Formulation of an intravenous dosage form comprising a poorly water soluble antifungal agent

Doctoral theses

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Introduction

Joseph Carson, a professor at the University of Pennsylvania pointed out the importance of solubility of drugs as early as 1863 in the summary of his lectures entitled Materia Medica and Pharmacy. According to the summary every material has to be solubilized for it to get into the circulation. He also mentioned the possibility of solubilizing poorly soluble potent molecules.

His findings are still important and relevant, because a great portion of the newly synthesized molecules possesses poor water solubility. This characteristic of the drugs pose a substantial problem in respect of their applicability as therapeutic agents even though that researchers have been working to overcome this issue for a long time.

Furthermore, nowadays the number of poorly soluble drugs is on the rise and so is the need to solubilize these compounds in a pharmaceutically acceptable solvent/solvent system with the help of an adequate technique or excipients. Furthermore, increasing the solubility of an existing drug improves its bioavailability and effectiveness, which is not only relevant in respect of the therapy, but it may also lead to higher market share. The reformulation of existing drugs (supergenerics) gives further possibilities for therapeutic use and might also give patent protection. Another important factor is that reformulation is much more cost effective than synthetizing a new pharmaceutically active entity.

Formulating poorly water soluble drugs into liquid dosage forms was attempted by many scientists and numerous techniques were developed,
such as setting the pH, the use of cosolvents, surfactants and the formulation of liposomes or micro- and nanoemulsions.

It is very important to distinguish between the techniques that increase the apparent solubility of molecules and the methods that increase the equilibrium solubility of the drugs. Only the latter can be advantageously applied in the formulation of liquid dosage forms.

In case of parenteral dosage forms where the drug is administered in a way – directly into the blood stream – that it eludes the gastro-intestinal tract, the choice of an appropriate solubilizing technique requires special care. Certain methods can only be used with restrictions while others cannot be used at all because in such a composition the properties of the organism have to be also kept in mind besides the characteristics of the drug molecule.
Aims

The aim of my doctoral work was to formulate a liquid intravenous dosage form comprising a poorly soluble azole type molecule (itraconazole, ketoconazole, miconazole). The importance of my work lies in the fact that the model drugs can be used in the treatment of the ever growing number of systemic mycoses. Thus the formulation of the dosage form will expand the small choice of parenteral dosage forms which can be used in such illnesses.

An important aspect of my work is that the composition should comprise excipients which are acceptable in parenteral dosage forms both in view of their toxicity and technological applicability. My aim was to develop a combined system that comprises the lowest amount of excipients which is still able to solubilize the drugs. My further aim was to formulate the solvent system without excipients that may cause adverse effect, such as Cremophor EL which was used as a solubilizer for miconazole in a marketed dosage form.

My specific aims were:

1) to improve the solubility of azole type antifungals with the help of pH adjusters, cosolvents, surfactants and to dissolve the drugs in a therapeutically effective dose with the optimal combination of the solubilizers.

2) Following solubilizing my aim was to optimize the excipient content of the solvent system in respect of its risk/benefit ratio keeping in mind
that the solvent system should still be able to solubilize the desired drug in the desired concentration.

3) Sterility of the product is a must, therefore my aim was to determine the composition’s stability upon various sterilizing methods.

4) Furthermore my aim was to determine the stability of the composition upon storage.

Methods

During the solubility enhancement experiments miconazole was used as the model drug and the following excipients were applied as solubilizers:

- pH adjusters (gluconate, phosphate, ammonium acetate)
- cosolvents (propylene glycol, glycerol, macrogol, ethanol)
- surfactants (polysorbate 20, 60, 80)
- binary combinations (ammonium acetate + cosolvents; ammonium acetate + surfactants)
- ternary combinations (ammonium acetate + ethanol + polysorbate)

The solubility of ketoconazole and itraconazole was determined only in the ternary solvent system.

The optimization experiments – performed with miconazole and ketoconazole – were divided into three steps:

- decreasing the concentration of polysorbate
- decreasing the concentration ethanol
- studying the effect upon dilution.

Sterilizing studies were performed with the ternary composition containing miconazole. The effect of heat sterilization and membrane filtration was
assessed. Membrane filter tests were divided into static filter tests, membrane compatibility tests and bubble point tests.

At the end of development, photostability and accelerated stability tests (over 12 months) were performed with the ternary solvent system containing miconazole as model drug.

An HPLC-UV method was used for the determination of ketoconazole, itraconazole and miconazole with a Merck-Hitachi HPLC-UV equipment. The separation was performed on an Agilent Zorbax C8 (4.6 mm x 150 mm, 5µm) column. Isocratic elution was performed with the mobile phase consisting of 0.05 M acetate buffer (pH = 3.5) and methanol 30:70 at a flow rate of 1.0 ml/min.

An HPLC-MS/MS method was developed for the determination of impurities and degradation products. The studies were run on an Agilent 6410 Triplequad LC/MS in scan and product ion mode with electrospray ionization in positive status.

Results

In my theses I presented the development work which was undertaken in order to formulate a poorly water soluble azole type antifungal agent into a dosage form which can be administered intravenously.

New scientific results of the theses:
- The results of the solubility enhancement experiments show that all of the excipients used during development show good solubilizing
properties for azole antifungals. The solubility of two azoles, miconazole and ketoconazole can advantageously be modified with pH adjusters, cosolvents and surfactants.

- I discovered binary and ternary solvent systems that show synergistic solubilizing characteristics and that increase the solubility of both ketoconazole and miconazole. The most effective solvent system comprises 5 % polysorbate 80 + 25 % ethanol + ammonium acetate (pH 3.1). This system was capable of solubilizing 42.46 ± 1.45 mg/ml of miconazole and 158.53 ± 30.40 mg/ml of ketoconazole. The solubility value of miconazole is much higher than the solubility of the drug in the previously marketed formulation (10 mg/ml).

- I proved that through optimizing the composition of the solvent system the solubility enhancing effect of the formulation does not decrease, while due to the decrease of the concentration of excipients the toxicity of the composition probably decreases.

- Through further optimization the applicability of the formulation was tested with experiments concerning stability upon dilution. It was proved that the system remains stable upon dilution with various large volume parenterals. Using these results the final composition comprises polysorbate 80 and ethanol in the optimal concentration in view of their physiological acceptability and solubilizing power.

- It was shown that both autoclaving and membrane filtration – with certain restrictions – is adequate for sterilizing the composition. The appropriate choice of membrane filters was determined and it was shown that cellulose nitrate based filters are incompatible with the formulation.
A novel LC-MS/MS method was developed for the determination of impurities and degradation products in samples stored under UV and visible light. Beside the impurities and degradation products two products of unknown origin were also identified and their possible structure was also given.

A number of these degradation products and impurities were also detected in samples stored for 12 months under accelerated stability conditions (40°C, 75%RH). Since the amount of these compounds was very low and the active ingredient content was within limits, the results prove good stability of the formulation.
Discussion

Practical results detailed in the theses:

- A dosage form comprising miconazole or ketoconazole was developed, which after patenting is ready for industrial production.
- Numerous ternary solvent systems which are capable of solubilizing miconazole and ketoconazole and possibly other imidazole type antifungals were developed. The practical applicability of the composition is not restricted to parenteral administration since the formulation meets the requirements set for oral or topical administration too.
- The optimization experiments proved that by choosing the appropriate concentration of excipients, the risk/benefit ratio of the composition can be advantageously modified.
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Papers connected to the theses


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