The role of dissolution testing in quality control

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Abstract

Semisolid systems (creams, gels etc.) for dermal application get more and more importance in pharmaceutical and cosmetic industry. However the number of methodologies for their physico-chemical characterization have been increasing; development of methods for the measurement of the active agent's release onto the skin surface is still a challenging task.

Beside measuring the amount of the active agent reaching the skin; dissolution testing (also called release testing) can be also a good indicator of product composition changes, therefore it can be used as quality control methodology.

The purpose of this study was to investigate the in vitro drug release of active agents from hydrogels, organogels, o/w and w/o creams, emulgels and w/o/w multiple emulsions for dermal use by means of the vertical diffusion cell methodology, for quality control purposes.

Keywords

semisolid systems · dermal use · dissolution test · drug release · QC control

1 Introduction

Dissolution studies are developed and are available mainly for solid dosage forms (tablets, capsules); different methodologies validated for these forms are detailed in the main Pharmacopoeias [1,2]. There is no compulsory method in any Pharmacopoeia for semisolid dosage forms; only two guidelines are available suggesting equipment for the measurement of drug release from these preparations. According to these guidelines and also based on literature data, drug release has been extensively investigated by means of the Franz cell diffusion system with a synthetic membrane [3-6].

The experimental conditions in drug release testing such as receptor phases, membrane-types, usage of different animal skin-models etc. depend on the purpose of the experiments; whether the aim is quality control or so called bioavailability testing in order to decrease the number of animal testing or eliminating them [7,8].

Concerning cosmetic products, the product behavior on the skin and also the release of the active agent content should be tested under in vitro conditions without animals; as the EU banned cosmetic testing on animals in 2009, therefore alternatives should be found for evaluation [9].

The following figure summarizes the role of drug release studies in case of semisolid dermal preparations (Figure 1.).

Predicting the practical applicability or changes within a given system with mathematical modelling [10,11] or different
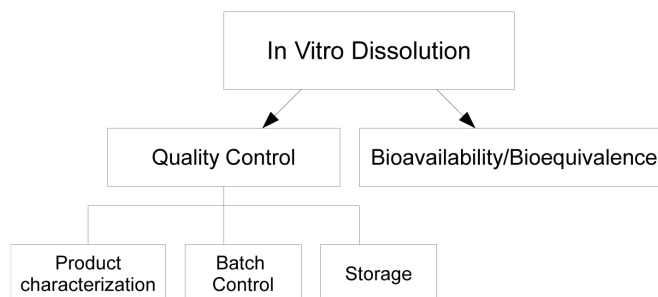
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Fig. 1. Application of dissolution testing in product characterization

experimental methods – such as this drug release/dissolution measurements has increasing importance nowadays. As seen on the Figure 1.; active agent release from a cosmetic or pharmaceutical product is an important quality indicator when (1) describing a given composition; (2) it's necessary to detect the effect of changes in components and manufacturing process; and (3) we have to follow up the changes during storage (stability testing). It can be also used as bioavailability testing in order to predict the „in vivo" performance of the developed product.

2 Aim

The aim of this study is to evaluate the applicability of drug release testing in following the composition changes in case of 17 cosmetic and pharmaceutical dosage forms. The in vitro drug release data in case of two active agents were measured from different vehicles (hydrogel, organogel, w/o and o/w creams, o/w emulgels and w/o/w multiple emulsions) for dermal use. The presented compositions were developed by our research group earlier [12,13].

3 Experiments
3.1 Compositions of the investigated products

The drug release process of 1.0 w/w% diclofenac sodium from different products (n=15) and 1.0 w/w% ketamine HCl containing systems (n=2) was measured through synthetic cellulose acetate membrane soaked in the receiving medium (Table 1, Table 2).

3.2 Drug release measurements

The Franz vertical diffusion cell system (Hanson Research Co.) containing 6 cells, and equipped with autosampler (Hanson Microette Autosampling System) was used for the drug release measurements.

The products were placed on the synthetic cellulose acetate membrane (Porafil, Macherey-Nagel, Germany) with pore size of 0.45 μm. The diffusion area was 1.767 cm^2. Experiments run at 32±0.5°C and 25±0.5°C (in case of w/o/w). 800 μl samples were taken after 0.5,1,2,3,4,5,6 hours. Phosphate buffer (pH 5.4±0.1) was chosen for receptor medium. Absorbance was measured by UV spectrophotometer (Unicam Helios α UV-Vis Spectrophotometer, England) at 275 nm and 269 nm (w/o/w). The blank agents without active agents served as references in the analytical method.

4 Results and discussion

The release profiles of hydrogels and w/o creams are illustrated in Figures 2-4.

Very low amount of active agent was released even after 6 hours of experiments in case of hydrogels and w/o creams. The difference in release rates between the 0.8 and 0.9 w/w% polymers containing products wasn't significant. A slightly

Tab. 1. Products containing 1 % diclofenac sodium

dosage form	composition	marked as:
hydrogel	polymer (Carbomer 934 P) content (w/w%): (1) 0.8 (2) 0.9 (3) 1.0	DSHG 0.8 DSHG 0.9 DSHG 1.0
organogel	gelling agent (sorbitan monopalmitate) content (w/w%): (4) 25.0 (5) 30.0 (6) 35.0	DSOG 25 DSOG 30 DSOG 35
o/w emulgel	polymer (Pemulen TR-2) containing aqueous phase (w/w%): (7) 40.0 (8) 45.0 (9) 50.0	DSGE 40 DSGE 45 DSGE 50
o/w cream	aqueous phase (w/w%): (10) 65.0 (11) 70.0 (12) 75.0	DSOV 65 DSOV 70 DSOV 75
w/o cream	aqueous phase (w/w%): (13) 40.0 (14) 45.0 (15) 50.0	DSVO 40 DSVO 45 DSVO 50

Tab. 2. Products containing 1 w/w% ketamine HCl

dosage form	composition	marked as:
w/o emulsion	(16) aqueous phase (w/w%): 75.0	w/o
w/o/w emulsion	(17) primary ((16)w/o emulsion) phase (w/w%):40.0	w/o/w

increased amount was released in case of 1 w/w% polymer content, which phenomena is due to the increased trietanolamine content, facilitating the diclofenac dissolution through the membrane.

Drug release from w/o creams is mainly driven by the diffusion capacity of the active agent through the compositions with slightly different viscosities (Figure 3.). No significant differences were found at this level of changes.

The following figure (Figure 4.) gives an overview about the release rates of some selected (based on the stability data) products from the different types. No significant differences in release rates were found in case of the following compositions: organogel containing 25.0 w/w% gelling agent (DSOG 25), the w/o cream with 45.0 w/w% internal water content (DSVO45) and the hydrogel product containig 1.0 w/w% polymer content (DSHG1).

The release rate from the emulgel with 45.0 w/w polymer containing water phase showed a slightly higher released acive agent amount after 6 hours, but still not evaluated as significant change. These compositions therefore, can be predicted to be equivalent in their „in vivo" performance; in spite of the fact, that they vary in composition and product type.

Significant difference from these products was found in case of the 75.0 w/w % external aqueous phase containing o/w cream (DSOV75).

Figure 5. shows the difference between the release rates of the primary w/o emulsion and a w/o/w product; after adding
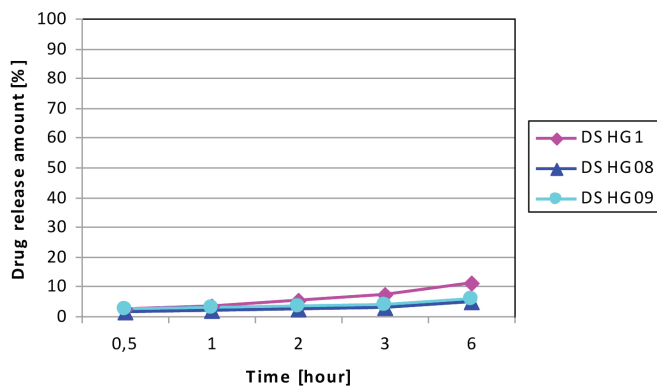
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Fig. 2. Drug release from hydrogels in case of different polymer content
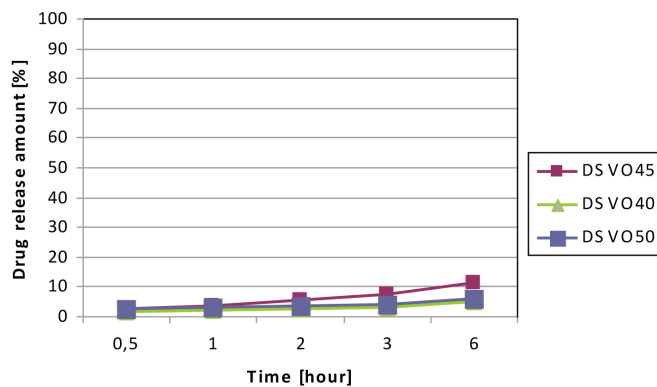

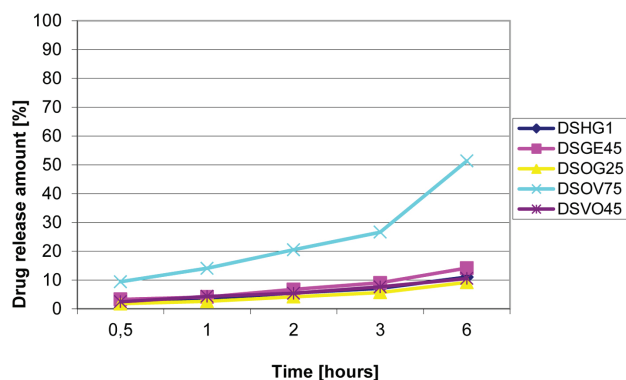**Fig. 3.** Drug release from w/o creams with different aqueous phase ratio

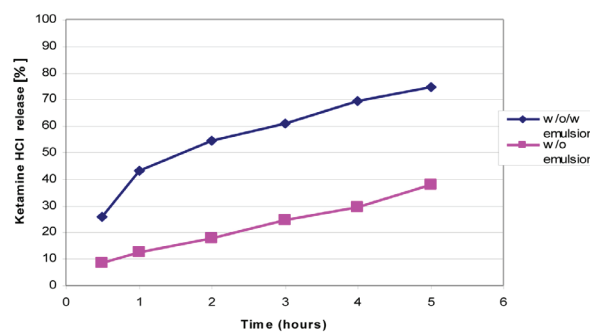**Fig. 4.** Drug release from different dosage forms

Fig. 5. Drug release from emulsions (primary w/o and the final w/o/w)

the external aqueous phase to the primary (w/o) one. The same amount of the active agent was incorporated into the aqueous phase of the primary; and in case of the inner and external water phases of the multiple emulsion. 75.0 % of the drug dissolved in the multiple emulsion released during 5 hours; while 37% from the primary simple one. The advantage of multiple emulsions for achieving faster drug release from its external phase, followed by a slower drug dissolution from the inner phases – could be detected.

5 Conclusions

Dissolution testing has an increasing role in case of all dosage forms in pharmaceutical dosage form design and development. Its applicability can be extended to cosmetic products as well; as alternative method instead of animal testing.

Different levels of product composition changes and "similarity" in case of different products can be detected only after a careful validation of the drug release measurement with Franz vertical diffusion cell system.

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