelucire® 50/13 were used as a conventional materials for preparation of solid dispersions. Gelucire® 50/13 is a saturated polyglycolized glyceride consisting of a well-defined mixture of mono-, di- and tri-glycerides and mono-, and di-fatty acid esters of polyethylene glycol, waxy solid with melting point 50 °C and hydrophilic–lipophilic balance value 13 and average molar mass 300–4000 g/mol, Gattefosse, France.

Hyperbranched polymers poly(ester amides), i.e., Hybrane S1200 and Hybrane HA1690 with hydroxyl and tertiary amine functional groups (Fig. 1B and C), respectively, were obtained from DSM, Netherland. Both properties and applications of Hybrane HB polymers have been reviewed and described previously (Froehling, 2004; Froehling and Brackman, 2000; Dritsas et al., 2008) (Table 1).

Solvents and chemicals used for the preparation and characterization of solid dispersions were all of analytical grade and supplied from Merck. Lactose was supplied from DMV international B.V., Netherland.

2.2. Preparation of solid dispersion

Since glimepiride thermally decomposes at temperatures 150 °C and above, a conventional solvent evaporation method (Sethia and Squillante, 2002; Fahr and Liu, 2007) was used for the preparation of solid dispersions, where glimepiride and carrier were dissolved in a mutual solvent, stirred definite time and then the solvent removed by evaporation.

Table 1
Characteristics of Hybrane hyperbranched polymers.

Name	Color	State	Solubility in		End groups	Average molecular weight
			Water	Ethanol		
Hybrane S1200	White	Solid	Soluble	Soluble	Hydroxyl	1200
Hybrane HA1690	Brown-yellow	Solid	Soluble	Soluble	Tertiary amine	1690

2.2.1. Preparation of solid dispersions using conventional materials

Glimepiride and poly(ethylene glycol) 6000 or Gelucire® 50/13 were weighted in a weight ratio of 5/95. The mixtures were dissolved in ethanol to obtain clear solutions. The solvent was then removed at slightly elevated temperature (40 °C) in vacuum. Dried solid products were then manually milled and sieved through a sieve with 250 μm pores. These samples were stored in a desiccated container until additional study.

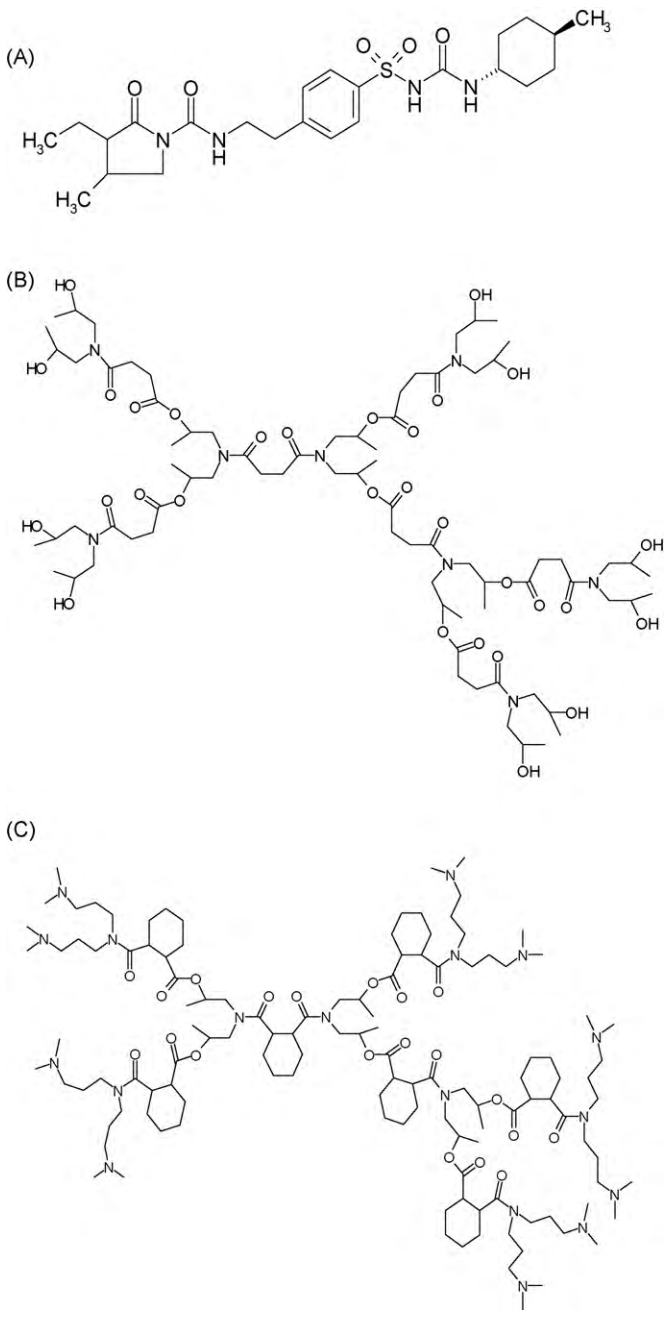

Fig. 1. Chemical structures of the studied compounds: glimepiride (A), Hybrane S1200 (B), and Hybrane HA1690 (C).

2.2.2. Preparation of solid dispersions using hyperbranched polymers

Solid dispersions of glimepiride and HB polymer were prepared in the weight ratios of 20/80, 12/88, 10/90, 7/93, 5/95 and 2/98. The mixtures were dissolved in ethanol at room temperature during continuous stirring with magnetic stirrer (480 rpm) for 1 h to assure the transparent solutions. Handling and storage of glimepiride and Hybrane S1200 solid dispersion were identical to those described in Section 2.2.1.

In the case of solutions containing glimepiride and Hybrane HA1690, semi-solid products were obtained after solvent evaporation. In order to obtain solid end-products solution of glimepiride and Hybrane HA1690 were sprayed onto lactose particles (1 part by weight of solution per 4 parts of lactose). Obtained granules were placed in a vacuum oven at 40 °C to evaporate ethanol. Solid end products were pulverized, sieved through a sieve with 250 μm mesh size and stored in dessicator.

The same granulation procedure was also applied for the solid dispersions containing glimepiride and Hybrane S1200 in ratios 20/80, 5/95 and 2/98, in order to confirm that improved glimepiride solubility is a consequence of its complexation with poly(esteramide) HB polymers and not a consequence of the introduction of additional inactive ingredient.

2.3. Characterization methods

2.3.1. X-ray powder diffraction studies (XRD)

X-ray patterns were obtained using X'Pert PRO MPD powder diffractometer. Samples were exposed to CuKα radiation in the range $2^\circ < 2\theta > 40^\circ$. The integration time per step was 50 s.

2.3.2. In vitro dissolution studies

In vitro dissolution studies were performed in phosphate buffer solution at pH = 6.8, physiologically relevant media, at 37 °C using an USP Dissolution Tester, Apparatus II (Paddle method) at a rotation rate of 75 rpm. The tested samples (pure glimepiride, solid dispersions and granulates) were added in the correct amount directly to 900 mL phosphate buffer solution to achieve a final glimepiride concentration of 4.4 μg/mL, which equals to the concentration of therapeutic dose dissolved in 900 mL. Experiments were performed in triplicates. Aliquots, each of 2 mL, were withdrawn from the dissolution medium at time intervals of 5, 15, 30, and 60 min. The sample aliquots were withdrawn through a syringe and filtered through Millipore filter (0.45 μm, PVDF). The sample aliquots were analyzed for the dissolved glimepiride content using reversed-phase HPLC method.

The amount of dissolved glimepiride was estimated by reversed-phase HPLC (Waters Alliance, USA) in a binary mode with a photodiode array detector at 230 nm. The analyses were performed on a C18 column (150 mm × 4.6 mm, 3.5 μm) placed in a column oven at 30 °C and a mobile phase: A (phosphate buffer, pH = 2.5:acetonitrile = 72:28) and B (phosphate buffer, pH = 2.5:acetonitrile = 30:70) delivered at a flow-rate of 1.5 mL/min under the following gradient conditions: 0–6 min (100% A–0% A): 6–6.5 min (0% A–100% A). The column equilibration time was

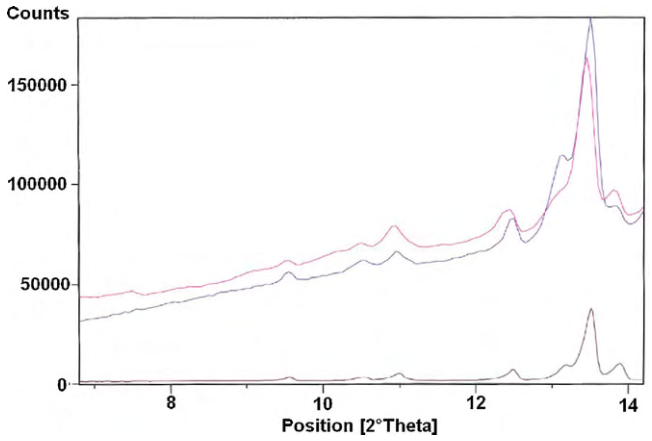

Fig. 2. X-ray powder diffraction patterns of pure glimepiride substance (bottom curve) and its solid dispersions of glimepiride with PEG 6000 (middle curve) or Gelucire® 50/13 (upper curve) in weight ratio of 5/95.

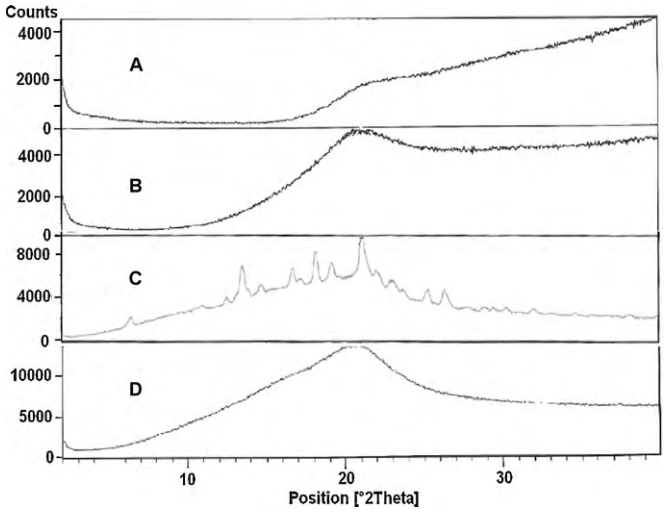

Fig. 3. X-ray powder diffraction patterns of solid dispersions containing glimepiride and HB polymer Hybrane S1200 in weight ratio of 2/98 (A), 5/95 (B) and 20/80 (C), and pure HB polymer Hybrane S1200 (D).

5 min. Retention time of the glimepiride was 4.0 min. The concentration of dissolved glimepiride was determined from the area of glimepiride peak using preformed calibration curve. Standard curve for glimepiride was measured over a range of 15–0.1 μg/mL and shown to be linear. The limit of detection was 0.005 μg/mL.

Drug loading capacity (LC) of polymers was determined from the results of *in vitro* dissolution experiments using reversed phase HPLC and calibration curve. The amount of loaded glimepiride into the polymers was determined using the following equation:

$$\mathrm{LC}\,(\%) = \frac{c(\mathrm{HPLC})}{c(\mathrm{theoretical})} \times c(\mathrm{SD})$$

where LC is the loading capacity in %, *c*(HPLC) is the concentration of glimepiride (in μg/mL) determined by HPLC after 60 min dissolution of solid dispersions (or granulates) in phosphate buffer (pH = 6.8), *c*(theoretical) is the theoretical concentration of glimepiride, i.e., 4.4 μg/mL, which equals to the therapeutic concentration and *c*(SD) is the Concentration of glimepiride in solid dispersions (2, 5, 7, 10, 12 or 20%, w/w).

2.3.3. IR-spectroscopy

The infrared spectra were recorded on a Perkin Elmer System 2000 spectrometer. Typically 256 scans were averaged and apodized with triangular functions at nominal resolution of 2 cm^{-1}. Spectra were measured at room temperature in ATR mode on a Specac Golden Gate ATR cell equipped with a diamond crystal. ATR spectra were used without additional processing such as corrections due to frequency dependent depth of penetration or spectral anomalies due to reflection.

3. Results and discussion

3.1. X-ray powder diffraction analysis (XRD)

X-ray diffraction analysis was used to assess the presence of crystalline glimepiride or its polymorph modifications within the solid dispersions. Namely, the change in drug morphology in the presence of hydrophilic polymers could be one of the reasons for the improved aqueous solubility of glimepiride.

X-ray diffractogram of the pure glimepiride shows that it is a crystalline drug, as demonstrate sharp and intense peaks in Fig. 2 (bottom curve) and correspond to those reported in the literature (Iwata et al., 1997). The diffraction patterns of glimepiride in solid dispersion with PEG 6000 or Gelucire® 50/13 (Fig. 2, middle and upper curve, respectively) are similar to those of the pure drug, indicating that the glimepiride crystalline form remains unchanged.

Higher intensities of glimepiride peaks observed in samples of solid dispersions (upper and middle curve) compared to those of pure drug (bottom curve) are a consequence of longer measurement period (40 times longer compared to routine measurement performed on pure drug sample).

Fig. 3 shows the X-ray powder diffraction patterns of glimepiride and Hybrane S1200 solid dispersions at 2/98, 5/95 and 20/80, drug to polymer ratios. In contrast to the X-ray patterns of solid dispersions of glimepiride with PEG 6000 or Gelucire® 50/13, which contained diffraction peaks at 5%, no peak was displayed at 2 and 5% (w/w) drug content in Hybrane S1200 solid dispersions. Patterns only show a broad amorphous halo, which is typical for amorphous polymers, in this case for Hybrane S1200. No characteristic peaks of glimepiride can be observed. This might be attributed to the destruction of glimepiride crystal lattice as a consequence of interaction of the drug with HB polymer (see Section 3.3, IR Spectroscopy). The peaks corresponding to crystalline glimepiride are observed in solid dispersion containing 20% (w/w) of glimepiride (Fig. 3C). From the presented results it emerges that glimepiride is in amorphous form within solid dispersions with Hybrane S1200 up to concentration of about 5% (w/w) whereas the solid dispersion with 20% (w/w) of glimepiride is oversaturated, and, as a consequence, glimepiride crystallizes as a separate solid phase during solvent evaporation.

In order to determine the highest amount of amorphous glimepiride within solid dispersion with HB polymer Hybrane S1200 more accurately, additional solid dispersions with 7, 10 and 12% (w/w) drug content were prepared.

The peaks corresponding to crystalline glimepiride are clearly observed only in X-ray diffractogram of solid dispersion containing 12% (w/w) of glimepiride (Fig. 4). The peak intensities of the crystalline glimepiride in solid dispersions containing drug in weight ratio of 7 and 10% (w/w) are at the limit of the detection (Fig. 4). Based on these results it is difficult to judge exactly at which glimepiride concentration the solid dispersion becomes oversaturated.

In the case of granulates containing the drug, Hybrane HA1690, and lactose only the peaks due to inactive lactose ingredient were observed in their X-ray diffractograms, whereas the peaks of glimepiride were not detected. Additionally, the concentration of glimepiride in granulates is below 0.4% (w/w) much lower than in solid dispersions. That is why we were not able to determine the polymorphic form of glimepiride within granulates.

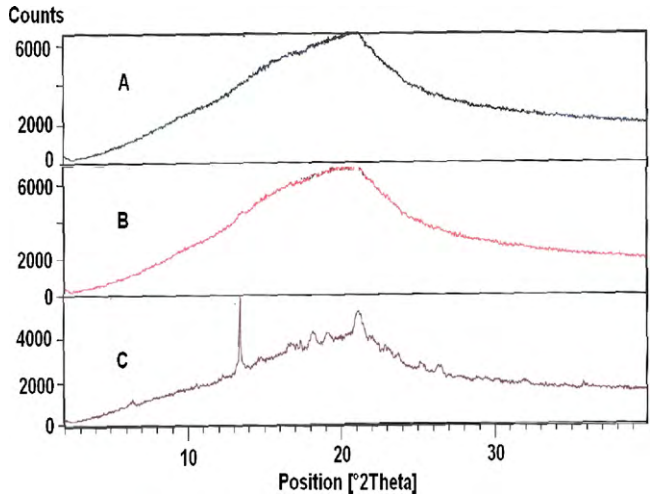

Fig. 4. X-ray powder diffraction patterns of solid dispersions containing glimepiride and HB polymer Hybrane S1200 in weight ratio of 7/93 (A), 10/90 (B), and 12/88 (C).

For these reasons the X-ray diffractograms of granulates are not presented.

3.2. *In vitro* dissolution studies

In order to assess if the goal of improving glimepiride solubility and its dissolution rate was reached by preparing solid dispersions with HB polymers, *in vitro* dissolution profiles of these samples were compared to those of pure glimepiride in crystalline and amorphous form and its solid dispersions with conventional materials, PEG 6000 and Gelucire® 50/13.

In dissolution studies, the dissolution rate of glimepiride was examined by plotting the concentration of dissolved drug as a function of time. The experiments were done in triplicates. The average values of three experiments were used for evaluation and the standard deviation was bellow 2%.

Glimepiride alone yielded the slowest initial dissolution rate with undetectable amount in 10 min. As shown in Fig. 5, the solubility as well as dissolution rate of pure glimepiride is very low regardless if it is in crystalline or amorphous form. After 60 min of dissolution time the amount of the drug was only around 0.2 and below 0.4 μg/mL for crystalline and amorphous glimepiride, respectively. Amorphous form of glimepiride shows only slightly higher solubility and somewhat faster dissolution rate as compared to its crystalline form.

On the contrary, both solid dispersions of 5% glimepiride with PEG 6000 and Gelucire® 50/13 show an increase in drug dissolution rate compared to the pure glimepiride (Fig. 5). After 60 min dissolution time the concentration of dissolved glimepiride was around 1 μg/mL for the solid dispersion of glimepiride with Gelucire® 50/13 and 1.2 μg/mL for the solid dispersion of glimepiride with PEG 6000, respectively. This might be due to the surface tension lowering effect of PEG 6000 and Gelucire® 50/13 to the medium, resulting in better wetting of hydrophobic glimepiride crystalline surface.

The dissolution profiles of solid dispersions of glimepiride with HB polymers have shown a significant increase in glimepiride solubility and its dissolution rate (Figs. 6–9) as compared to pure crystalline or amorphous glimepiride as well as its solid dispersions with investigated PEG 6000 and Gelucire® 50/13.

Solid dispersions based on HB polymers are dissolved in phosphate buffer solution practically immediately. Thus a steady concentration of dissolved glimepiride in solution was reached already after a few minutes of dissolution time. Improved

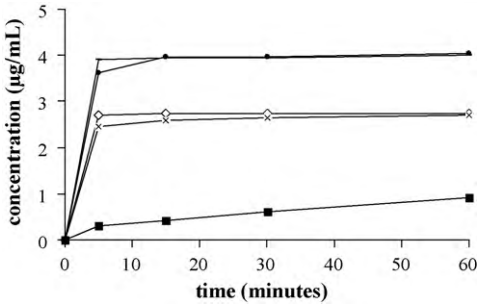

Fig. 6. *In vitro* dissolution profiles of solid dispersions containing glimepiride and HB polymer Hybrane S1200 in weight ratio of 5/95 (●); 2/98 (◊) %, and granulates prepared by spraying the solutions containing glimepiride and HB polymer S1200 in weight ratio of 20/80 (■); 5/95 (–); 2/98 (×) onto lactose inert particles.

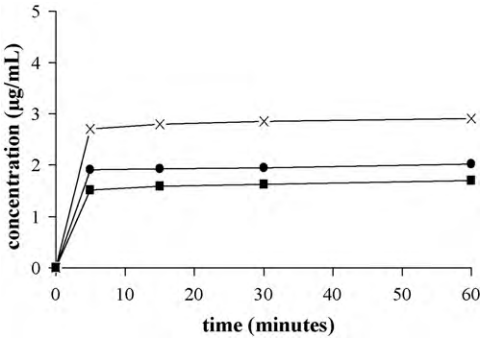

Fig. 7. *In vitro* dissolution profiles of additionally prepared solid dispersions containing glimepiride and HB polymer Hybrane S1200 in weight ratio of 7/93, (×); 10/90 (●) and 12/88 (■).

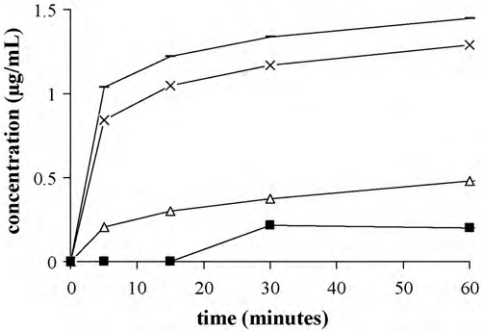

Fig. 5. *In vitro* dissolution profiles of pure glimepiride in crystalline (■) and amorphous (△) form and its solid dispersions with Gelucire® 50/13 (×) and PEG 6000 (–).

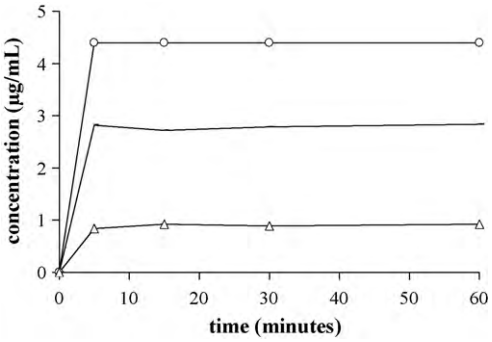

Fig. 8. *In vitro* dissolution profiles of granulates prepared by spraying the solutions containing glimepiride and HB polymer S1690 in weight ratio of 20/80 (△), 5/95 (○), 2/98 (–) onto lactose inert particles.

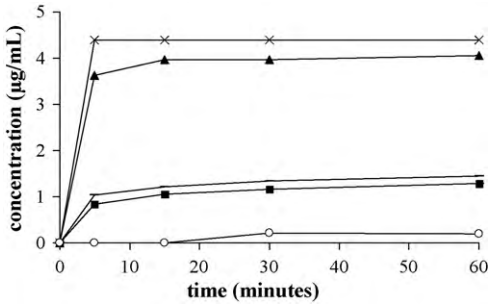

Fig. 9. Comparison of *in vitro* dissolution profiles of pure crystalline glimepiride (○) and its solid dispersions with PEG 6000 (–), Gelucire® 50/13 (■), Hybrane S1200 (▲). The concentration of glimepiride was in all solid dispersions 5% (w/w). In the case of Hybrane HA1690, the granulate was prepared by spraying the solution containing glimepiride and HB polymer S1690 in weight ratio of 5/95 onto lactose particles (×).

glimepiride solubility and therewith associated dissolution rate were ascribed to interaction of glimepiride with poly(esteramide) HB polymers. Faster dissolution rate of solid dispersions based on HB polymers compared to that of solid dispersions based on conventional materials (PEG 6000 and Gelucire® 50/13) could also be a consequence of the branched structure and presence of a high number of polar functional groups (hydroxyl or tertiary amine) in HB polymers. These intrinsic features of HB polymers are known to enhance their solubility as compared to conventional materials (PEG 6000, Gelucire® 50/13).

From the results *of in vitro* dissolution measurements we estimated the amount of glimepiride complexed with particular HB polymer (loading capacity) in solid dispersions (Table 2). The maximum loading capacity of glimepiride for both HB polymers is around 5% (w/w) meaning that HB polymers of different chemical composition, i.e., Hybrane S1200 or Hybrane HA1690 do not show any significant differences. Only solid dispersions containing 2% (w/w) of drug show lower complexation efficiency as compared to other samples. This is most probably a consequence of a very high polymer concentration which prevents complete dissolution of the drug (the so-called matricial effect) (Suttiruengwong et al., 2006; Pignatello et al., 2001).

The comparison of dissolution profiles of solid dispersions made of glimepiride and HB polymer S1200, and granulates prepared by spraying the solutions containing dissolved HB polymer S1200 and glimepiride onto lactose inert particles shows that the incorporation of lactose into final formulation does not affect the solubility characteristics of glimepiride (Fig. 6). These results confirmed that solubility of glimepiride is improved by formation of solid dispersions or granulates based on HB polymers due to complexation of glimepiride with poly(esteramide) HB polymers.

Table 2
Calculated amount of glimepiride complexed with particular HB polymer (loading capacity).

Type of HB polymer	Glimepiride in SD[a] (%, w/w)	Dissolved glimepiride in 60 min (μg/mL)	Loading capacity (%, w/w)
Hybrane S1200	2.0	2.74	1.3
	5.0	4.05	4.6
	7.0	2.91	4.6
	10.0	2.02	4.6
	12.0	1.63	4.4
	20.0	0.92	4.2
Hybrane HA1690	2.0	2.80	1.3
	5.0	4.40	5.0
	20.0	0.92	4.2

[a] SD = solid dispersion.

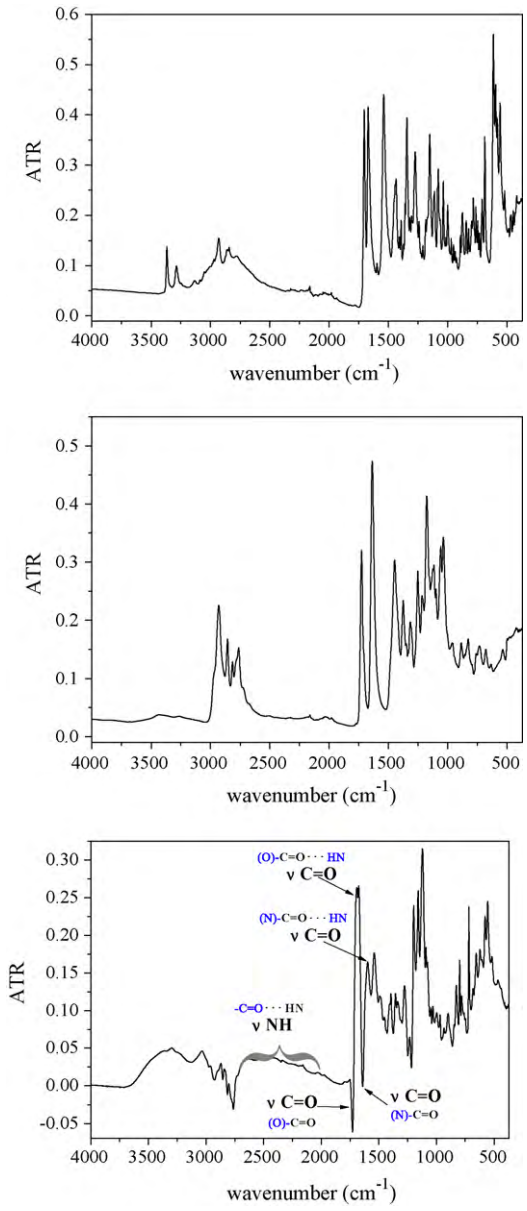

Fig. 10. ATR spectra of glimepiride and Hybrane HA1690 (upper and middle spectrum). Typical bands are assigned in Table 3. Bottom spectrum presents the difference spectrum obtained by the subtraction of pure HB polymer spectrum from the spectrum of solid dispersion containing HB polymer and 5% glimepiride. The changes due to H-bond formation between glimepiride and HB polymer are marked with arrows.

3.3. IR-spectroscopy

The most elegant way to study the interactions between the polymer and the drug by infrared light is the application of ATR technique. Since the light penetration depth was reproducible and comparable for all studied samples, the ATR spectra were suitable to study the spectral changes caused by polymer–drug interactions.

The band frequencies retrieved from glimepiride, Hybrane HA1690 and Hybrane S1200 ATR spectra are given in Table 3. The ATR spectra of glimepiride and Hybrane HA1690 are presented in Fig. 10 (upper and middle spectrum). The interactions between glimepiride and HB polymers in solid dispersions were studied using difference spectroscopy. The ATR spectra of pure HB polymers were subtracted from the spectra of solid dispersions containing glimepiride and HB polymer in weight ratio of 5/95% (w/w). The

Table 3
The frequencies of the most intense bands in ATR spectra of Glimepiride, Hybrane HA1690, and Hybrane S1200.

Glimepiride		Hybrane HA1690		Hybrane S1200	
Assign.	ATR (cm^{-1})	Assign.	ATR (cm^{-1})	Assign.	ATR (cm^{-1})
νNH	3368, 3287			νOH	Broad 3375
H-bonded NH	Broad ~2900				
νC=O	1703	ν(O)–C=O	1726	ν(O)–C=O	1728
Amide I	1670	ν(N)–C=O	~1636	ν(N)–C=O	1616
Amide II	1539	δCH	1447	δCH	1448
$\nu_{as}SO_2$	1344	νC–O	1176	νC–O	1176
$\nu_{s}SO_2$	1151				

difference spectrum for Hybrane HA1690 is presented in Fig. 10 (bottom spectrum).

The most prominent changes in the infrared spectrum due to interactions between Hybrane HA1690 and glimepiride are the appearance of a broad absorption with the centre at ~2450 cm^{-1} and red shifts of ν(O)–C=O and (N)–C=O bands (Fig. 10). The appearance of the negative band at 1725 cm^{-1} and positive at 1691 cm^{-1} is the result of frequency downshift of the (O)–C=O stretching band of Hybrane HA1690. Similar frequency shift is observed for (N)–C=O stretching, which shifts from 1636 cm^{-1} to 1598 cm^{-1}. Such frequency shifts are characteristic for hydrogen bond formation. Further evidence for hydrogen bond formation caused by complexation between the drug and HB polymer is a broad absorption of the NH stretching band near 2450 cm^{-1}. Significant broadening and shifting of the NH stretching band to lower wave numbers (~2450 cm^{-1}) announce the presence of relatively strong hydrogen bonds in glimepiride/Hybrane HA1690 complex (Michael, 1999; Joesten and Schaad, 1974).

Similar difference spectrum was obtained by subtracting the pure spectrum of Hybrane S1200 from its complex with glimepiride. The red shift of the (O)–C=O and (N)–C=O stretching band and the appearance of the broad absorption due to hydrogen bonded NH groups are also present in this type of difference spectrum. In the regions characteristic for vibrations of hydroxyl groups of Hybrane S1200 functional groups no noticeable changes were observed, meaning that hydroxyl groups do not participate in H-bonding.

The observed changes in both infrared difference spectra imply the existence of hydrogen bonds between the NH groups of glimepiride and carbonyls of ester (O)–C=O and amide (N)–C=O groups of Hybrane polymers. The type of hydrogen bond formation between the drug and HB polymer is similar in both Hybrane polymers. From the presented results we can conclude that HB polymers serve mainly as a source of proton acceptor groups to which NH groups of glimepiride establish hydrogen bonds.

4. Conclusion

In the present work we studied and evaluated two commercially available hyperbranched poly(ester amide)s, Hybrane S1200 and Hybrane HA1690, as solubilization enhancers for poorly water-soluble antidiabetic drug glimepiride. We prepared solid dispersions of glimepiride and hyperbranched poly(esteramide)s as well as solid dispersions of glimepiride and conventional inactive ingredients, poly(ethylene glycol), and stearoyl polyethylene glyceride (Gelucire® 50/13). The comparison of the results of *in vitro* dissolution studies showed that solid dispersions based on poly(ester amide) hyperbranched polymers showed significantly enhanced aqueous solubility of glimepiride and its dissolution rate as compared to pure glimepiride in crystalline or amorphous form as well as its solid dispersions with conventional inactive ingredients.

The loading capacity for both hyperbranched polymers was estimated to be around 5% (w/w) of glimepiride. Solid dispersions containing higher amounts of glimepiride appear to be oversaturated, so that non-complexed glimepiride crystallizes as a separate solid phase during the solvent evaporation.

The results of X-ray diffraction study suggest that glimepiride is in amorphous form within solid dispersions containing HB polymer. IR results indicated that glimepiride form complex with hyperbranched poly(esteramide)s through hydrogen bonds between the NH groups of glimepiride and carbonyls of ester (O)–C=O and amide (N)–C=O groups of hyperbranched polymers. Therefore, the improved glimepiride solubility was ascribed to complex formation between glimepiride and poly(esteramide) hyperbranched polymers.

Glimepiride poor aqueous solubility and slow dissolution rate may lead to irreproducible clinical response or therapeutic failure due to subtherapeutic plasma drug levels. From the economical point of view, low oral bioavailability results in wasting of a large portion of an oral dose and adds to the cost of drug therapy, especially in the case of expensive drugs. The hyperbranched polymers used in the present work proved to be very effective in the dissolution of glimepiride. The development of the final dosage form and *in vivo* studies shall be the course of the future work. Before that, a number of important factors for applying these hyperbranched polymers in the field of pharmacy such as toxicity and biocompatibility need to be tested.

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References

Ammar, H.O., Salama, H.A., Ghorab, M., Mahmoud, A.A., 2006a. Formulation and biological evaluation of glimepiride–cyclodextrin–polymer systems. Int. J. Pharm. 309, 129–138.

Ammar, H.O., Salama, H.A., Ghorab, M., Mahmoud, A.A., 2006b. Implication of inclusion complexation of glimepiride in cyclodextrins-polymer systems on its dissolution, stability and therapeutic efficacy. Int. J. Pharm. 320, 53–57.

Ammar, H.O., Salama, H.A., Ghorab, M., Mahmoud, A.A., 2007. Inclusion complexation of glimepiride in dimethyl-β-cyclodextrin. Asian J. Pharm. Sci. 2., 44–55.

Bansal, S.S., Kaushal, A.M., Bansal, A.K., 2007. Molecular and thermodynamic aspects of solubility advantage from solid dispersions. Mol. Pharm. 5, 794–802.

Brabender, E.M.M., Meijer, E.W., 1993. Poly(propylene imine) dendrimers: large-scale synthesis by hetereogeneously catalyzed hydrogenations. Angew. Chem. Int. Ed. Engl. 32, 1308–1311.

Buhlein, E., Wehner, W., Vögtle, F., 1978. "Cascade"- and "Nonskid-Chain-like" syntheses of molecular cavity topologies. Synthesis 2, 155–158.

Dritsas, G.S., Karatasos, K., Panayiotou, C., 2008. Investigation of thermodynamic properties of hyperbranched poly (ester amide) by inverse gas chromatography. J. Polym. Sci. B: Polym. Phys. 46, 2166–2172.

Fahr, A., Liu, X., 2007. Drug delivery strategies for poorly water-soluble drugs. Expert Opin. Drug Deliv. 4, 403–416.

Fini, A., Moyano, J.R., Gines, J.M., Perez-Martinez, J.I., Rabasco, A.M., 2005. Diclofenac salts. II. Solid dispersions in PEG6000 and Gelucire 50/13. Eur. J. Pharm. Biopharm. 60., 99–111.
Florence, A.T., 2005. Dendrimers: a versatile targetting platform. Adv. Drug Deliv. Rev. 15, 2104–2105.
Fréchet, J.M.J., 1994. Functional polymers and dendrimers: reactivity, molecular architecture, and interfacial energy. Science 263, 1710–1715.
Frick, A., Möller, H., Wirbitzki, E., 1998. Biopharmaceutical characterization of oral immediate release drug products. In vitro/in vivo comparison of phenoxymethylpenicillin potassium, glimepiride and levofloxacin. Eur. J. Pharm. Biopharm. 46, 305–311.
Froehling, P., 2004. Development of DSM's Hybrane(®) hyperbranched polyesteramides. J. Polym. Sci. A 42, 3110–3115.
Froehling, P., Brackman, J., 2000. Properties and applications of poly(propylene imine) dendrimers and poly(esteramide) hyperbranched polymers. Macromol. Symp. 151, 581–589.
Gao, P., 2008. Amorphous pharmaceutical solids: Characterization, stabilization and development of marketable formulations of poorly soluble drugs with improved oral absorption. Mol. Pharmaceutics 5, 903–904.
Gillies, E.R., Frechet, J.M.J., 2005. Dendrimers and dendritic polymers in drug delivery. Drug Discov. Today 10, 35–43.
Hilden, R.L., Morris, K.R., 2004. Physics of amorphous solids. Minireview 93, 3–12.
Hult, A., Johansson, M., Malmström, E., 1999. Hyperbranched polymers. Adv. Polym. Sci. 143, 1–34.
Ilić, I., Dreu, R., Burjak, M., Homar, M., Kerč, J., Srčič, S., 2009. Microparticle size control and glimepiride microencapsulation using spray congealing technology. Int. J. Pharm. 381, 176–183.
Iwata, M., Nagase, H., Endo, T., Ueda, H., 1997. Glimepiride. Acta Cryst. C 53, 329–331.
Joesten, M.D., Schaad, L.J. (Eds.), 1974. FTIR Hydrogen Bonding. Marcel Dekker Inc, New York.
Kerč, J., Srčič, S., Kofler, B., 1998. Alternative solvent-free preparation for felodipine surface solid dispersions. Drug Dev. Ind. Farm. 24, 359–363.
Kolhe, P., Misra, E., Kannan, R.M., Kannan, S., Lieh-Lai, M., 2003. Drug complexation, *in vitro* release and cellular entry of dendrimers and hyperbranched polymers. Int. J. Pharm. 259, 143–160.
Liu, C., Deasi, K.G., 2005. Characteristics of rofecoxib-polyethylene glycol 4000 solid dispersion and tablets based on solid dispersions. Pharm. Dev. Technol. 10, 467–477.
Luna, B., Feinglos, M.N., 2001. Oral agents in the management of type 2 diabetes mellitus. Amer. Farm. Phys. 63, 1747–1756.
Malmström, E., Hult, A., 1997. Hyperbranched polymers: a review. J. Macromol. Sci. Rev. Macromol. Chem. Phys. 37, 555–579.
Michael, S. (Ed.), 1999. FTIR Szycher's Handbook of Polyurethanes. CRC Press.
Mishra, M.K., Kobayashi, S., 1999. Star and Hyperbranched Polymers. Marcel Dekker, New York.
Narang, A.S., Srivastava, A.K., 2002. Evaluation of solid dispersions of clofazimine. Drug Dev. Ind. Pharm. 28, 1001–1013.
Narendra, K.J., Gupta, U., 2008. Application of dendrimer–drug complexation in the enhancement of drug solubility and bioavailability. Expert Opin. Drug Metab. Toxicol. 4, 1035–1052.
Newkome, G.R., Moorfield, C.N., Baker, G.R., 1992. Building blocks for dendritic macromolecules. Aldrichim. Acta 25, 31–38.
Okonogi, S., Puttipipatkhachorn, S., 2006. Dissolution improvement of high drug-loaded solid dispersion. AAPS Pharm. Sci. Technol. 7, 1–6.
Palmieri, G.F., Wehrle, P., Martelli, S., 1998. Interactions between lonidamine and β- or hydroxypropyl-β-cyclodextrin. Drug Dev. Ind. Pharm. 24, 653–660.
Pignatello, R., Ferro, M., De Guidi, G., Salemi, G., Vandelli, M.A., Guccione, S., Geppi, M., Forte, C., Puglisi, G., 2001. Preparation, characterization and photosensitivity studies of solid dispersions of diflunisal and Eudragit RS100® and RL100®. Int. J. Pharm. 218, 27–42.
Seedher, N., Bhatia, S., 2003. Solubility enhancement of Cox-2 inhibitors using various solvent systems. AAPS Pharm. Sci. Technol. 4, 1–9.
Seedher, N., Kanojia, M., 2009. Co-solvent solubilization of some poorly soluble antidiabetic drugs. Pharm. Dev. Technol. 14, 185–192.
Serajudin, A.T.M., 1999. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. 88, 1058–1066.
Sethia, S., Squillante, E., 2002. Physicochemical characterization of solid dispersion of carbamazepine formulates by supercritical carbon dioxide and conventional solvent evaporation method. J. Pharm. Sci. 91, 1948–1957.
Sunder, A., Heinemann, J., Frey, H., 2000. Controlling the growth of polymer trees: Concepts and perspectives for hyperbranched polymers. Chem. A Eur. J. 6, 2499–2506.
Suttiriuengwong, S., Rolker, J., Smirnova, I., Arit, W., Seiler, M., Lüderitz, L., Perez de Diego, Y., Jansens, P.J., 2006. Hyperbranched polymers as drug carriers: microencapsulation and release kinetics. Pharm. Dev. Technol. 11, 55–70.
Tomalia, D.A., Baker, H., Dewald, J.R., Hall, M., Kallos, G., Martin, S., Roeck, J., Ryder, J., Smith, P., 1984. New class of polymers: starburst-dendritic macromolecules. Polym. J. 17, 117–132.
Wysowski, D.K., Armstrong, G., Governale, L., 2003. Rapid increase in the use of oral antidiabetic drugs in the United States, 1990–2001. Diabetes Care 26, 1852–1855.
Yalkowsky, S.H., Roseman, T.J., 1981. Solubilization of drugs by co-solvents. In: Yalkowsky, S.H. (Ed.), Techniques of Solubilization of Drugs. vol. 12, 12. Marcel Dekker Inc, New York, NY, pp. 91–134.
Žagar, E., Žigon, M., 2002. Characterization of a commercial hyperbranched aliphatic polyester based on 2,2-bis(methylol)propionic acid. Macromolecules 35, 9913.
Žagar, E., Huskić, M., Žigon, M., 2007. Structure-to-properties relationship of aliphatic hyperbranched polyesters. Macromol. Chem. Phys. 208, 1379–1387.