Drug bioavailability increasing by formulation of liquisolid systems

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Theoretical part

Bioavailability of drugs after oral administration depends on several factors such as aqueous solubility, drug permeability, dissolution rate, first-pass and presystemic metabolism or susceptibility to efflux mechanisms. Poor solubility and low permeability represent the most frequent causes of limited bioavailability for a number of drugs. The improvement of drug solubility remains one of the most challenging aspects of the drug development process especially for solid dosage forms designated for systemic absorption of the drug after oral administration[1]. Therefore, one of the most important and promising parts of modern pharmaceutical technology is focused on the formulation and evaluation of solid dosage forms with enhanced bioavailability of poorly soluble drugs. These drugs represent up to 40% of commonly used active substances and almost 70% of newly synthesized molecules. Different techniques have been described in the scientific literature to enhance the dissolution profile, the absorption efficiency and bioavailability of water insoluble and/or liquid lipophilic drugs. Reduction of the particle size via micronization or nanonization leading to increased surface area; use of surfactants; lyophilization; co-solvents use; self-emulsification and self-micro-emulsification; inclusion of APIs into cyclodextrins; use of pro-drugs and drug derivatization; formation of solid solutions or amorphous solids; microencapsulation and inclusion of drug solutions or liquid drugs into soft gelatine capsules or sealed hard shell capsules are some of the methods practically used to enhance dissolution characteristics of water insoluble or poorly soluble drugs[2–5].

One of the promising technologies of how to ensure sufficient bioavailability of drugs with limited water solubility, represents the preparation of liquisolid systems (LSS). The functional principle of these formulations is the sorption of drug in a liquid phase to a porous carrier (aluminometasilicates, microcrystalline cellulose, etc.). After addition of further excipients, in particular a coating material (colloidal silica), the powder with the properties suitable for conversion to conventional solid unit dosage forms for oral administration (tablets, capsules) is formed. The drug is subsequently administered to the GIT already in a dissolved state, and moreover, the high surface area of the excipients and their surface hydrophilization by the solvent used facilitates its contact with and release into the dissolution medium and GI fluids. This technology represents, due to its ease of preparation, an interesting alternative to the currently used methods of bioavailability improvement[6, 7]. Due to its advantages, a number of poorly soluble drugs (such as atorvastatin[8], carbamazepine[9], furosemide[10], indomethacin[11], etc.) have been formulated as liquisolid systems to ensure enhanced drug release and improved bioavailability of active ingredients.

Experimental part

The experimental study was focused on the preparation, *in vitro* testing and evaluation of differences of liquisolid systems with varying amounts of the liquid state containing hypolipidemic drug. Rosuvastatin was chosen as the model drug in the experiment. Rosuvastatin is a highly potent HMG-CoA reductase inhibitor which has one of the most positive effects on LDL and HDL cholesterol levels of all available statins. Rosuvastatin belongs to statins with greater hydrophilicity (also pravastatin), which have lower rates of passive diffusion and exhibit high rates of uptake only in cells such as hepatocytes that express active transporters with high affinity for organic anions. Consistent with its relatively hydrophilic character, rosuvastatin exhibits minimal metabolism via the cytochrome P450 (CYP) system, including little or no metabolism via CYP 3A4, the isoenzyme implicated in a wide variety of drug/drug interactions.

Propylene glycol (PG), polyethylene glycol (PEG) 200 and PEG 400 were used as non-volatile solvents, magnesium aluminometasilicates – Neusilin® US2 (SSA=300 m^2/g) and NS2N (SSA = 250 m^2/g) as carriers and colloidal silica as coating material. Crospovidone, croscarmellose and sodium starch glycolate were employed as disintegrants, and lactose, microcrystalline cellulose, calcium sulphate dihydrate and dibasic calcium phosphate dihydrate were used as fillers with the aim to ensure suitable disintegration of tablets prepared by direct compression and their optimal dissolution profiles.

The first part of the research was focused on the amount of the liquid (solution of rosuvastatin in PEG) which can be retained by Neusilin® US2, while maintaining good flowability and sufficient compressibility of the final blend. Several mixtures were prepared by simple blending or fluid-bed spraying, with different contents of drug solution (from 30% to 120%) in relation to the weight of Neusilin®. However, tablets containing more than 70% of liquid drug showed lower hardness and insufficient friability. Samples containing about 60% of the liquid

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were chosen for the next processing according to their values of hardness, friability, disintegration time and dissolution profile.

After finding of the optimal amount of the drug in the liquid state in relation to the amount of the carrier, properties of tablets were modified by changing of non-volatile solvents. During compression, it was observed that tablets containing PG showed the "liquid-squeezing out" phenomenon. On the other hand, blends containing PEG 200 can be compressed without observing this phenomenon. The maximum amount of rosuvastatin solution in PEG 200 which can be retained by Neusilin® US2 was higher in comparison with PEG 400 (up to 140%). Nevertheless, tablets with more than 80% of the liquid showed insufficient mechanical properties.

From the evaluation of tablets containing different types of the disintegrant it was observed that the optimal time for disintegration were shown by tablets with croscarmellose. A change in the filler has no significant effect on the properties of the final liquisolid tablets.

Neusilin® NS2N was also used as a carrier material. This type of Neusilin® can adsorb only 100% of the liquid vehicle in comparison with Neusilin® US2. However, the hardness of Neusilin® NS2N tablets was higher than the hardness of tablets with Neusilin® US2.

Nowadays, selected tablets are tested for their stability (20 °C/60% RH and 40 °C/75% RH). After 3 and 6 months no changes were observed in the properties and dissolution profiles of liquisolid tablets.

In the future, liquisolid systems containing lovastatin as the model drug will be prepared and liquisolid systems with the optimal composition will be evaluated also *in vivo*.

Conflicts of interest: none.

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