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Original article

Oral Lipid Formulation Type IV as an Approach in the Formulation of Solid Dosage Forms with Poorly Soluble Substances: Chremophor®RH 40 as a Surfactant Phase

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Summary. The aim of this study was to investigate solid oral lipid formulations with poorly soluble substance gliclazide, using non-ionic surfactant Cremophor®RH40. The use of a new approach to the formulation of type IV of solid oral lipid formulations is described. Drug/surfactant solution was adsorbed on magnesium-aluminum metasilicate (Neusilin®UFL2) carrier with or without addition of super disintegrant and filled into hard gelatin capsules or compressed into tablets. In this way, a very fast and complete dissolution of poorly soluble drug is achieved. This study shown that with proper selection of ratio of drug/surfactant/adsorbent, with or without super disintegrant in formulation, it is possible to achieve rapid dissolving of poorly soluble drug from solid dosage forms.

Key words: Gliclazide; Cremophor®RH40; Oral solid lipid formulations; Neusilin®UFL2

Introduction

Gliclazide is used to treat type 2 diabetes, and has anti-radical, and anti- inflammatory effects (1). Gliclazide has poor water solubility and high inter-individual variations in absorption, limiting its application in type 1 diabetes (1). There are a large number of drugs that are poorly soluble in water, thus reducing the oral bioavailability. For improvement of the oral bioavailability of poorly soluble substances, lipid-based formulations are used. Lipid formulations are defined as mixtures of drug, oils, surfactants, and co-surfactants that are suitable for oral administration. Pouton classified lipid formulation according to the content of excipients in the so-called lipid classification system (2,3) (Table 1).

In the lipid classification system, mixture consisting of a drug, surfactants, and hydrophilic co-solvents, represents a Type IV lipid formulation. This lipid formulation is actually surfactant system, and does not contain in its composition

lipid components (even it is called "lipid"). Surfactant systems have significant solubilization capacity for a large number of poorly soluble substances, such as paclitaxel, tacrolimus, lorazepam, propanidid etc. (4,5).

In the formulation of surfactant system with insoluble drugs, the surfactant should have a high HLB (Hydrophilic lipophilic barrier) value in order to provide quick and easy dispersion, the formation of O / W emulsion and decreased precipitation of drug substance in the GIT (Gastrointestinal tract). Natural surfactants (lecithin, Akoline ®, medium chain monoglycerides (MCM), and Peceol ®) are safer, but their emulsification capacity is often worse than that of synthetic. Examples of surfactants used in oral lipid formulations are: Cremophor ® RH 40, Cremophor ® RH 60, MCM Campul ®, Gelucire ® 44/14, Labrafil M2125 ®, Tween ® 80 (6).

Table 1. Lipid Classification System (3)

Table 1: Lipid Classification System of excipient	**Composition of formulation(%,w/w)**				
	Type I	Type II	Type IIIa	Type IIIb	Type IV
Oil: triglycerides or mixed mono-and diglycerides	100	40-80	40-80	<20	-
Lipophilic surfactants (HLB<12)	-	20-60	-	-	0-20
Hydrophilic surfactants (HLB> 12)	-	-	20-40	20-50	30-80
Hydrophilic cosolvents (propylene glycol, PEG...)	-	-	0-40	20-50	0-50

To overcome disadvantages the liquid lipid formulations, solid formulations can be created by liquid adsorption on inert solid carriers (7). This approach has several advantages such as stability, facility of manufacturing process, dose accuracy and patient compliance. In recent years, various silica-based structures have been synthesized and analyzed as potential drug carriers in order to address problems of limited drug solubility, e.g., synthetic ordered mesoporous silica materials, MCM – 41 and SBA – 15 as well as magnesium-aluminum metasilicate carriers (8).

The main objective was to improve drug release rate of gliclazide, poorly soluble drug, in solid dosage forms (tablets or capsules), using lipid formulation type IV (according to Pouton's lipid formulation classification system). Lipid formulation type IV were prepared as drug/surfactant mixtures and subsequently absorbed onto solid carriers.

Materials and Methods

Materials

Gliclazide was used as a model drug; following surfactants/solvents were used: Labrafil®M 1944 CS, Labrafil®2130 CS, Labrafil® M 2125 CS (Gattefosse, France), Chremophor®RH40 (BASF, Germany) and Gelucire®44/14 (Gattefosse, France). Mixtures of drug and Chremophor®RH40 were adsorbed on Neusilin®UFL2 (magnesium-aluminum metasilicate, Fuji Chemical Industries, Japan). Finally, in some formulations Ludiflash® (BASF, Germany) as super disintegrant was added. All used excipients are intended for oral use and have no toxic effects.

Methods

In this study 14 formulations (either capsules or tablets) have been prepared according to Table 2. In a preliminary phase, surfactants were varied. Gliclazide was dispersed nonionic surfactants: Labrafil ® M 1944 CS, Labrafil ® M 2130 CS, Labrafil ® M 2125 CS, Chremophor®RH40, Gelucire®44/14 in ratio 1:20. When Chremophor®RH40 was selected as a surfactant phase, drug/Chremophor® RH 40 mixture was adsorbed on NeusilinUFL®2. Finally, super disintegrant has been added in different concentrations. All formulations, except formulations F8, F12, F13 and F14 were filled in capsules No 3. Formulations F8, F12, F13 and F14 were compressed into tablets.

Preparation of tablets

Mixtures of drug and excipients are compressed using appropriate compression force on tablet press in a way that each tablet formulation has tablet hardness 60 N.

Tablets were made by direct compression on the eccentric tablet press (Eco Korsch, Germany). Tablets weight was 550 mg, 13mm diameter.

Drug Release Study

In vitro dissolution study was performed using a rotating basket apparatus (Erweka DT600, Hausenstamm, Germany), in a phosphate buffer (pH 7.5, 900ml, 100 rpm). Samples were collected at 5, 10, 15, 20, 30 and 45 minutes. Individual samples were filtered through a membrane filter. The amount of substance released was determined by measuring the absorbance at a wavelength λ = 230 nm using UV/VIS spectrophotometer. The results are presented as the average

Table 2. Composition of formulation

Formulation	Surfactant	Adsorbent Neusilin UFL ® 2	Ludiflash
F1	Labrafil ® M 1944 CS	/	/
F2	Labrafil ® M 2130 CS	/	/
F3	Labrafil ® M 2125 CS	/	/
F4	Chremophor ® RH 40	/	/
F5	Chremophor ® RH 40	adsorbed on Neusilin ratio 1:1	/
F6	Chremophor ® RH 40	adsorbed on Neusilin ratio 1:1	10% added
F7	Chremophor ® RH 40	adsorbed on Neusilin ratio 1:1	20% added
F8*	Chremophor ® RH 40	adsorbed on Neusilin ratio 1:1	50% added
F9	Chremophor ® RH 40	adsorbed on Neusilin ratio 2:1	/
F10	Chremophor ® RH 40	adsorbed on Neusilin ratio 2:1	10% added
F11	Chremophor ® RH 40	adsorbed on Neusilin ratio 2:1	20% added
F12*	Chremophor ® RH 40	adsorbed on Neusilin ratio 2:1	50% added
F13*	Chremophor ® RH 40	/	80% added
F14*	Chremophor ® RH 40	/	95% added

*F8, F12, F13 and F14 are tablets

value of six replicates. As a reference, gliclazide release from commercial product was tested as well (Glioral® 80 mg tablets, Galenika, Serbia).

Results and Discussion

Gliclazide was dispersed or dissolved in non-ionic surfactants: Labrafil ® M 1944 CS, Labrafil ® M 2130 CS, Labrafil ® M 2125 CS, Chremophor ® RH 40, Gelucire ® 44/14 in ratio 1:20. Obtained dispersions were filled into hard gelatin capsules. Each capsule contained 80 mg of gliclazide.

Based on these results (Figure 1), it can be seen that the highest percent of gliclazide released was obtained with non-ionic surfactants Chremophor®RH40 and Gelucire®44/14. According to the lipid classification system these two solutions with non-ionic surfactants belong to the type IV surfactant systems. Formulation with Chremophor®RH40 was chosen for the further course of the experimental work.

The resulting solution (gliclazide: Cremophor® RH40, 1:20) was adsorbed on Neusilin®UFL2, which was translated into powder and filled into hard gelatin capsules. The ratio of the solution (gliclazide in Cremophor®RH40) and Neusilin®UFL 2 was 1:1 and 2:1. Figure 2 presents gliclazide release from formulations with Chremophor®RH40 (formulation F4) and adsorbed formulations (F5 and F9). Formulations with adsorbent showed less release of gliclazide comparing to the release of drug from the solution in Cremophor®RH40. Gliclazide release was faster when ratio of solution and adsorbent was 1:1. This suggests that the UFL Neusilin®2 probably tightly bounds gliclazide. Therefore, we added super disintegrant in formulation, in order to enhance the release of drug.

In the formulation of gliclazide solution in Cremophor®RH40, which is adsorbed on Neusilin® UFL2 in the ratio 1:1 and 2:1, super disintegrant

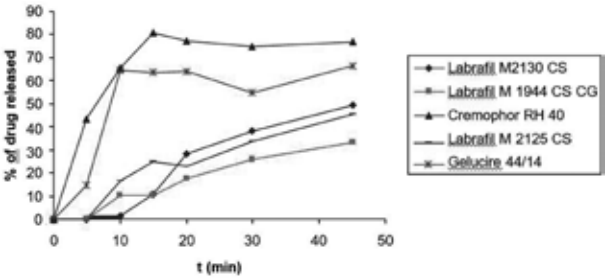

Figure 1. Gliclazide release profiles from formulations with different surfactants

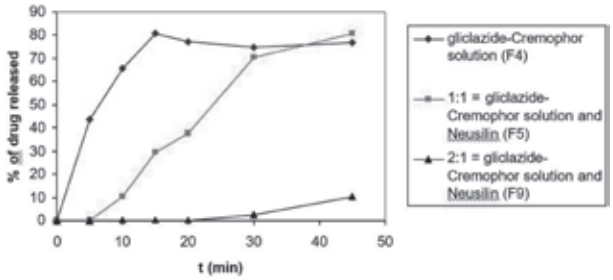

Figure 2. Gliclazide release profiles from formulations in which the adsorbent is present in different ratios and with absence of adsorbent (formulations F4, F5 and F9).

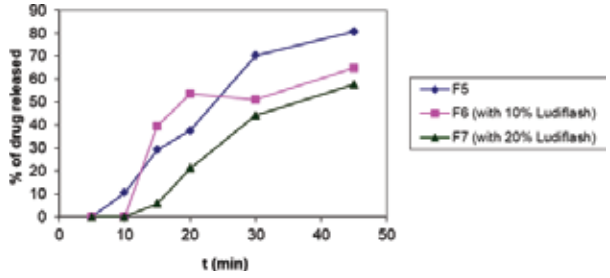

Figure 3. Gliclazide release profiles from formulations F5, F6 and F7.

was added at different concentrations: 10% and 20% and subsequently filled in hard gelatin capsules (formulations F6, F7, F10 and F11). Drug release profiles from these formulations are presented in Figures 3 and 4.

In formulation where gliclazide/Cremophor® RH40 and Neusilin®UFL2 are in the ratio 1:1, the higher percentage of drug release was obtained when 10% of Ludiflash ® was used, compared to the formulation in which the Ludiflash® is present at a concentration of 20%. This formulation shows better release even comparing to gliclazide solution in Cremophor®RH 40 (Figure 3).

When the ratio of gliclazide solution in Cremophor®RH40 and Neusilin®UFL2 was higher (2:1), obtained results showed that super disintegrant influence is extremely favorable (Figure 4). Increasing Ludiflash® concentration in the formulation, drug release increased.

Along with the preparation of hard gelatin capsules and tablets are prepared by direct compression. The formulations in which the ratio of gliclazide

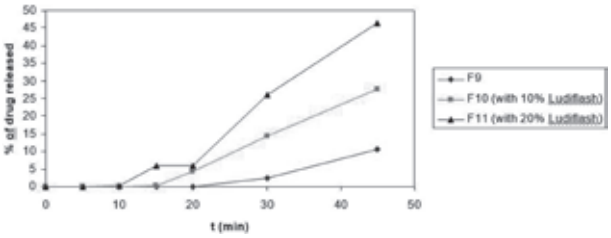

Figure 4. Gliclazide release profiles from formulations F9, F910 and F11.

Figure 5. Tablets appearance after in vitro dissolution test (left-formulation F8; right- formulation F12).

solution in Cremophor®RH 40 and Neusilin®UFL2 were 1:1 and 2:1, super disintegrant was added in concentrations of 50% (formulations F8, F12). The formulation F12, disintegrated after 45 minutes of in vitro dissolution test, while tablet formulation F8 remained unchanged (ratio of gliclazide in Cremophor®RH40 and Neusilin®UFL 2 was 1:1), as presented in Figure 5.

Comparing drug release from tablets and capsules (Figure 6) it was observed that a faster release of gliclazide was obtained from formulations filled into hard gelatin capsules, and that the only improvement in drug release from tablets occurs within the first 5 minutes of the experiment as a result of higher contact surface of tablet and media.

It is possible that there is a physical interaction between Cremophor®RH40 and Neusilin®UFL2 in tablet formulations where the ratio of the solution (gliclazide in Cremophor®RH40) and adsorbent Neusilin is 1:1 and 2:1, in the presence of 50% Ludiflash®, wich prolong release of drug. Therefore, tablets are prepared without Neusilin®UFL2. Gliclazide solution in Cremophor®RH40 was adsorbed on super disintegrant Ludiflash®, which is possible because it contains 90% mannitol. Tablets are manufactured with different concentration of Ludiflash®, 80.05% and 95% (F13 and F14, respectively). Drug release profiles from

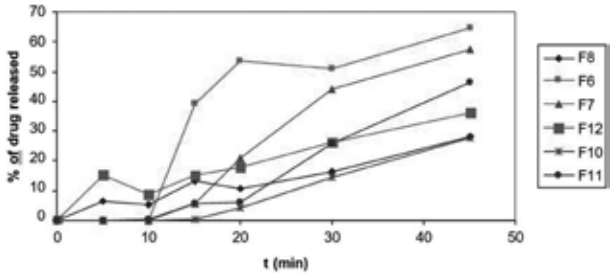

Figure 6. Drug release profiles from tablets (formulation F8 and F12) and capsules (formulations F6, F7, F10, F11).

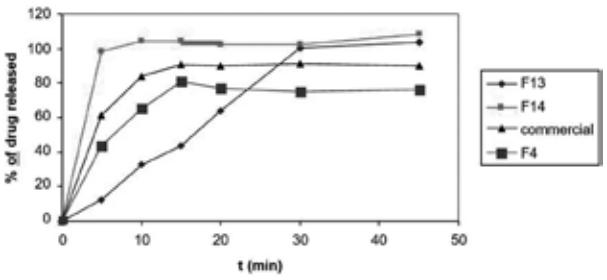

Figure 7. Gliclazide release from tablets (F13, F14), commercially available tablets and capsules filled with drug solution in Chremophor®RH40 (F4).

these tablet formulations, as well as from commercially available tablets and capsule formulation F4, are presented in Figure 7.

The fastest release was obtained with tablet formulation F14, where 95% of Ludiflash was applied in the formulation.

Conclusion

Obtained results showed that the formulations of gliclazide with non-ionic surfactant Cremophor®RH40, can significantly improve the dissolution rate. Excipients, such as Neusilin®UFL2 and Ludiflash® showed impact on the gliclazide release profiles. With proper selection of excipients, as well as their ratio, very fast and complete release of drug can be achieved. Gliclazide formulation in Cremophor ® RH 40 filled into hard gelatin capsules showed fast drug release. The highest release rate of the drug substance, with complete release of drug in the first few minutes, was obtained in the tablet formulation with high content of super disintegrant.

Obtained results showed that Neusilin ®UFL2, as well as combination of Neusilin®UFL2 and Ludiflash® can be used in capsule and tablet formulation with poorly soluble substances.

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