ELSEVIER

Il Farmaco 57 (2002) 349–353

IL FARMACO

www.elsevier.com/locate/farmac

Influence of processing conditions in the manufacture of O/W creams
II. Effect on drug availability

Nicola Realdon [a,*], Eugenio Ragazzi [b], Margherita Morpurgo [a], Enrico Ragazzi [a]

[a] *Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Padova, Via F. Marzolo 5, I-35131 Padova, Italy*
[b] *Department of Pharmacology, Faculty of Pharmacy, University of Padova, Via F. Marzolo 5, I-35131 Padova, Italy*

Received 28 December 2000; accepted 25 August 2001

Abstract

O/W creams prepared in three mechanical conditions (F with a hand blender; S turbomixer; T vacuum turbo-emulsor) produced different dispersion grades of the internal phase and different rheological characteristics by using surfactants of different chemical nature (polyoxyethylene-cetostearyl alcohols and polyglyceryl-3-methylglucose distearate). Three tests were used (an in vitro release test across a porous membrane; an in vitro simulated absorption test across a porous membrane impregnated with isopropyl myristate; an in vivo absorption test based on the intensity and duration of the erythema produced by methyl nicotinate after application of the cream on the skin) to assess whether the different physical characteristics influence drug availability from the creams. The different physical characteristics due to the mechanical conditions of emulsifying and gelification appeared not to influence drug release and in vivo absorption.

Keywords: O/W creams; Polyoxyethylene-cetostearyl alcohols; Polyglyceryl-3-methylglucose distearate

1. Introduction

In a previous work [1], we observed that the rheological characteristics of a formulation of lipogels may exhibit significant changes according to gelification conditions. The difference in in vitro drug release rate corresponded to differences in viscosity. In a successive work [2], a series of lipogels prepared in various gelification conditions and processed in different mechanical conditions produced significant differences in drug availability in vitro, in both release and simulated absorption tests, which was linked to the rheological characteristics of batches obtained in different operating conditions. Nevertheless, in the in vivo absorption test the rheological differences did not influence drug availability.

In the first part of this study [3], the same formulation of an O/W cream displayed different physical characteristics, particularly the rheological, when manufactured in different emulsifying conditions: using a hand blender (F), turbomixer (S) or vacuum turbo-emulsor (T). A microscope image analysis revealed different sized droplets of the internal oil phase and a different structure of the emulsion system. Compared with lipogels, the creams present further availability factors of the system, particularly the nature of the surfactant used, interface area and drug partition between emulsion phases.

In this second part of the work, the effect of the above parameters on drug availability was studied. Methyl nicotinate was used as the test drug. It was considered suitable for both the release and simulated absorption tests in vitro and the colorimetric determination of skin absorption in vivo because of the intensity and duration of the vasodilatation produced after application of the cream [4,5].

2. Experimental

2.1. Materials

The materials were the same as those used in the first part of the work [3].

* Corresponding author.
E-mail address: nicola.realdon@unipd.it (N. Realdon).

0014-827X/02/$ - see front matter
PII: S0014-827X(02)01214-4

2.2. Creams

The O/W creams used were the same as in the first part of the work [3], with the general composition as follows: Eutanol G (12.5), Cutina MD (10.0), glycerol [6], methylparaben (0.07), propylparaben (0.03), water (68.4). In the series: (A) creams, polyoxyethylene-cetostearyl alcohols (Eumulgin B1 and B2, 1:1) were used; and (B) polyglyceryl-3-methylglucose distearate (Tego Care 450), both at a concentration of 3%. Methyl nicotinate (20 mM) was used as the test drug.

The creams were manufactured in six batches in three different mechanical conditions: with a Philips hand blender (F), a Silverson turbomixer (S) and a Dumek vacuum turbo-emulsor (T).

2.3. In vitro drug release [2]

Samples of cream (ca. 35 g) were placed in six Perspex cells (90 mm diameter, 10 mm depth). A cellulose acetate dialysis membrane (Visking Tubing, London, UK), soaked in water for 20 h, was positioned on the surface of the samples. Each cell was placed in 2 l beaker containing 1 l phosphate buffer 1/15 M, pH 7.4, at 37 °C with continuous stirring (100 rpm). At 15 min intervals, 2 ml of diffusion fluid was drawn and the concentration of methyl nicotinate was determined spectrophotometrically at 263 nm.

2.4. In vitro simulated drug absorption [2]

The procedure for the release test described in Section 2.3 was used, except the membrane was formed of two different coupled membranes [6]: a cellulose mixed ester membrane (Millipore HAWP09000 type, 90 mm diameter) soaked by immersion for 1 h in isopropyl miristate [7–9], then wiped between two disks of filterpaper, and a cellulose acetate membrane (Visking) soaked in water for 20 h. The membranes were made to adhere well by using a rubber roller. The coupled membrane was placed with the cellulose membrane in contact with the cream sample.

2.5. In vivo drug absorption [2,4]

The extent of absorption of methyl nicotinate was estimated by calculating the intensity and duration of the erythema produced on the skin of volunteers with a X-Rite 918 tristimulus reflection colorimeter (X-Rite Inc., Grandville, MI, USA). The instrument measures surface colour and surface darkness/lightness by illuminating the site of interest. The detected signal is converted into the three co-ordinates (L^*, a^* and b^*) of a three-dimensional colour system recommended by C.I.E. (Commission International de l'Eclairage) in which L^* represents the value of darkness/lightness between black and white, a^* indicates relative chromaticity between red and green and b^* is the balance between yellow and blue. The erythema induced by methyl nicotinate on skin was expressed as parameter a^*. Measurements of a^* before cream application were considered as baseline values.

Samples of creams (0.5 g), covering an area of 2.25 cm^2 were applied to the volar forearm of healthy volunteers (age 24–30 years, four females and two males). After 15 min of application the excess lipogel was removed and the skin was gently washed with purified water (at 32 °C) and patted dry. The erythema produced was determined by subtracting baseline a^* from actual a^*. A parallel test for detecting erythema induced by the excipient itself was performed with a sample of cream without drug. No significant variation in redness compared with baseline was detected. Each determination was obtained as duplicate measurements repeated three times in the area of cream application. To evaluate the experimental data the area under the curve (AUC) was calculated for the time-course of erythema persistence from time 0 to 180 min after cream application.

2.6. Statistical analysis

Data were expressed as mean $\pm$ SD. The significance of differences was determined using an ANOVA, followed, when appropriate, by the Newmann–Keuls multiple comparison test. Differences were considered significant when $P < 0.05$ (two-tailed).

3. Results

Each of the batches manufactured in the three mechanical conditions F (hand blender), S (turbomixer) and T (vacuum turbo-emulsor) were subjected to the in vitro release test across a porous membrane to an acceptor aqueous phase in order to evaluate the ability of the creams to render the drug available for absorption. In vitro, the creams were also subjected to a simulated absorption test across a porous membrane impregnated with isopropyl miristate to investigate the mechanism by which the released drug penetrates the skin, as simulated by the lipoid barrier impregnating the membrane [5–8]. The same batches were tested in vivo for absorption on the basis of the intensity and duration of the erythema produced by methyl nicotinate after skin application of the cream sample [4].

3.1. Creams obtained with polyoxyethylene-cetostearyl alcohols

All characteristics of the creams and results of the tests are shown in Fig. 1. The size of the dispersed

droplets decreased as the mechanical energy used increased, proceeding from F conditions to S and T [3], that is as the degree of dispersion of the oil phase increased. At the same time, cream viscosity increased considerably.

The AUC values (% drug released × time) of the in vitro release test across a porous membrane of the different batches obtained in each of the three operating conditions, was not significant ($P < 0.05$) at ANOVA test. The corresponding AUC values of simulated absorption tests also demonstrated substantially analogous behaviour with no significant differences between operating conditions and batches ($P < 0.05$).

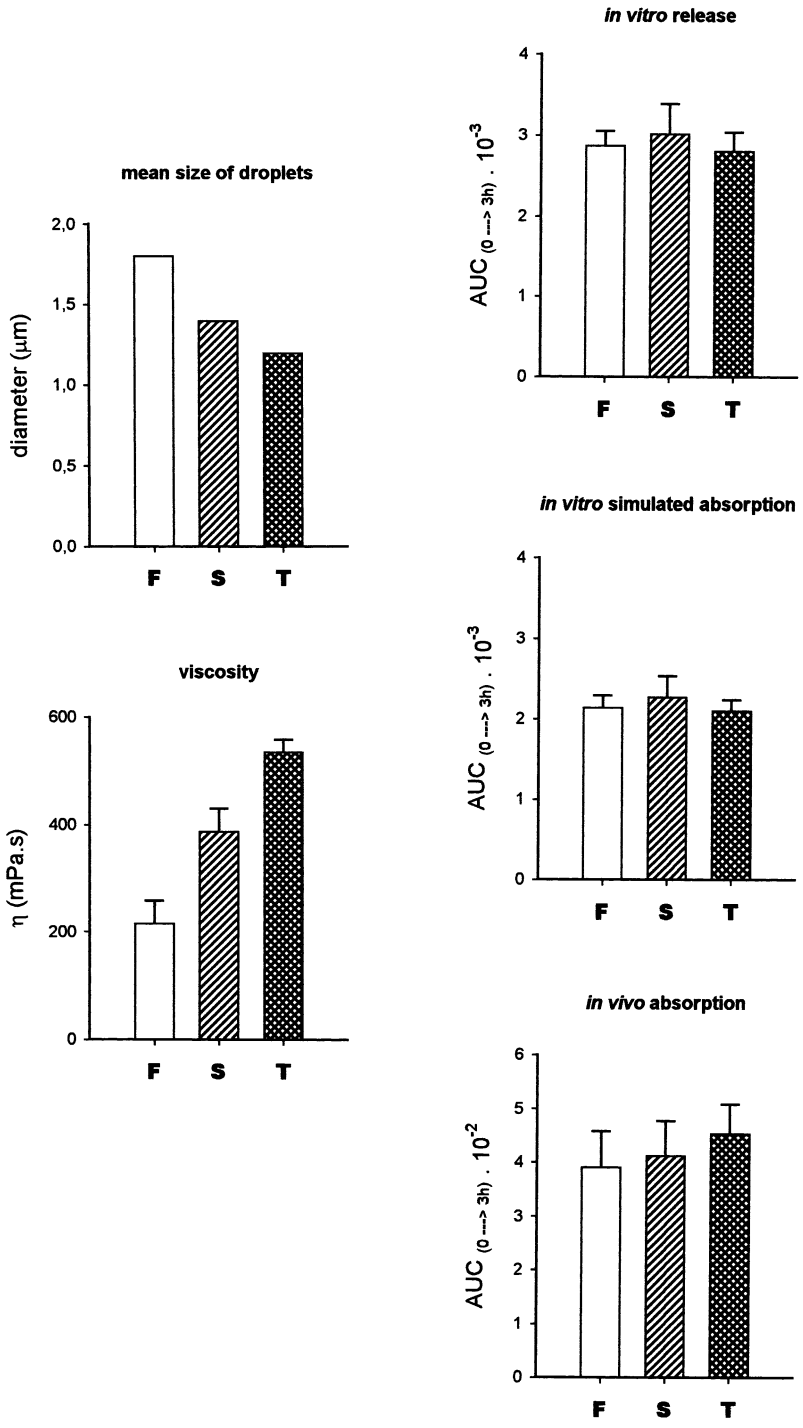

Fig. 1. Physical characteristics and mean AUC values of drug availability test results for creams prepared with polyoxyethylene-cetostearyl alcohols in the three manufacturing conditions F (hand blender), S (turbomixer), T (vacuum turbo-emulsor).

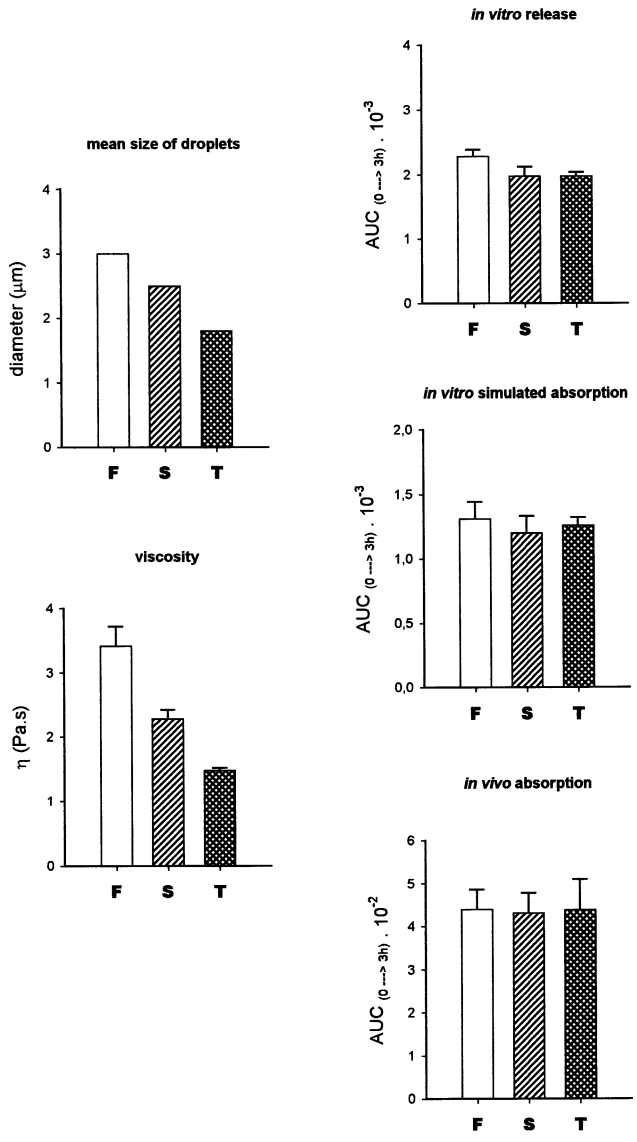

Fig. 2. Physical characteristics and mean AUC values of drug availability test results for the creams prepared with polyglyceryl-3-methylglucose distearate in the three manufacturing conditions F (hand blender), S (turbomixer), T (vacuum turbo-emulsor).

The results have therefore shown that droplet size of the dispersed phase and viscosity of the emulsion system affected neither drug release rate nor simulated availability through the skin.

The same creams were tested in vivo [4,5]. The AUC values of the intensity in time of skin erythema produced by the methyl nicotinate (a^* values × time) were compared with the ANOVA test. The difference between batches was not significant ($P < 0.05$), although the mean values of the batches prepared in T conditions was lower than those in the F and S conditions.

The in vivo test confirmed the in vitro tests, showing that differences in degree of oil phase dispersion and the rheological parameters due to different manufacturing conditions, did not affect drug availability.

3.2. Creams obtained with polyglyceryl-3-methylglucose distearate

The physical characteristics of the creams are compared with the results of availability tests in Fig. 2. As in the preceding case, an increase in degree of dispersion, with oil phase droplets becoming smaller and smaller, was observed proceeding from the F to S and T conditions. Viscosity, on the other hand, decreased compared to the structure of the system as indicated in the first part of the study [3].

The AUC values of the release curves were significantly higher ($P < 0.01$) for the batches prepared in F conditions (with larger droplets and higher viscosity). Release was lower and the same for the batches obtained in the two other conditions, S and T (with smaller droplets and lower viscosity). This confirms that viscosity of the emulsion does not produce an effect on drug release, or droplet size, even if the structure of the system cannot be considered extraneous. The results of the simulated absorption test were analogous. Nevertheless, differences between the various batches were not significant ($P < 0.05$). Differences between the results of the in vivo absorption test were likewise not significant.

In this second series of creams differences in degree of dispersion and viscosity were also evident. However, there was no practical effect on drug availability.

3.3. Effect of the surfactant chemical structure

The mean values of the results obtained from the two series of creams are compared in Fig. 3. The composition of the two series remained constant and differed only in type of surfactant, although in the same concentration. Differences in results of the tests carried out between series can be ascribed to the effect of the surfactant.

The most evident effect was found in viscosity. At the same concentration, polyglyceryl-3-methylglucose distearate produced viscosities five to six times higher. This is probably due to the binding of the surfactant which produces a more compact texture [10], as advanced in the first part of the study [3].

The differing results of the in vitro release test and simulated absorption tests may be linked to conspicuous differences in viscosity: drug diffusion rate should decrease with increasing viscosity. However, viscosity itself proved not to be determining since the differences in viscosity within each series did not correspond to significant differences in release rate or simulated absorption (see Figs. 1 and 2). Differences between the two series of creams could be ascribed to the structure of the emulsion system due to the nature of the surfactant.

In any case, the surfactant did not significantly modify absorption ($P < 0.05$) in vivo.

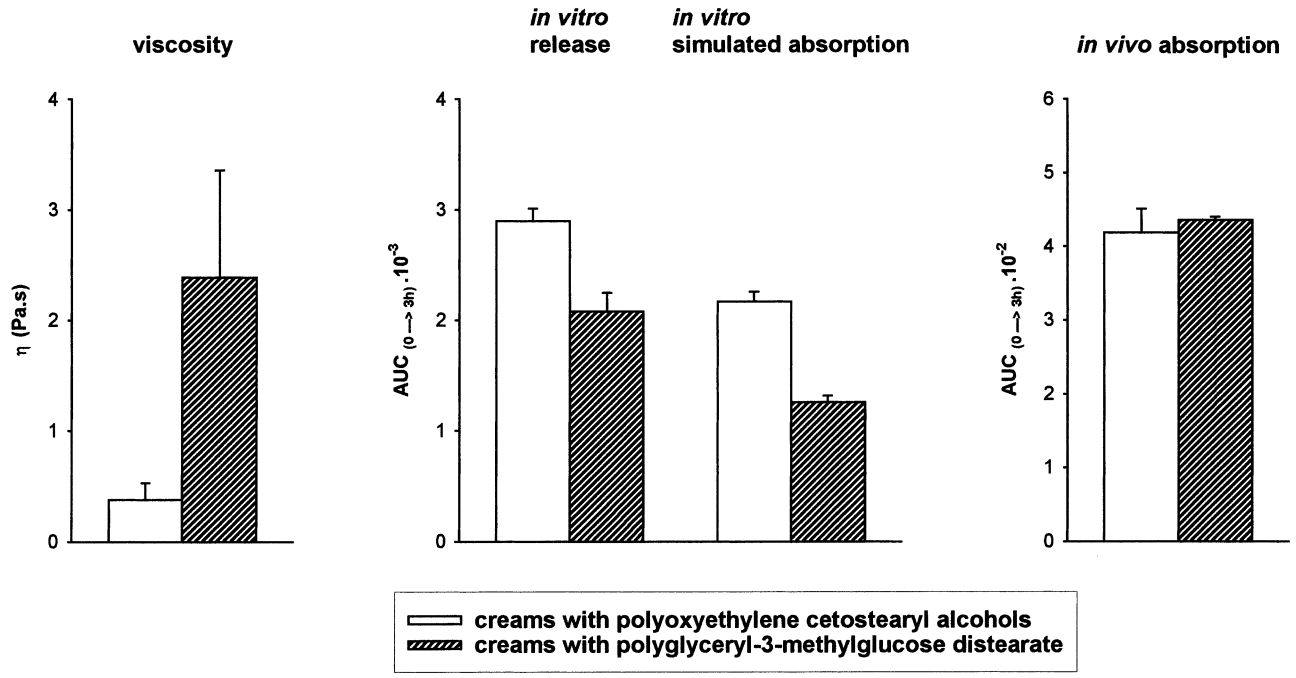

Fig. 3. Differences between mean viscosity values and mean AUC values of availability test results for creams obtained with the two different surfactants.

4. Discussion

The conditions of manufacture and gelification of a cream can greatly influence dispersed phase droplet size, structure of the system, and therefore the rheological characteristics [3]. Variations in these characteristics were also observed between batches obtained in the same technical conditions. In any case, the above-mentioned physical characteristics did not influence the release and absorption of the drug.

On the basis of the results obtained, if produced according to the drug bioavailability requirements, the same formulation could be manufactured as batches of any quantity, and using different machinery, without compromising the therapeutic response, even if the physical characteristics of the product change.

References

[1] N. Realdon, M. Dal Zotto, E. Ragazzi, G. Dalla Fini, Drug release from lipogels according to gelling conditions and mechanical treatment, Drug Dev. Ind. Pharm. 22 (1996) 125–134.
[2] N. Realdon, Eug. Ragazzi, Enr. Ragazzi, Effect of gelling conditions and mechanical treatment on drug availability from a lipogel, Drug Dev. Ind. Pharm. 27 (2001) 165–170.
[3] N. Realdon, Eug. Ragazzi, Enr. Ragazzi, submitted to Farmaco for publication 2001.
[4] N. Realdon, Eug. Ragazzi, M. Dal Zotto, Enr. Ragazzi, Influence of ointment formulation on skin erythema induced by nicotinate esters, Pharmazie 50 (1995) 603–606.
[5] N. Realdon, Eug. Ragazzi, M. Dal Zotto, Enr. Ragazzi, Kinetics of release and simulated absorption of methyl nicotinate from different ointment formulations: in vitro–in vivo correlations, Pharmazie 51 (1996) 113–116.
[6] H. Loth, A. Holla-Beninger, Studies on the drug release from ointments. Part I. Development of an in vitro release model, Pharm. Ind. 40 (1978) 256–261.
[7] J. Hadgraft, G. Ridout, Development of model membranes for percutaneous absorption measurements. I. Isopropyl myristate, Int. J. Pharm. 39 (1987) 149–156.
[8] J. Hadgraft, G. Ridout, Development of model membranes for percutaneous absorption measurements. II. Dipalmitoyl phosphatidylcholine, linoleic acid and tetradecane, Int. J. Pharm. 42 (1988) 97–104.
[9] P.G. Green, J. Hadgraft, M. Wolff, Physicochemical aspects of the transdermal delivery of Bupranolol, Int. J. Pharm. 55 (1989) 265–269.
[10] Goldschmidt Technical Report.