Ezetimibe solid dispersions: technological and industrial development and validation

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INTRODUCTION AND AIMS

One of the main problems currently facing the pharmaceutical industry is that around 40% of the New Chemical Entities (NCE) are poorly soluble in water, a fact that may imply low bioavailability, which may impede the arrival of the compound on the market or force it to be overdosed.

These drugs are classified by the Biopharmaceutical Classification System (BCS) as Class II (low solubility and high permeability) or Class IV (low solubility and low permeability) and improving their oral bioavailability is one of the greatest challenges during drug development. One of the strategies used to achieve this goal is the preparation of solid dispersions. For this purpose, Spray-drying (SD) technology may be of interest to facilitate the optimization and reproducibility of the manufacturing process.

The aim of this study was to define a methodology to develop, scale up and manufacture efficiently, solid dispersions with the objective of improving the solubility of class II drugs according to the Biopharmaceutical Classification System (BCS). For this purpose, ezetimibe (BCS class II) was chosen as the model drug.

MATERIAL AND METHODS

PRE-FORMULATION	LAB-SCALE DEVELOPMENT	PRE-INDUSTRIAL DEVELOPMENT
Raw materials	*Solid dispersions prepared by spray drying (Buchi B290)*	*Solid dispersions prepared by spray drying (GEA Niro QSD 0.8)*

- Thermal analysis. (Differential scanning calorimeter (DSC)
- Impurity levels (HPLC)
- Assay test (HPLC)
- Dissolution studies (paddle method (USP Type II); 500 ml 0,1% SLS in 0.05 M acetate buffer, pH 4,5 at 37°C at 50 rpm; n=6)
- Solubility studies (Orbital shaker 500 ml 0,1% SLS in 0.05 M acetate buffer, pH 4,5 at 37°C at 50 rpm. Sampling time: 1h)
- Loss on drying test. (Performed at 105ºC until constant weight)
- Residual solvents (ethanol). (HS - HPGC)
- Particle size distribution (PSD). (Laser diffraction in a Mastersizer)
- Stabiility studies
- X-ray powder diffraction
- Rheological characterization

RESULTS

PRE-FORMULATION

After selecting a set of excipients, a drug - excipient compatibility study by DSC and HPLC analysis was carried out.

All the excipients selected, except PEG 6000 and Poloxamer 188 were compatible with the drug.

DRUG AND EXCIPIENT SELECTION AND COMPATIBILITY STUDY

Table 1. Excipients included in the study and their function.

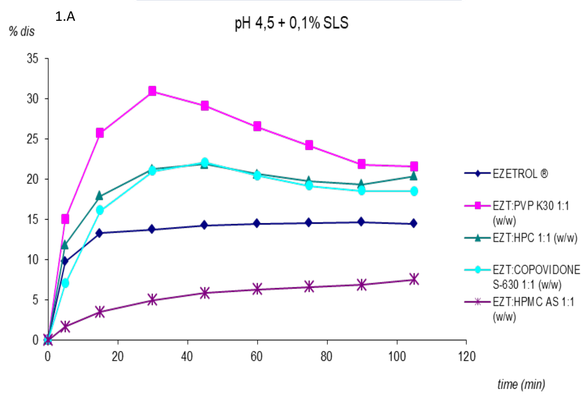
EXCIPIENT	FUNCTION	POLYMER	FUNCTION
Lactose (fast flo®)	Diluent	PVP K30	Carrier
Cellulose microcrystalline (Avicel PH 102 ®)	Diluent	Poloxamer 188	Carrier
Sodium croscarmellose (Acdisol®)	Disintegrant	HPMC AS (Aquasolve HG®)	Carrier
Crospovidone	Disintegrant	Copovidone (Plasdone S-630®)	Carrier
Colloidal silicon dioxide (Aerosil®)	Glidant	HPC (Klucel EF®)	Carrier
Sodium Stearyl Fumarate	Lubricant	PEG 6000	Carrier

LAB-SCALE DEVELOPMENT

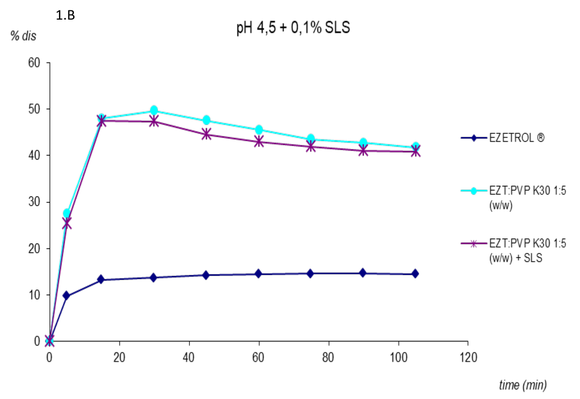
By carrying out dissolution tests on hard gelatine capsules containing minimally formulated spray-dried solid dispersions the effects of different polymers, drug: polymer ratio, the addition of surfactants and the concentration of the atomized solution were studied.

The results obtained are shown in figure 1.

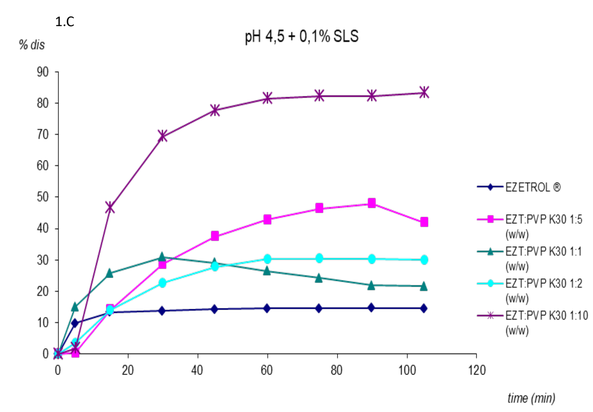
I. POLYMER SCREENING



II. BINARY vs TERNARY SCREENING



III. DRUG LOAD SCREENING



IV. FEED SOLUTION SCREENING

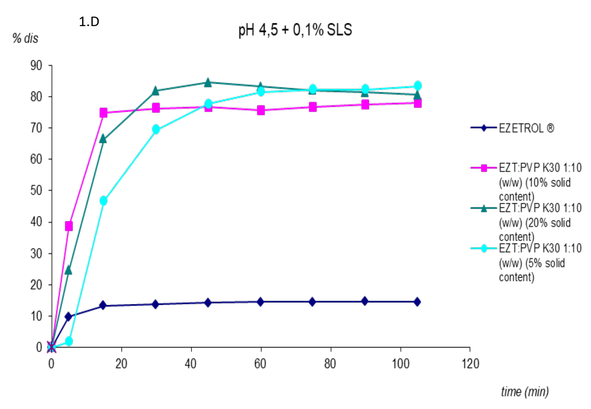


Figure 1. Comparison of dissolution profiles of solid dispersions with different polymers (drug: polymer 1:1 w/w) (1.A) with and without surfactant (1.B), different drug: polymer ratio (1.C) and obtained through solutions with different solids content (1.D).

The chosen polymer for further development was PVP K30 in an Ezetimibe : Polymer ratio of 1:10 (w/w).

It was concluded that the addition of a surfactant was not necessary and that the solution of the drug and the polymer in 96% ethanol can be concentrated up to 20% in solids content without observing significant negative effects on its dissolution properties.

PRE-INDUSTRIAL DEVELOPMENT

A full factorial Design of Experiments (DoE) of 3 factors and 2 levels with a central point (in triplicate) was carried out. The factors studied were the inlet temperature (120 and 150 ºC), the solids content (5 and 20%) of the solution and the feeding speed (40 and 80% of the peristaltic pump performance, corresponding to 1.6 and 3.2 L/h (approx.) respectively).

The results regarding solubility (% dissolved drug) and ethanol content (%) are shown in Figures 2 and 3. (P<0,05; Lack of fit> 0,05).

SPRAY – DRYING DESIGN OF EXPERIMENTS (GEA NIRO QSD 0.8)

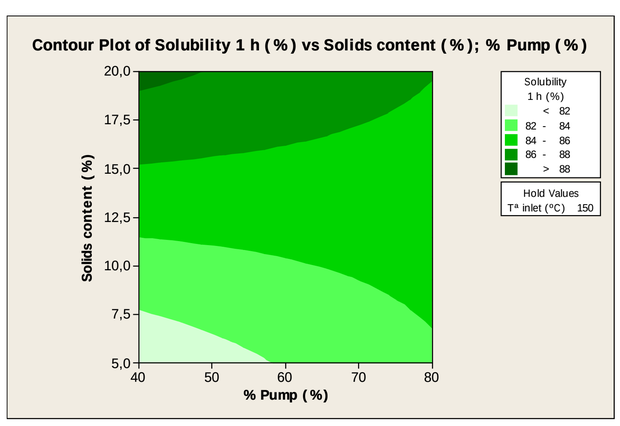


Figure 2. Contour plot of DoE solubility results as a function of solids content (%) and feeding speed at 150 ºC of inlet temperature.

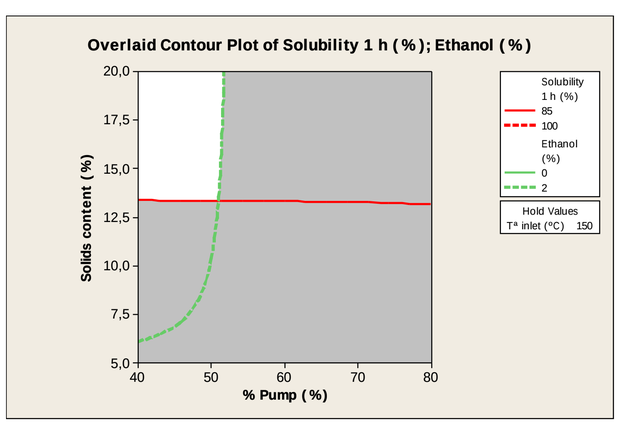


Figure 3. Overlaid contour plot of DoE solubility and residual ethanol results as a function of solids content (%) and feeding speed at 150 ºC of inlet temperature. The white zone indicates the work space where a solubility greater than 85% of the dose is achieved with an ethanol content below 2%.

It can be concluded that with an inlet temperature fixed at 150ºC and a solid content greater than 15%, a solid dispersion can be obtained that can dissolve more than 85% of the drug working at any feeding speed.

It can also be observed that to achieve these solubility values with a residual ethanol value less than 2%, the drying process should be carried out at less than 50% of peristaltic pump performance and the solution should contain at least a 13% of solids (approx).

CONCLUSIONS

All the excipients studied are suitable to be employed during development with the exception of PEG 6000 and Poloxamer 188, as they were shown to be incompatible with the drug.