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Self-emulsifying pellets prepared by wet granulation in high-shear mixer: influence of formulation variables and preliminary study on the in vitro absorption

Erica Franceschinis[a], Dario Voinovich[a,*], Mario Grassi[b], Beatrice Perissutti[a], Jelena Filipovic-Grcic[c], Anita Martinac[c], Francesco Meriani-Merlo[a]

[a] *Department of Pharmaceutical Sciences, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy*
[b] *EURAND, Research Department, Via del Follatoio 12, 34148 Trieste, Italy*
[c] *Department of Pharmaceutics, Faculty of Pharmacy and Biochemistry, University of Zagreb, A.Kovacica 1, 10000 Zagreb, Croatia*

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Abstract

A method of producing self-emulsifying pellets by wet granulation of powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and di-glycerides, polisorbate 80 and water, in a 10-l high shear mixer has been investigated.

The effects of the formulation variables on pellets characteristics were evaluated by mixtures experimental design and by a polynomial model, in order to describe the phenomenon, to verify eventual interactions among components of the mixture and to investigate the feasibility of scaling-up. After determination of size distribution, the pellets were characterised by scanning electron microscopy, dissolution and disintegration tests, and by in vitro absorption test

Such an approach, applied to the development of a self-emulsifying system for nimesulide as poorly water-soluble model drug, resulted in different formulations with improved drug solubility and permeability characteristics. The data demonstrate that pellets composed of oil to surfactant ratio of 1:4 (w/w) presented improvement in performance in permeation experiments.

Keywords: Pelletisation; High-shear mixer; Mixture experimental design; Self-emulsifying pellets; Intestinal permeability

1. Introduction

Self-emulsifying drug delivery systems are known to be useful for the improvement of oral bioavailability

* Corresponding author. Tel.: +39 040 5583106; fax: +39 040 52572.
E-mail address: vojnovic@univ.trieste.it (D. Voinovich).

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of poorly water soluble drugs (Constantinides, 1995; Humberstone and Charman, 1997). In particular, they are able to self-emulsify rapidly in the gastro-intestinal fluids, forming, under the gentle agitation given by gastro-intestinal motion, fine O/W emulsions. In such a system, the lipophilic drug is present in solution, in small droplets of oil. The large interfacial area generated by these small droplets, promotes drug diffusion into intestinal fluids (Pouton, 2000; O'Driscoll, 2002). Moreover, the emulsion droplets lead to a faster and more uniform distribution of the drug in the gastrointestinal tract, minimizing the irritation due to the contact between the drug and the gut wall (Charman et al., 1992; Shah et al., 1994; Khoo et al., 1998). In addition to the effects described above, the improved drug bioavailability could be partly ascribed to the effect of the monoglyceride components of such self-emulsifying systems, which are supposed to increase membrane permeability (Chicco et al., 1999)

Such systems are normally prepared as liquid dosage forms that can be administrated in soft gelatine capsules, which have some disadvantages especially in the manufacturing process (in-process controls), with consequent high production costs. An alternative method which is currently investigated by several authors, is the incorporation of liquid self-emulsifying ingredients (oil/surfactant/water mixture) into a powder in order to create a solid dosage form (tablets, capsules). Examples of such solid systems are pellets produced by extrusion/spheronisation, which can finally be incorporated into hard gelatine capsules (Newton et al., 2001) or the inclusion in microporous or cross-linked polymeric carriers (Chiellini et al., 2003).

The purpose of the present work was to investigate the feasibility to incorporate a mixture of mono- and di-glycerides, polysorbate 80 and water into a powder mixture of microcrystalline cellulose, lactose and nimesulide as water-insoluble model drug, in order to obtain self-emulsifying pellets using the 10-l Roto-J Zanchetta high shear mixer.

Formulations with different component ratios were investigated by mixture experimental design. The results were statistically analysed in order to evaluate the effects of formulation components on the granulometric characteristics of the pellets and to investigate the feasibility of scaling-up.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Microcel 101®, Faravelli, Milano, Italy); lactose monohydrate (Granulac 200®, Meggle, Wasserburg, Germany); mono- and di-glycerides (Cithrol GMO®, Croda, Singaphore); polysorbate 80 (Montanox 80 VG PHA®, Seppic, Castris, France) and nimesulide reagent-grade (Prodotti Gianni, Milano, Italy) were used as starting materials.

2.2. Experimental design and statistical analysis

Some experimental analyses were carried out with Roto-J, in order to value the feasibility of the wet granulation for the production of solid self-emulsifying systems. These analyses were used for the optimisation of process variables and for quality control of granulation characteristics. The resulting information allowed to extrapolating the quantitative limitations for each component of the mixture, obtaining an irregular experimental region, which represents only a restricted part of the study's area (Table 1 and Fig. 1a).

In order to explore the restricted region, an experimental strategy for mixture was followed; this strategy allowed to decrease the number of analysis and to achieve the optimisation of the system. The study's area can be represented in the mixture space by an ellipsoid with the following general Eq. (1):

$$\sum_{i=1}^{q}\left(\frac{x_i - x_{0i}}{h_i}\right)^2 \leq 1 \quad (1)$$

where x_{0i} represents the proportion of each mixture component for point x_0 (overall centroid of the

Table 1
Lower and upper limits of the formulation components

Components	Lower constraints (%)	Upper constraints (%)
Lactose (X_1)	16	24
Microcrystalline cellulose (X_2)	27	37
Water (X_3)	37.5	42.5
Polysorbate 80 (X_4)	2	8
Mono- and di-glycerides (X_5)	1	5