University of Szeged Faculty of Pharmacy
Institute of Drug Regulatory Affairs

Summary of PhD Thesis

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Regulatory evaluation of drug release from dermal semisolid dosage forms

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1. INTRODUCTION

In the pharmaceutical industry *in vitro* dissolution testing - which methodology has been established for solid dosage forms - is an important tool in both drug development and quality control (QC). Dissolution testing is frequently used also in the examination of other dosage forms and it is quite widespread in case of semisolid dosage forms.

Properties of and drug release from semisolid preparations have recently found the interest of researchers from application and regulatory perspective as well as regarding their effects on the skin. Although many *in vitro* methods are used for studying the penetration through the skin, moreover, guidelines and recommendations are also available, in contrast to solid dosage form testing, there are neither generally accepted pharmacopoeial methods available to date for their *in vitro* characterization nor adequate *in vivo* sampling techniques for their investigation.

The goal of regulatory authorities is reducing the number of animal studies and substitute their use with *in vitro* investigations. At present, *in vitro* studies are not required by regulators. Fundamental requirement for these studies is the establishment of the *in vitro-in vivo* correlation (IVIVC) posing a major challenge not only for solid, but also for semisolid dosage forms.

The guidelines mostly recommend the use of Franz vertical diffusion cell as the *in vitro* testing apparatus which is widely used by researchers as an analytical tool. However many critical points were observed in connection with the methodology itself such as the very low amount of receiving medium, the complicated tube system and the possibility of bubble formation. They emphasize the necessity to validate the method.

Another apparatus to study *in vitro* drug release from semisolid preparations has recently been offered. Hanson Research Company has extended its SR8-Plus Test Stations for a small-volume system. This device is an adaptation of the United States Pharmacopoeia (USP) Apparatus 2. It has a special small-volume vessel (Hanson Ointment Cell, modified holding cell) and a mini-paddle. The former includes a donor chamber for topical drug application. After mounting a selected membrane on the mouth of the chamber it is immersed in the receiving medium before starting the test.

The technical differences between the Franz vertical diffusion cell (which will referred to as Franz cell) and the modified holding cell - mini-paddle system (which will be referred to as the modified USP) are as follows:

- cell volume: 7 ml (which is most commonly used) *versus* 70 ml,
- sample volume: 800 µl (replaced with fresh receiving medium) *versus* 2.00 ml (not replaced),
- semisolid sample amount: 0.24-1.65 g *versus* 0.40-0.70 g,
- stirring rate: 450 rpm *versus* 100 rpm,
- sampling: automated *versus* manual.

The sample surface is 1.767 cm^2 in both cases.

For quality control and product development purposes, however, simple (non-impregnated), inert, porous synthetic membranes are recommended. In our study a cellulose acetate membrane of 0.45 µm average pore size was used with and without isopropyl myristate (IPM) impregnation.

2. OBJECTIVES

In order to filling the gap of regulatory requirements of semisolids, the aim of my thesis was the evaluation of drug release from dermal semisolid dosage forms with different testing methodologies.

The following purposes can be summarized:

- development of semisolid compositions,
- their comparison to reference (marketed) products,
- rheological study of semisolid dosage forms,
- biopharmaceutical evaluation of dermally used semisolids and
- verifying the results by statistical analysis.

The biopharmaceutical studies include:

- *in vivo* measurement of the anti-inflammatory effect of my compositions,
- *in vitro* drug penetration/absorption testing and
- *in vitro* drug release studies.

The *in vivo* data were compared to *in vitro* drug penetration and *in vitro* drug release ones to assess whether there is an *in vitro-in vivo* correlation or not.

The comparison of two *in vitro* dissolution methods, the Franz vertical diffusion cell and the USP method with modified holding cell was carried out. Performances of the two apparatus were studied.

The aim was:

- to investigate the release rates of diclofenac sodium (DS) from my bases and from the reference gels through synthetic membrane with the two equipments *in vitro*,
- to compare the drug release data generated by the two cells,
- to observe critical parameters and technical differences between the apparatuses and
- to evaluate the investigated pharmaceutical dosage forms with the use of similarity (f2) and difference (f1) factors.

3. MATERIALS AND METHODS

3.1. Materials

3.1.1. Active agent - diclofenac sodium

Because of its good tolerability administration of diclofenac, a non-steroidal anti-inflammatory agent is one of the most commonly prescribed drug worldwide.

The sodium salt of diclofenac, micronized diclofenac sodium (DS, sodium-[(dichlorophenyl)amino]-phenylacetate, complying with the European Pharmacopoeia [Ph.Eur.], TEVA-Human Co., Debrecen, Hungary) was chosen as a model hydrophilic drug.

3.1.2. Preparation of semisolid compositions

Different semisolid formulations were developed and investigated in my study, such as hydrogels, organogels, gel-emulsions, oil-in-water and water-in-oil creams.

The semisolids formulated in-house were compared to two marketed reference medicines. The **reference hydrogel (REF HG)** and the **reference gel-emulsion (REF GE)** were Diclofenac-Ratiopharm® (Ratiopharm Hungaria Ltd. Budapest, Hungary) and Voltaren Emulgel® 1% (Novartis Hungaria Consumers Healthcare Ltd., Budapest, Hungary), respectively and were purchased from Hungarian pharmacies.

3.2. Methods

3.2.1. Rheology

A HAAKE RS1 (Thermo Electron, Germany) rheometer was used with cone-plate configuration (1/35 TI). All measurements were carried out in triplicates at 25 ± 0.1 °C. Experiments were run in the shear rate range 0.1 - 100 1/s.

Controlled rate-ramp ($\Delta\gamma/\Delta t = 0.333$) was applied in up and down cycle and the result was recorded as $\tau = f(\gamma)$ rheograms and $\eta = f(\gamma)$ viscosity curves. Thixotropy was defined as the area between the up- and down curves [Pas/s]. Data were evaluated with RheoSoft 2.84.

3.2.2. Biopharmaceutical studies

3.2.2.1. *In vivo study*

Products for *in vivo* testing were selected based on my *in vitro* results. The gel-emulsions prepared in-house were not tested. A carrageen-induced oedema study was used to test *in vivo* efficacy of the formulations. The experiments were approved by the Animal Ethics Committee of the University of Szeged, Hungary (IV/01758-6/2008). Male Wistar rats (150-181 g) were used. All measurements were performed at 24 ± 1°C in an air-conditioned room. The animals were kept under standard 12 h light/12 h dark conditions with food and water *'ad libitum'*. All experiments were carried out in the same period of the day (1-4 p.m.) to exclude diurnal variations in pharmacological effects. Each rat was tested only once. One day prior to the application of the preparations, the back of each rat (15 cm^2) was carefully shaven and depilated by Veet® depilatory cream (Reckitt Benckiser, Massy, France) in 5 minutes under 2.5-3.5% isoflurane anaesthesia (Forane® solution, Abbott Laboratories, Budapest, Hungary). The skin of

the animals was cleaned by wiping with water containing cotton. The rats were dried under infrared lamp for 10 minutes.

On the day of the experiment, the animals were anaesthetized with Forane® solution and exposed to different test compositions. A 300 mg sample from each formulation was applied onto the depilated dorsal skin of the rat. Local inflammatory response was elicited by 0.1 ml subplantar injection of carrageen (Viscarin, Marine Colloids Inc., Springfield, USA) solution given into the right hand paw one hour after the treatment. The concentration of carrageenan solution was 0.5% which was prepared in a physiological saline solution. The left paw, used as the control, was treated without carrageenan. Paw volume was measured with a plethysmometer (Hugo Sachs Elektronik, March, Germany) 5 hours after the injection.

The volume differences between the carrageenan- and saline-injected paws were used for the evaluation of the inflammatory response.

3.2.2.2. *In vitro* study

3.2.2.2.1. Drug penetration/absorption study

Cellulose acetate membranes (Porafil, Machenerey-Nagel GmbH, Düren, Germany and Pall Life Sciences, Batavia, USA) with an average pore size of 0.45 µm were used. The area for diffusion was 1.767 cm^2. The penetration process from different bases (n=12) and 2 reference gels were measured through synthetic cellulose acetate membrane soaked in isopropyl myristate.

The receiving medium was to mimic the penetration through the skin surface and the *stratum corneum*. A phosphate buffer of pH 5.4 ± 0.1 (Orion Star pH, Thermo Electron Co., Singapore) was chosen as the receiving medium. Its temperature was maintained at 32 ± 0.5°C to reflect the usual external skin temperature.

The absorbances of the samples were measured by UV spectrophotometry (Unicam Helios α UV–Vis Spectrophotometer, Cambridge, England) at 275 nm and their diclofenac content calculated using a calibration curve. The blank ointment bases (compositions without DS) were also tested but, for their absorbance remained below 2% of those of the diclofenac containing samples throughout the experiments; the blank values were not taken into account.

The experiments were run in triplicate. The results, because of their calculated precision, as a general rule, were rounded to three digits.

3.2.2.2.1.1. Equipment

The **Franz vertical diffusion cell** system (Hanson Research Co., Chatsworth, USA) used contained 6 cells and equipped with an autosampler (Hanson Microette Autosampling System). The receptor chamber volume was 7 ml. The membranes, soaked previously in IPM (see above) were mounted on the top of the cells. A stirring rate of 450 rpm was set. Quantities of 0.24-1.65 g ointment samples (depending on the type and consistency of the different compositions) were placed evenly on the surfaces of the membranes. 800 µl samples were taken after 0.5, 1, 2, 3 and 6 hours and replaced with fresh receiving medium.

3.2.2.2.2. Drug release

Cellulose acetate membranes (Porafil, Machenerey-Nagel GmbH, Düren, Germany and Pall Life Sciences, Batavia, USA) with an average pore size of 0.45 µm were used. The area for

diffusion was 1.767 cm^2. The rates of release of the active pharmaceutical ingredient DS were studied by using non-impregnated, but soaked in phosphate buffer cellulose acetate membranes.

A phosphate buffer of pH 5.4 ± 0.1 (Orion Star pH, Thermo Electron Co., Singapore) was chosen as the receiving medium. Its temperature was maintained at 32 ± 0.5°C to reflect the usual external skin temperature.

The absorbances of the samples were measured by UV spectrophotometry (Unicam Helios α UV–Vis Spectrophotometer, Cambridge, England) at 275 nm and their diclofenac content calculated using a calibration curve. The blank ointment bases (compositions without DS) were also tested but, for their absorbance remained below 2% of those of the diclofenac containing samples throughout the experiments; the blank values were not taken into account.

The experiments were run in triplicate. The results, because of their calculated precision, as a general rule, were rounded to three digits.

3.2.2.2.2.1. Equipments

The **Franz vertical diffusion cell** system (see above, *3.2.2.2.1. Drug penetration and absorption study*) was used. Compared to drug penetration/absorption study the difference is, that the membranes, soaked previously in phosphate buffer (see above) were mounted on the top of the cells.

The **modified USP apparatus** was the SR8-Plus Dissolution Test Station (Hanson Research Co., Chatsworth, USA) with modified holding cell for semisolids. It was used for release studies exclusively. The apparatus contained 8 cells with 70 ml volumes. Quantities of 0.40-0.70 g samples were placed on the membrane surfaces of the small ointment sample holders which were then dropped into the glass vessels containing the receiving medium. The stirring rate was set to 100 rpm. 2 ml samples were taken manually after the same time intervals as described for the Franz cell.

3.2.3. Data and methods for statistical comparison

CIs are confidence intervals at 95% significance level ($p<0.05$). They could be calculated by using the simple method proposed by Shah et al.

In order to compare not fully linear experimental curves, I applied the studies of the dissolution from solid dosage forms where there are methods when not the apparent rate constants but the curves itself are compared. This is the utilisation of the difference (f1) and similarity (f2) factors.

4. RESULTS

4.1. Rheological characteristics of investigated products – hydrogels

The DS incorporation in the hydrogels did not influence the viscosity of the formulation remarkably. It could be established, that the structure of the hydrogels could be deformed slightly easily as the structure of the reference products (Figure 1). The flow, viscosity characteristics and yield value of the hydrogel samples were similar to the reference products. With decrease of the yield value and shear stress, the spreadability of the products increased, which effected a higher anti-inflammatory effect in therapy.

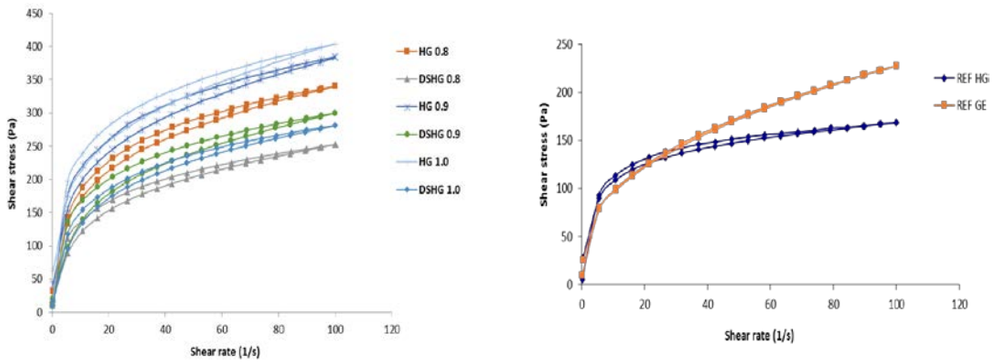


Figure 1a) Flow curves of hydrogels and **b)** reference products

4.2. Results of biopharmaceutical data

4.2.1. Evaluation of *in vivo* data

The carrageenan-induced oedema study was used to test *in vivo* efficacy of the formulations by me. Its results were then compared to the *in vitro* penetration and release rate data to evaluate IVIVC.

The data (average swelling %) are presented in an easy-to-compare way in Figure 2. Diclofenac sodium 1% (w/w%) in 40% and 45% w/o creams ($p<0.05$, labelled with *) exerts only a moderate oedema inhibition compared to the control group. One percent (w/w%) of the active ingredient DS incorporated in 50% w/o cream, in the o/w cream basements, in hydrogel and organogel preparations and in case of both marketed reference products showed to be efficient in comparison with the non-treated group ($p<0.001$, labelled with ***). The highest oedema swelling inhibition rate was measured in case of the 35% emulsifier containing organogel, which effect was more significant than both of the registered products. The lowest effect was observed in the 45% water containing w/o formulation.

Similar to a previous study of Csóka et al., I also found that our hydrogel samples showed to be efficient in the *in vivo* investigations.

In the *in vivo* experiments the average order of the preparations is as follows: reference gel-emulsion > hydrogels > organogels > o/w creams > reference hydrogel > w/o creams.

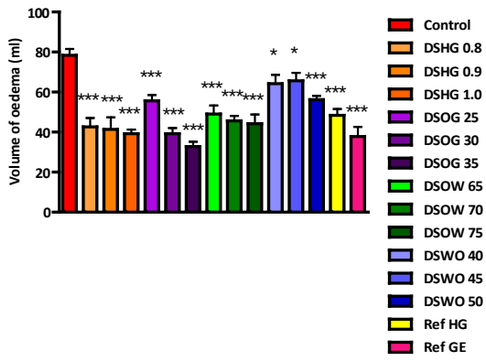


Figure 2 Anti-inflammatory effect of different preparations containing 1% diclofenac sodium on carrageenan-induced oedema in rats

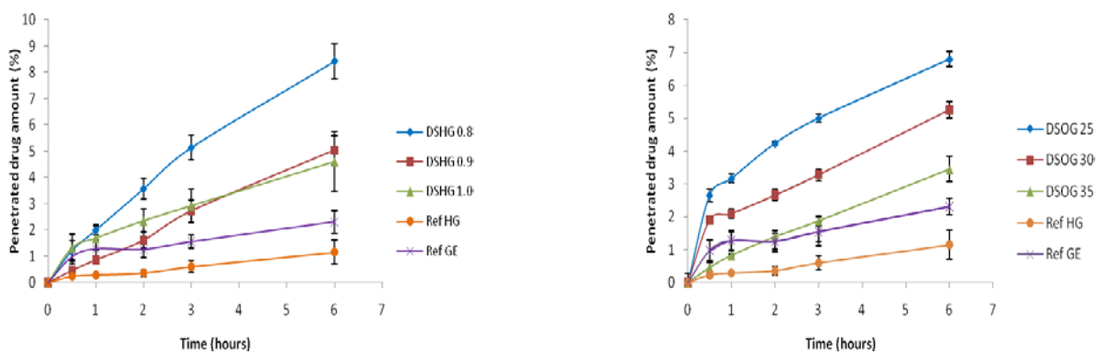
More than half of my developed products reached and exceeded the oedema decreasing effect of the reference hydrogel, and one preparation exceeded the value of reference gel-emulsion.

4.2.2. Evaluation of *in vitro* drug penetration/absorption data

Based on the *in vitro* penetration results many products could be excluded because of their low penetration rate, although they were effective in the *in vivo* studies.

The Franz diffusion cell was used.

Figure 3 shows the penetrated diclofenac sodium amounts (in percentages) against time through IPM soaked membrane.



a) **b)**

Figure 3a-b) Cumulative penetrated diclofenac sodium amounts through IPM soaked synthetic membrane plotted against time

It can be seen that all of my products reached the drug penetration level of the marketed (reference) gels (1.16% and 2.31% for reference hydrogel and reference gel-emulsion, respectively). The hydrogel samples containing the 0.8% polymer showed the highest *in vitro* penetration rate (8.41%) and the reference hydrogel was the last in the order.

The standard deviations (SD) were changing in the range from 0.46% (DSOG 25) to 2.29% (DSHG 1.0).

The penetration through the IPM soaked membrane decreased in the following order: hydrogels > organogels > w/o creams > o/w creams > reference gel-emulsion > reference hydrogel.

4.2.2.1. *In vitro* penetration – *in vivo* correlation

Moderate (x<0.90), significant (0.90<x) or no correlation at all were measured between the *in vitro* penetration results compared to that of *in vivo* efficiency studies with difference fitting.

Best IVIVC was established in case of IPM soaked membrane in o/w creams and in organogel samples in case of linear fitting and in o/w creams in case of power trend line fitting. IVIVC rate was not remarkable in w/o samples.

It can be concluded, that o/w creams had the best (0.9732 and 0.9714) and w/o creams the worst fitting (0.0403 and 0.0228) also in case of linear and power trend line fitting.

In contrast with the investigation of Csóka et al., in my experiments correlation was found between the *in vitro* penetration and *in vivo* data of organogels, o/w creams and moderate IVIVC was found in case of hydrogels.

Evaluating the data and IVIVC results I can offer our hydrogel and organogel compositions for clinical use.

4.2.3. Evaluation of *in vitro* drug release data

4.2.3.1. Characteristics of diclofenac release from semisolid preparations and its transport through cellulose acetate membrane

In my experiments the highest amounts dissolved were around 1100 and 2500 µg in the Franz cell and modified USP studies, respectively. Characteristic release curves (one composition each) are shown on Figures 4 (Franz cell method) and Figure 5 (modified USP method).

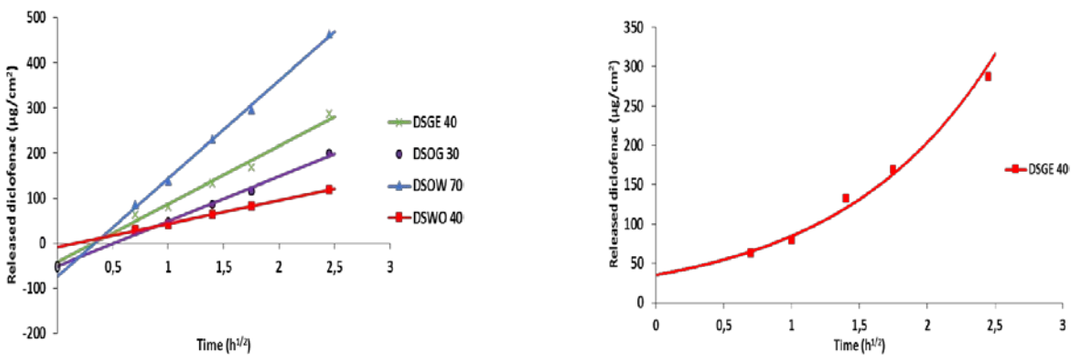


Figure 4a) Released diclofenac sodium with the Franz cell method
(the best linear fit and **b)** a non-linear, exponential best fit indicated)

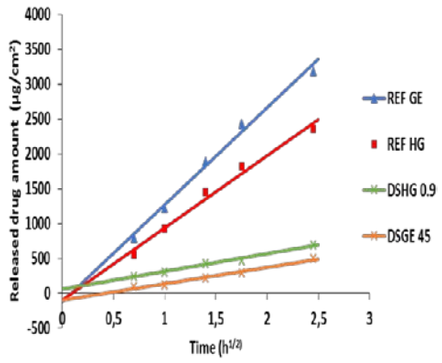


Figure 5 Released diclofenac sodium with the modified USP method
(the best linear fit indicated)

4.2.3.2. Statistical evaluation by comparing the CIs

The CIs of the apparent release rate constants were calculated and compared to those of the *in vivo* swelling % data.

The CIs are shown on Figure 6.

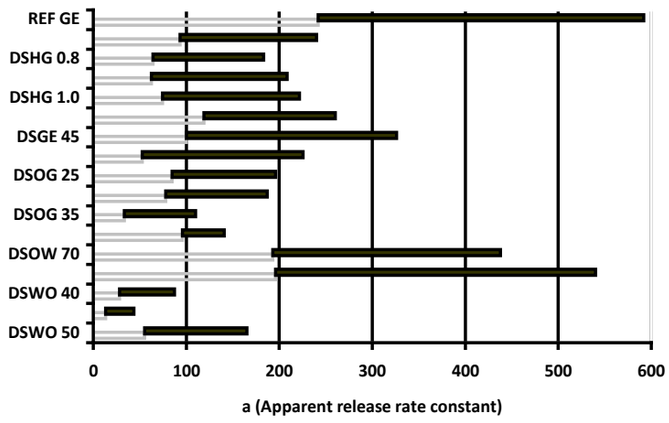


Figure 6 CIs of the apparent release rate constants in the Franz cell experiments

This evaluation of the data was done comparing the CIs looking for significant ($p<0.05$) differences. However, it resulted only in limited information, for the CIs of the *in vitro* results were quite wide.

4.2.3.2.1.Statistical comparison of release curves based on the difference and similarity factors

It should be remarked that the $f1_{rel}$ and $f2_{rel}$ values indicated the same results in all cases, i.e. when two curves were found "different" ($f1_{rel}>10$) then they were also "not similar" ($f2_{rel}<50$).

Use of these factors indicates the differences (non-similarities) of the experimental curves in a much more sensitive way than the CIs of the apparent release constants. Only the release curves of the DSHG series, when tested with the modified USP holding cell became "not different/similar".

4.2.3.3. *In vitro* drug release – *in vivo* correlation

In this part of the work the correlation between *in vivo* swelling % results and the average apparent rate constants or Q (cumulative amount [µg/cm^2]) of the diclofenac released in 6 hours) released values generated in the two *in vitro* dissolution methods was studied.

4.2.3.3.1. Correlation between the slopes (apparent release rate constants) and swelling data

When all data generated either with the modified USP or with the Franz cell method were correlated with the *in vivo* swelling % results, no correlation was found. Thus, neither of these two methods was predicting IVIVC, in general. The same is valid for the correlation of the two *in vitro* methods.

However, varying the concentrations of the components within one type of composition, a good correlation was be achieved between *in vitro*, generated by the modified USP method and *in vivo* data in the DSHG, DSOG and DSOW series. Similar findings, with a somewhat poorer correlation, can be observed with the Franz cell and *in vivo* data for the DSHG, DSOW and DSWO series. The IVIVC was the best for both *in vitro* methods in the case of the DSOW compositions. Only one of the two *in vitro* methods gave somewhat acceptable correlation in the case of the DSOG and DSWO preparations using the modified USP and Franz cell methods, respectively.

4.2.3.3.2. Correlation between Q and swelling data

Correlations for the cumulative amount dissolved in 6 hours (Q) data, as a rule, were much poorer that those for the slopes. The slope was determined by the whole curve characterizing the main release process.

5. SUMMARY

The aim of my research work was to study the drug penetration and release processes of semisolid dosage forms and to evaluate existing methods from regulatory points of view.

5.1. *In vitro* drug release from semisolid dosage forms

Results of my work:

- I compared the performances of the Franz cell and the modified USP holding cell in studies of drug release from semisolid dosage forms. To my knowledge, no such comparison was described in the literature before.
- I recognized that the release was not necessarily a fully diffusion controlled process, for the released amounts *versus* time$^{1/2}$ curves were not completely linear. To my knowledge this is a new finding in the literature. In order to overcome the above biases, first in the literature I applied the f2 similarity (and also f1 difference) factors (in their relative forms) to compare drug release curves from semisolid dosage forms.

5.2. *In vitro-in vivo* correlation

- My semisolid formulations were able to show anti-inflammatory effects and to decrease the carrageenan-induced oedema in rats. More than half of my products reached or exceeded the oedema decreasing effect of the reference (marketed) hydrogel.
- The clinical relevance of my findings might be that my hydrogel and organogel samples showed significant anti-inflammatory effects. Rheological characteristics of both formulations showed that they can be easily spread on the skin. They exceeded the value of the reference gel-emulsion and showed a significant IVIVC in the penetration studies. However, no correlation was found between the *in vitro* and *in vivo* results in case of reference gels.
- My experiments showed that when using a non-impregnated cellulose acetate membrane neither the modified USP nor the Franz cell is suitable to establish IVIVC although these *in vitro* and the *in vivo* qualitative pictures may coincide within given types of bases.

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Cumulative IF: 2.608

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