Summary of Ph.D. Thesis

Optimization and evaluation of topical used pharmaceutical organogels

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Szeged

2005

INTRODUCTION

Organogels are such gels based on nonaqueous liquid phase (e.g. oils). Several organic (cholesterol, hydrostearic acid) and inorganic (organoclays, fumed silica oxide) compounds were described and others were synthesized (polyethylene glycols, polyacrylates) as organogelator agents, and there are such organogelators which form gels only in the presence of water (lecithin, gelatine).

Organogels have been mentioned for a long while in different pharmacopoeias for suitable delivery of lipophilic drugs. In addition, in the nineties, since the discovery of novel, simple organogelator molecules which can be used in small quantities, the organogels were investigated for purpose of preparative chemistry, biotechnology, besides their application in pharmaceutical technology. Recently, several new-generation organogels have been described as effective vehicles for transdermal delivery, and they have also proved useful as ophthalmic and rectal vehicles.

Surfactant organogels are promising dermatological vehicles, since the non-ionic surfactant components are able to form gel-network, to modify consistency and to act as penetration enhancer. The advantage of these biocompatible products is their simple and economic preparation, and that the reduction of the number of the ingredients contributes to the less risk of skin irritancy.

OBJECTIVES

The investigations of the following phenomena were the objectives of my research:

- Development of novel surfactant organogels
- Investigation of the conditions and terms of the formation (*rheology*)
- Texture optimization according to the consumer's requirements (*rheology, sensory analysis*)
- Description of the structure and the stability (*light microscope ,oil number, rheology*)
- Investigation of the vehicle effect on the *in vitro* drug release (*vertical diffusion cell method*)
- Investigation of the vehicle effect on the drug bioavailability (*rat paw oedema test*)

The novel organogels were compared with some traditional organogels as regards to the above-mentioned viewpoints.

RESULTS AND DISCUSSION

Development of novel organogel compositions

The melt-type organogels arisen from the melted mixture of the various surfactant and oils on cooling, when the solubility of the surfactant was decreased and aggregates were formed, and the transparent sol become an opaque gel. Among the surfactant tested, the esters of stearylic acid were found to be the most effective gelators of both semipolar and apolar oils. About 50°C the stearate group undergoes a crystalline–amorphous transition, and on cooling recrystallise in aggregates which may serve as connecting points. Sorbitan and glyceryl monostearate (GMS) molecules have ideal geometry to form bilayers, which constitute rod-like aggregates (the structure elements of the gel-network).

Commercially available GMSs are obtained from different sources and by different methods, hence they have different composition regarding to the mono- and diester type and ratio. In my study, four GMSs and their organogels were investigated. The liquid phase selected for these glyceryl monostearate organogels (GMSOs) was a biocompatible oil, which can be absorbed easily from the skin and is penetration enhancer (Table 1).

The gelation process

Rheokinetic analysis of the GMSO formation was performed on the base of the Kolmogorov–Johnson–Mehl–Avrami equation, assuming that the reaction advance is proportional to the increase in the storage modulus, *G'* due to the increase in elastic active bonds within the colloidal network, and related to the aggregation.

Table 1. Composition and code of the organogels studied (% w/w)

Glyceryl monostearate organogels (GMSO)	Miglyol® 812 + 13% of Tegin® Pellets (G1), Tegin® 90 Pellets (G2), Tegin® M Pellets (G3), Imwitor® 900 (G4)
Silicoparaffin Ointment (SP), Unguentum silicoparafini – Hungarian National Formulary 6th Edition	
Oily Ointment (OL), Unguentum oleosum – Hungarian Pharmacopoeia 7th Edition	
Paraffin Ointment (PR), Unguentum paraffini – Hungarian Pharmacopoeia 7th Edition	
Simple Ointment (SX), Unguentum simplex – Hungarian Pharmacopoeia 7th Edition	

During the rheological oscillatory *temperature sweep*s (HAAKE RS1 rheometer, ThermoElectron, Germany), it was found that the start and the rate of the gelation are influenced by the surfactant type, and both of them are concentration-dependent.

Investigations of the texture properties

Changing the GMS amount (5 – 17%) resulted in great variety of consistency of the GMSOs from lotions to creams. These changes of the texture were reflected in the pronounced alteration of *viscosity*, *yield value*, *viscoelasticity* and *spreadability*.

In the sensory test performed upon the ASTM E–1114 Guideline, the trained panels found that 13% surfactant result in optimally firm organogels — independently of the surfactant type (*simple ranking test*), whereas the samples with 9% GMS were termed too soft and those with 17% too firm (*just right test*). As compared the rank sum of the samples to their rheological data, we could establish that τ_0 of approximately 20 – 30 Pa was defined as optimal in GMSOs by the panels.

As compared with the traditional organogels, G2 (evaluated as the best in the previous tests) had significantly better overall liking, macroscopic appearance and texture than those of OL, and the same finding was made in case of SP. The overall liking of G2 was significantly better than those of SX. Regarding to the skin feel there was no significant difference between the samples tested.

Characterization of the structure

Under light microscope (Zeiss, Germany) rod-like aggregates were observed in the GMSOs, which connected to each other and intermesh throughout the oil phase.

The shear rate dependence of GMSOs (*flow curves*) was described with the Cross model. In addition, the oscillatory rheological tests (*frequency sweeps*) demonstrated that GMSs (13%) resulted in a structure with moderate energy. The crystalline structure is fragile, but before a critical yield value shows elastic deformation (*stress sweeps*).

As compared with the traditional organogels, solid paraffin (PR) resulted in similar fragile crystalline structure than the GMSOs. However, the highly intermeshed networks of SX and OL (surrounded by fibres of Lanolin Alcohols and with amorphous wax) are more restricted, characterized with more viscous behaviour. The network of silica oxide (SP) is formed by interparticle hydrogen bonding due to the surface silanol group, which interaction reveals highly elastic behaviour.

Stability tests

Except of G2 organogels, thermal load of GMSOs were resulted great *oil number*, i.e. syneresis, indicating weak adsorption interaction between the gel network and the oil. Among the GMSs, Tegin 90® showed the best wetting with Miglyol® 812 (*contact angle of wetting*, OCA 20, DataPhysics, Germany), and G2 had the smallest oil number values, suggesting that the stronger the interaction between the solid and liquid phases, the less influenced by the temperature is, i.e. thermal load will result less syneresis. As compared with the traditional organogels, the oil numbers of the GMSOs were significantly higher, except of G2 organogels.

Testing the mechanical stability of GMSOs, it was revealed that the structures were broken down at small stress values, which is identical of physical networks.

During 4 weeks of storage the changes of the rheological parameters (*flow curve, thixotropic area*) indicated hardening of G2-4 organogels and weaking of the network in G1.

Drug release profile

1% of piroxicam (Px) was used as model drug, which is a NSAID indicated in case of inflammatory diseases, articular complaints and osteoarthritis. If these are to be treated locally, a vehicle capable of ensuring the deep skin penetration has to be used. Resulting from their surface active nature, different GMSs included in the GMSOs can disorder the lipid structures of the *stratum corneum*, contributing to the overall percutaneous penetration enhancement of Px.

***In vitro* prediction of skin penetration**

Investigating the release and the penetration of Px from the different GMSOs in Franz type vertical diffusion cell (Hanson Research, USA), using a cellulose membrane soaked in isopropyl myristate, there were no significant differences between them. Hence, according to this prediction, different GMSs will have similar effect on the penetration of Px *in vivo*. The *in vitro penetration profiles* were described mathematically with the Higuchi's diffusion model.

As compared with the traditional organogels, the amount of Px penetrated from the GMSOs *in vitro* were significantly greater, probably because their relatively high surfactant contents.

As studied the effect of the surfactants on the psycho-chemical properties of Px, it was found that even the GMSs have changed the *solubility* of Px in hidrophilic medium, these effects could only reveal when the GMSs got through the lipophilic barrier (*lipophilic/hydrophilic partition*).

When the surfactant concentration and consequently viscosity of G2 organogels was increased, both the rate of diffusion and the penetrated Px amount decreased. However, remaining in the concentration range which result proper consistency for topical use, there were no differences between the *in vitro* penetrations.

Based on the Guy-Plot theory, skin penetration can be predicted via the *in vitro penetration coefficient*, which correlates with log *P*, and a good potency of penetration is most probable when *logP*~2. From the log *P* value of Px which was influenced by the various GMSs, the sequence of skin penetration from the GMSOs should be: G2>G4>G3>G1.

***In vivo* anti-inflammatory effect**

When G1 and G2 were applied *in vivo* to *inhibit the acute formation of carrageenan-induced rat paw oedema* (plethysmometer, Hugo Sachs Elektronik, Germany), it was found that Px incorporated into the organogels produced not only a local, but also a systemic anti-inflammatory effect.

When Px pretreatment was applied locally to the carrageenan-treated area, both GMSOs proved effective oedema inhibition as compared with the control group treated with placebo, with no significant difference between them. However when Px pretreatment was applied on the dorsal skin, the oedema-inhibiting ability of G1 was slight comparing to G2, which is assumed to be the presence of the more lipophilic Tegin® 90 promoting the diffusivity of Px into the skin more effectively.

Within the concentration range examined, the degree of *in vivo* oedema inhibition increased with increasing Px dose in accordance with a power law.

When the surfactant amount (penetration enhancer) increased in that concentration range resulting in optimal consistency, there were no significant differences between the systemic oedema-inhibiting effects.

When used locally, G1 and G2 were more effective than SX, but they did not exhibit a significant difference as compared with SP. As concerns the *in vivo* systemic effect, G2 was more effective than SX and SP, but there was no significant difference between G1 and either SX or SP. Furthermore, the systemic oedema-inhibiting effect of G2 was compared with those

of an o/w cream and those of a hydrogel containing carbamid as penetration enhancer, and it was found that G2 showed approximately the same oedema-inhibiting effect than the hydrogel and it was found better than the o/w cream. Consequently, hydrophilic vehicles could be preferred to the lipophilic ones because of the ease of washability and less residue left on the skin, but they are not more effective than GMSOs respectively to the bioavailability of Px.

***In vitro – in vivo* correlation**

The extent of *in vivo* skin absorption was in accordance with the *in vitro* penetration coefficient, while the *in vitro* penetration through a synthetic membrane did not correlated with the *in vivo* results. The reason of these differences could be arisen from the different nature of the model barriers used. The i*n vitro* applied synthetic membrane is inert, and the test can serve model for the release followed by the lipophilic/hydrophilic partition process. However, *in vivo* percutaneous absorption is more complex, because both the penetration enhancers and certain drugs can interact with the multilamellar lipid matrix of the *stratum corneum*, thus skin behaves as an active barrier.

SUMMARY

- GMSs results in stable organogels already at low concentrations using several apolar and semipolar oils.
- The following differences are between the organogelator behaviours of the commercially available GMSs obtained from different sources and by different methods:
  - The gel points depend on the surfactant type and concentration.
  - Textures depend on the surfactant type and concentration.
  - Oil number correlates with the surfactant wetting with the oil.
  - Upon storage the structures of G2-4 show hardening while G1 shows weakening.
  - Px penetration correlates with the log *P* influenced by the surfactants.
- Under light microscope the heterogeneous network structure can be clearly recognised, which consists of rod-like GMS aggregates connecting to each other and intermeshing throughout the oil.
- Changing the ratio of the two ingredients will change of the yield value, viscoelasticity, viscosity and spreadability of the GMSOs. From the aspect of the product optimization, this provides a quite simple way.

- 13% of GMS result in optimal consistency for dermal pharmaceutical application. As comparing to some traditional organogels, the overall liking of GMSOs is found to be better than those of SX and OL. The overall liking correlates with the macroscopic aspect and with the skin feel.
- The network energies of GMSOs are moderate. The fine crystalline structures building up the gel network resulted in fragility, thus GMSOs show low yield value.
- As comparing to the traditional organogels, the thermal stability of GMSOs is significantly smaller, except those of G2 organogels.
- Px incorporated into G2 organogels exhibits a notevole oedema-inhibition effect either when applied locally, or via transdermal absorption. Comparisons with traditional organogels revealed that the relative biological availability of Px was better from G2 organogels. Thus, Tegin® 90 could be suitable penetration enhancer in Px formulations.
- *In vivo* results correlate with the *in vitro* penetration coefficients. However, care must be taken when conclusions are drawn from comparison between the results of application of a synthetic barrier *in vitro*, for prediction of the actual *in vivo* skin penetration.

ACKNOWLEDGEMENTS

I would like to express my thanks to **Prof. István Erős**, for offering me the opportunity to work in his department and for providing me the professional and financial background for my studies. I would like to thank him as my supervisor for his support. I am also grateful to **Ildikó Csóka** for her support and encouragement.

Furthermore, I am greatly indebted to **Prof. Carla Caramella** and **Prof. György Falkay** for providing me possibility to work in their departments.

I also wish to thank to my co-authors: **Franca Ferrari**, **Silvia Rossi**, **Gábor Blazsó**, **Zoltán Aigner**, **Prof. Maria Fernanda Bahia** and **Isabel Almeida** for the pleasant co-operation and inspiring discussions.

I am likewise grateful to my **colleagues** for stimulating me to complete the thesis.

I would like to thank to **my family** for the patient and for giving me a peaceful background.

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