Summary of Ph.D. Thesis

In vitro and in vivo evaluation of semisolid dosage forms for transdermal application of Ketamine

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1. Introduction

In the past decade there has been an increase interest toward dermal and transdermal products which offer several advantages compared to traditional dosage forms. USA data show that out of 129 drug delivery candidates, 51 dermal or transdermal products are listed. There are 77 candidate products in preclinical development of which 30% represent such drug delivery. Novel approaches and devices have been manufactured in recent years, parallelly with the development of in vitro and in vivo test methodologies and mathematical description of the processes involved in skin delivery.

These new innovations (dosage forms, devices) made several active agents useful therapeutically, which couldn't serve as medicinal uses before, due to their sensitive structures (e.g. peptides), or because a lack of suitable devices or methodologies to carry them through e.g. the skin layers.

Parallelly with these new possibilities, there is also an increasing demand from clinicians' side toward non-invasive therapies - like transdermal delivery - generally and also in the case of special patient groups, such as children.

These abovementioned facts give drive to dosage form designers for creating novelties and making efforts to develop new dosage forms and widen their usage to incorporate more medicinal substances.

This work was initiated by the clinicians' side, as there was a need for a non-invasive technological delivery alternative of Ketamine for pediatric usage.

2. Aim

Clinicians for a while have been looking for an alternative for the induction of anesthesia. This procedure has been normally performed by inhalation or injection which being uncomfortable for adults, in painful for children, and can have long-term psychological side effects. A technological alternative is very much in demand. I have chosen Ketamine a dissociative anaesthesia for the induction of anesthesia by the transdermal route. Ketamine hydrochloride is a water-soluble salt, which has difficulty in penetration of the skin to be able to have systemic effect.

My project was to take 4 different vehicles: hydrogel, organogel, liquid crystals and emulsions (w/o, w/w/e) to use for the application of Ketamine. The result will be to see which vehicle will provide the best penetration for the drug to be able to formulate the right design for transdermal application in the form of a transdermal patch as an end result.

The process will include:

1. In vitro experiments with the Hanes Vertical Diffusion Cell Apparatus with
   a) Phosphate soaked membrane;
   b) IPM soaked membrane

This is to see if the drug can pass the artificial membrane to determine the feasibility to proceed to in vivo experimentation.

2. In vivo experiments with the application of the vehicle on the skin of Wistar rats
To observe the actual amount of the drug and see the effect the drug has on the physiological functions.

3. Blood will be taken to measure plasma levels of Ketamine with an HPLC apparatus to assess the actual penetration effect each vehicle has on the skin.
3. Literature Survey

1. General overview of transdermal drug delivery

There have been large studies in topical delivery research during the past 60 years. The years between the 1940's to 1980 have been formative years for current understanding of transdermal delivery. Part of the difficulties was in accessing the information from the databases. In the 50's and the 60's there was research to identify the barrier properties of the skin, in the 60's Higuchi introduced mathematical modeling of percutaneous penetration, in the late 60's thermodynamic activity of chemical potential was studied in terms of supersaturation, and in the 70's when the structure of the Stratum Corneum (SC) was found to be like a brick and mortar wall they understood that percutaneous route was the transport route for the drug in the SC and it is this structure that gives the skin a rate controlling membrane. Finally it was in the mid 70's that Franz invented the Franz diffusion cell for in vitro analysis and during this time various membranes started being used for testing like cellulose acetate.

The concept of a transdermal patch was introduced in the 1970's. The first transdermal patch manufactured was for systemic effect with the active ingredient scopolamine to treat motion sickness. It was made in 1981 by Ciba-Geigy using the name Transderm V (It is now sold as Transderm Scop). Walters and Roberts defined the basal layers in the dermal absorption of drugs and compounds, such as local effect (corticosteroids), systemic effect (mucosal patch), surface effect (sunscreens, cosmetics), and deeper effect (NSAID's) for muscle inflammation, which gave the basis also for patch designers to develop this possibility for various drugs that are available on the market in the form of a transdermal patch. They include: Nitroglycerine (angiis), Isopropamide (isopropanol), Fentanyl (fentanyl), Nicotine (nicotine spray), Estrogen (hormone replacement therapy), Testosterone (male hypogonadism), Clonidine (hypertension), Lidocaine (local anesthetics).

There are also new transdermal patches that are now available or will be soon on the market. They include mediated: Lidocaine (pads of sponges in herpes zoster), Methyldiphenidate (attention deficit hyperactivity disorder ADHD) and non mediated: thermal and cold patches, weight loss patch, nutrient patch, therapeutic and cosmetic patches, aroma patch for appetite suppression, and a patch to measure light exposure.

2. Vehicles

Emulsions and creams are very popular among the dosage forms used in topical delivery, where the main components are lipids and water, stabilized by emulsifiers. Developments within this field are the usage of vegetable oils and new types of surfactants e.g. PEG-free, and also new emulsion types are used as well. One of the most popular new emulsion types is the water-in-oil-in-water (W/O/W) multiple emulsions, where small water droplets are entrapped within larger oil droplets that in turn are dispersed in a continuous water phase. Multiple W/O/W emulsions contain both W/O and O/W simple emulsions and requires at least 2 emulsifiers to be present in the system.

Lyotropic liquid crystals are fairly new members of topical dosage forms, formed by amphiphilic molecules and exhibit a phase of matter that has properties between those of a conventional liquid, and those of a solid crystal.

In contrast to emulsions, gels generally do not comprise two immiscible phases of opposite hydrophilicity. Therefore, the solubility and solubilization characteristics of the incorporated substances are either hydrophilic or hydrophilic in origin. The consistency of gels is caused by gelling agents, which belong mainly to polymers (but they can be emulsifiers as well). These polymers build up a three dimensional network. Intermolecular forces bind the organic molecules to this polymeric network and then, due to the reduced mobility of these molecules in structured systems with increased viscosity, exhibit vesiculolthic properties. The most important and already well-known polymers for forming hydrogels are polyacrylic acid derivatives like carboxymethyl, different cellulose derivatives like hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxyethylcellulose-sodium etc.

These above mentioned dosage forms can be used in their semisolid form, but also their incorporation into transdermal patches is a common process. In this case these patches have their own devices, or parts, as follows: The basic design of a transdermal patch is a release liner, pressure-sensitive adhesive, and a backing layer. These 2 basic transdermal delivery systems that can be described by their basic design:

1. Drug in adhesive – The drug is incorporated into the adhesive
2. Drug in matrix – The drug is dispersed in a polymeric matrix
3. Drug in reservoir (membrane patch) – There is a rate-controlling membrane between the reservoir and the skin

This work does not detail these devices, as the basic aim was the development and testing of the dosage form itself.

5. Skin factors relevant to transdermal absorption of active agents

The skin being the largest organ of the body covers an area of 2m² and is on the average 0.5 mm thick. The skin as a barrier can withstand various degrees of temperature and water content. The skin is composed of three layers and several appendages, which contribute to the homeostasis function of the skin. According to the different skin layers each has unique characteristics which influence the penetration of the drug into the body.

The stratum corneum (SC) is the outermost membrane of the skin that consists of a heterogeneous membrane with lipids and proteins in a "brick and mortar" morphology giving it its barrier function. The lipid concentration will give the SC a lipophilic environment and it is through this barrier that the drug has to partition first. The first layer is the epidermal layer. It senses damage caused by substances that pass the SC or other metabolizes it or causes an inflammatory response. This layer has an aqueous environment and acts as a hydrophilic layer of which lipophilic drugs have difficulty partitioning into. The following layer is the dermal layer, which supplies nutritive and immune support to the epidermis. This is due to the neural and blood supply of the dermis. When the drug reaches this layer it is distributed to the body by the blood supply for elimination or systemic effect. Finally the last layer subcutaneous tissue is composed of a network of fat cells, which carry the vascular and neural systems for the skin. Depending on the state of the vascular supply it will determine the target of the drug. In a vasodilated state the drug will remain local and in a vasoconstricted state the drug will be transported to the systemic circulation.

According to Zabier and Davis there are various factors that influence the absorption of a drug from topical preparations which include skin moisture, skin pH, cutaneous blood flow, surface lipids, anatomical site of application, and influence of appendages. There are also other factors that have been studied which are:
4. Development of transdermal drug delivery systems

According to Katz et al. and Margerith et al., the path that the drug follows is (a) release of the drug from the formulation, (b) partition into the SC, (c) diffusion through the lipophic environment of the SC, (d) partition into the aqueous environment of the epidermis, (e) diffusion through the epidermis to the dermis, and finally, (f) uptake by the capillary network to the systemic circulation. When examining the route the drug has to take to penetrate the skin we have to take into consideration the polarity of the SC (lipophillic) and the epidermis (hydrophillic) when choosing a drug as a candidate for transdermal delivery. The drug must possess both lipoidal and aqueous solubility. A drug that is too lipophillic will not transfer into the SC and if it is too hydrophillic it will remain in the SC.

Transdermal drug delivery can be optimized by various methods. These methods vary from changing the drug, parameters such as the vehicle and/or application of special additives called enhancers (chemical and physical) in order to modify the barrier function of the skin.

5. Medical needs for non-invasive Ketamine products

The need for transdermal Ketamine delivery was initiated from the clinician’s side. It is well known, that induction of anaesthesia by inhalation or injection is a stressful procedure in children. In addition, painful and frightening experiences may cause long-term psychologic complications and make subsequent contacts with health professionals more difficult. As a result, a variety of premedications administered via various routes have been introduced, e.g. rectal administration of Ketamine. It has been shown that rectally administered Ketamine alone produced dose-dependent sedative effects in children. Only a few studies reported about the antinociceptive potential of the transdermal Ketamine, but nobody has investigated the hypnotic effects of this drug at low local administration. Quan et al. have shown that topical Ketamine reduced pain in patients with no systemic side effects, indicating negligible or no generalized absorption. Azavedo et al. have found that a controlled transdermal delivery of Ketamine prolonged the time to first rescue analgesic medication without adverse effects after minor gynecological surgery.

6. Possibilities for enhancement of Ketamine absorption through the skin

As Ketamine hydrochloride is a hydrophillic drug, the possibility for enhancement is either (1) the hydration of the skin containing urea or (2) by the addition of penetration enhancers such as surfactants and (3) the use of special vehicles such as organogel, hydrgel, liquid crystals. Some of these possibilities are used in the experimental part of this work.

4. Materials

The active agent was Ketamine hydrochloride (Ketamine) a dissociative anesthetic (chemical name: (1R,2S)-2-(2-chlorophenyl)-2-methylamino) cyclohexanone hydrochloride; molecular formula: C13H16ClNO; MW: 274.79). Ketamine was used in solution form (Cypalon®, Richter Ltd.). Another agent used was Ephedrine hydrochloride a sympathomimetic (chemical name: (1R,2S)-2-(2-chlorophenyl)-2-methylamino) cyclohexanone hydrochloride; molecular formula: C13H16ClNO; MW: 274.79). Ephedrine was used in solution form (Cypalon®, Richter Ltd.).

The following materials were used as components for organogel, w/w cream, hydrogel, reference gel and liquid crystal. Polyvinylpyrrolidone, isopropyl myristate, cetoconazole, cetyl alcohol, Polysorbate 80, PEG 6000, (poly-vinylpyrrolidone-10-cetyl ether) (ICI Hungary Ltd., Budapest), Carbopol 940, 971P (SNF Chemicals Ltd.) Miglyol 812 (Fractionated coconut oil), Inicrot 900 (Dynaflex Nobel Huls AG Witten, Germany), other additives: urethanolamine, carbomer, sodium hyorurate, glicerol (Hungaropharma Co., Budapest)

The materials for w/w (multiple) emulsions were as follows: 2.2,4,6,8-hexamethylidibromone (Cibacron HD), Uniquem, Uniquem grade) and vegetable oil derivatives: avocado oil, Panicum Gratissimum (Oxinate, Cosmetics grade), corn germ oil (Zai Hans) (Natural, Cosmetics grade), polyvinylpyrrolidone (30) hydrolsyrat (PEG-30 Polyedrosyrat) (Austinal P35, Uniquem, Uniquem grade), black copolymer of polyethylene oxide and polypropylene oxide (Ficoll 407) (Synperon PE F 127, Uniquem, Uniquem grade) carboner (Carbopol Ultrez-10, BF Goodrich, Philips F 41h).

The polymer for the representative hydrogel systems for rheologial evaluation was Histacron PN 73 (polymethylene sodium-polyvinylsodium copolymer) in concentrations between 1-3% (Hoechst).

All components were used were of Ph Eur 4th grade.

Preparation of developed products

Hydrogel type gels were formulated as follows: reference gel was a Carbopol 940 gel, neutralized by means of sodium hydroxide, in case of the hydrogel, Carbopol 971P was used and it was added first to distilled water. Then carbamide and 1% Ketamine was dissolved, followed by adding trihexanadine for neutralization. In case of the hydrogel, Hystacron Gel, Histacron PN 73 to the water and let it sit for 10 minutes. Then carbamide and 1% Ketamine was dissolved.

The organogel was prepared by heating a mixture of Miglyol 812 and Inicrot 900 to 70 °C. The melt was left to cool down at room temperature under continuous stirring, while the aqueous solution of Ketamine was added drop wise.

The hypotonic liquid crystal samples were produced by heating the mixture of the low concentration, the glycerol and of Ethyl 95% to 80 °C. Distilled water was heated up to the same temperature and was added during constant stirring at 500 r/s (Laminar RET-G magnetic stirrer). Stirring was continued until the mixture cooled down to room temperature.

The preparation of the w/w cream was performed as follows: Polysorbate 80, cetoconazole alcohol and isopropyl myristate were melted together and mixed. The aqueous phase containing carbamide was then heated up to similar temperature. Finally the phases were mixed.

Multiple w/v emulsions were formulated with the two-step technology. The two-step technology was started as follows: the simple w/v emulsion was prepared by adding the w/v aqueous phase to the oil phase.
containing the hydrophobic surfactant. Both phases were heated separately to 75 °C and then mixed. After the homogenization process (3 minutes at 1000 - 13 500 rpm), the emulsion was cooled down to room temperature with gentle stirring. This w/o emulsion was dispersed - at a low stirring rate of 500 rpm (THORNB. LE-402 LABORATORIUM, Hungary; DI 25 ISA-VERKE GmbH Germany) - in the w/o aqueous phase at room temperature. Ketamine was dissolved in the water of both phases.

5. Methods

1. Evaluation of rheological properties of different dosage forms

A Haake Rheometer 1 rheometer (Thermo Electron, Germany) was used to measure the rheological properties of the cream. The flow curve test (increased shear rate at constant shear time and temperature) and constant stress tests were carried out as viscosity measurements. Cone-plate (CP4-40 and 1:25° TT) combinations were used as measuring systems. The temperature of the sample was 25 ± 0.1 °C. The tests were performed at least in triplicate. Relative standard deviation was 1.5 - 6.9%.

The cone angle was 1 degree, and the thickness of the sample was 0.048 mm in the middle of the cone. The measurements were performed at room temperature. The samples were kept in a space saturated with vapour during measurement in order to prevent evaporation. The linear viscoelastic range was determined in the first step by examining the complex modulus as a function of shear stress at a given frequency (1 Hz). Based on these experiments, the value of shear stress was set at 25 Pa during the dynamic test as this value was always within the linear viscoelastic range, then the values of the storage and loss moduli were examined as the function of frequency.

2. In vitro drug release studies

Franz Diffusion Cell System (Hanson Research Co.) containing 6 cells, and equipped with autosampler (Hanson Microette Autosampling System) was used for the measurement of drug in vitro drug release and penetration. The area for diffusion was 1.37 cm², and the receptor chamber volume was 7 ml. Cellulose acetate membranes (Shonkyo-Nagai Co., Japan) with an average pore size of 0.45 μm were used. Pretreatment of the membrane was achieved by soaking in the receiving medium for the drug release studies. The receptor medium was phosphate buffer (pH 7.4). The experiments ran at 32 ± 0.5 °C. 0.40 g samples of different compositions were placed evenly on the surface of the membrane, and 800 μl samples were taken after 0, 1.5, 2, 3, 4.5, and 6 hours and replaced with fresh receptor medium. The absorbance was measured by UV-spectrophotometer (Unicam UV-VIS Spectrophotometer) at 366 nm in the case of Ketamine, and at 256 nm in the case of Ephedrine hydrochloride. The blank vehicles without active agents served as references. Results of a 6 hours time period were plotted according to the diffusion model of Higuchi. The results were expressed as the mean ± S.D. of four experiments.

3. In vitro penetration experiments

All the experimental conditions were similar to that of in vitro drug release studies, except the fact that the synthetic membrane used was soaked in n-propanol instead (IPA).

4. In vivo studies of physiological changes after drug administration

After Institutional approval had been obtained from the animal care committee, male Wistar rats weighing 240 ± 48 g were studied. The animals were kept on a 12 h light/12 h dark cycle with food and water ad libitum. All experiments were carried out in the same period of the day (1 to 4 p.m.) to exclude diurnal variations in pharmacologic effects. Each rat was tested only once. One day prior to the application of the cream, the back of each rat was carefully shaved and the skin was cleaned by wiping with water-containing cotton under sedation-xylazine anesthesia. On the day of the experiment, the animals were anaesthetized with the intraperitoneal injection of Sedanar® and xylazine (1 mg/kg and 10 mg/kg intraperitoneal, respectively). Each cream (10 g) was applied onto the dorsal skin of rat (about 15 cm²) 5 min after the injection and covered with a protective overlay, an elastic adhesive bandage. The nonwoven PE cloth was fixed with Coban® adhesive wrap. Control animals were applied to the placebo cream (vehicle without active agent) in the same amount. The cream and the overlay were removed after the termination of the experiment.

Loss of the righting reflex was used to determine the presence of anesthesia, and its length in minutes was referred to as the duration of hypnosis. This technique is widely used for the measurement of anesthesia in rodents, and good agreement has been observed between the results with general anesthetics presented in various papers. Hypnosis was regarded as the state in which an animal could be placed on its back without righting itself. During the anesthesia the breathing was also determined every 5 minutes (breathing frequency). 90 min after the Ketamine administration the animals were overdosed with Phenothiazine and 2nd blood sample was taken for HPLC study.

The rats were treated randomly according to one of the following protocols: Controls received vehicle (n=10), experimental animals were exposed to different vehicles (hydrogel, liquid cream) (n=4-7) containing 1% w/w Ketamine. Data are presented as means ± S.E.M. The statistical analysis of differences between different treatments was performed with the Student’s t test. A probability level less than 0.05 was considered as significance.

5. Evaluation of systemic absorption of Ketamine

Sample preparation involved extraction into diethyl ether and back extraction to 0.025 M sulphuric acid and as reported by Adams et al. The aqueous phase was dried and reconstituted in 0.01 M sodium hydrogencarbonate and loaded onto the chromatographic column. Separation of Ketamine was performed on the method described by Gross et al. The HPLC (Khauer, Berlin, Germany) comprised a single pump isocratic system connected to a flow-through UV detector measuring absorption at 215 nm. Chromatograms were collected and evaluated using [Biochrom 2000] software. The analytical separation was carried out on a reversed-phase Ultrames 5 μm CN column (250 - 4.6 mm) (Phenomenex, Torrence, CA, USA). The mobile phase was
### Table 1: Released Ketamine amounts after 0.5, 1, and 2 hours of treatment through buffer-absorbed membrane

<table>
<thead>
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<th>Formulation</th>
<th>0.5 hours</th>
<th>1 hour</th>
<th>2 hours</th>
</tr>
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<tr>
<td>O.1 cream</td>
<td>111.41</td>
<td>131.81</td>
<td>125.84</td>
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<td>Liquid cream</td>
<td>32.3</td>
<td>36.95</td>
<td>32.8</td>
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<tr>
<td>Reference gel</td>
<td>134.3</td>
<td>154.2</td>
<td>145.3</td>
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<tr>
<td>Reference oil</td>
<td>103.2</td>
<td>123.1</td>
<td>115.2</td>
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</table>

### Table 2: Released Ketamine amounts after 0.5, 1, and 2 hours of treatment through lipid-soluble membrane

<table>
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<th>Formulation</th>
<th>0.5 hours</th>
<th>1 hour</th>
<th>2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.1 cream</td>
<td>13.34</td>
<td>13.64</td>
<td>13.8</td>
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<tr>
<td>Liquid cream</td>
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<td>Reference gel</td>
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<tr>
<td>Reference oil</td>
<td>57.4</td>
<td>61.5</td>
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### Experiment Procedures
1. In vitro drug dissolution
2. In vivo drug absorption
3. Results and discussion
4. Conclusion

**Results and discussion**

The release process from different vehicles was measured by the following equation, which was volatilized in the receiver tube from the liposome-based vehicle.

**Conclusion**

The following equation was studied as in Table 2, the parameters of the data presented here are as follows: 1. the
I used an emulsion type dosage form as a vehicle in this experiment and I wanted to see if it would be better to use a single or a multiple emulsion. As seen in figures 3 and 4, the multiple emulsion had a higher release rate compared to the simple emulsion.

Figure 3: Percentage of Ketamine release from emulsions plotted against time.

Figure 4: Concentration of Ketamine release from emulsions plotted against square root of time (%).

At the end of the in vitro experiments, I decided to use the hydrogen, organogel, liquid crystal, and a simple w/o emulsion as vehicles. I decided not to use the w/o multiple emulsion because it was found to be unstable as there was separation of the components and as a result liquified.

We investigated the in vitro release and in vivo penetration of Ketamine vs. viscosity of matrices relationship, but there was not a significant correlation between pharmacokinetic data (eg released drug amount, rate of release, rate of penetration) and the rheological data of matrices with different chemical composition.

3. In vivo studies of physiological changes after drug administration

Products containing 1% Ketamine, selected on the basis of the in vitro experiments were evaluated by different physiological tests. Fig. 5 shows the effect of Ketamine containing products on breathing frequency, on the ascorping time, and on the duration of sleep. The time needed for the appearance of the first arane was also detected.

Figure 5: The in vivo effect of Ketamine on the different physiological parameters in anesthetized rats. * = significant difference.

There were no significant differences between the groups in respect of the onset of hypnosis, however the duration of hypnosis significantly increased in the Ketamine developed products compared to the reference product. The breathing frequency significantly decreased in the Ketamine developed product group compared to the other two groups.

My results show that the developed products (hydrogel, liquid crystal, and o/w cream) containing Ketamine in 1%, have a significant potency in in vivo circumstance, while the reference gel does not have any potentiating effect on the duration of the hypnosis nor significantly influence in the breathing frequency.

4. Evaluation of systemic absorption of Ketamine

The plasma levels of Ketamine were determined 90 minutes after topical application of various formulations by HPLC with UV detection (Fig. 6, 7).
The retention time of Ketamine was 5.0 min. A measurable amount of Ketamine was detected, but there was no significant differences between the hydrogel and the liquid crystal products. Significant differences in the breathing rate and the duration of sleep measured, made necessary to investigate the blood level in time course. Fig. 8 shows the results of these experiments. After the application of Ketamine containing preparations, the drug appeared in the blood, while it did not occur in the control group. The lowest level was 75 ng/ml while in some animals it reached 550 ng/ml (not shown in graph). The lowest level could be observed with 0.1% cream, while the highest level with the hydrogel, but the difference was not significant between the two groups.

Fig. 7: Ketamine blood concentrations from different vehicles (*: significant differences from the control group), taken 90 minutes after topical application.

Fig. 8: Ketamine plasma levels from preparations containing 1 and 4% Ketamine taken 30, 60, and 90 minutes after topical administration of a hydrogel.

My results show that Ketamine diffused through the skin and it appeared in the blood. All the developed products might be good for this drug administration, however, the 1+ Ketamine cream in this volume is a low dose. Even when I used 4% concentration, there was a negligible difference between the two.

It can be also concluded, that the in vitro evaluation method was more sensitive and the difference among the vehicles was overestimated in these cases. Further studies should be performed with higher drug concentrations for the characterization of the differences in the pharmacodynamics of the drug with different vehicles and to evaluate the correlation between the in vitro and in vivo absorption.
A technological alternative for the induction of anesthesia has been long sought after by clinicians to reduce or eliminate the pain associated with this procedure. It is even more beneficial in the situation of children. I have chosen Ketamine, a water soluble salt to be administered transdermally. The ideal method for administration would be a transdermal patch, which contains a semisolid dosage form. As a result, I have chosen 4 vehicles: hydrogel, organogel, liquid crystals, and emulsion. The vehicles were tested by the Franz Diffusion Cell System which contains 6 cells (2 cells contained the vehicle only and the other 4 had the vehicle with Ketamine). The experiment took 6 hours during which samples were taken at 0, 5, 1, 2, 3, 4, 5, 6 hours. The first time the membrane was soaked in buffer solution to simulate hydrophilic conditions and the second time the membrane was soaked in IPM to simulate lipophilic conditions. In both situations all the vehicles showed significant penetration through the membrane. It was high in the buffer soaked membrane due to the fact a hydrophilic drug was used, and it was lower in the IPM soaked membrane but there still was significant penetration enhanced effects from the vehicles.

I chose hydrogel to compare the influence of viscosity on the release of the drug because it had the highest penetration rate. Two hydrogels were prepared, one with Carbopol and the other Hecarmer PM73 as polymers with concentrations from 1-3%. The Hekarmer Rhoctress 1 Rheometer was used to measure the rheological properties. It was shown as the polymer content increased the viscosity also increased but the release of the drug decreased accordingly. It was also shown that there was a difference of the two polymers in regards to the release of the drug. The drug release was higher in the case where the chains were flexible and had more of a tendency for alignment.

Because of the positive results for the in vitro experiments in two experiments were performed by applying the vehicles on Wistar rats and the sleeping time, first urine, breathing rate, and duration of sleep were observed. There were no significant differences between the groups in respect of the onset of anesthesia. However, the duration of the anesthesia significantly increased in the Ketamine developed product compared to the reference product. The breathing frequency significantly decreased in the Ketamine developed product group compared to the other two groups. After 90 minutes of the vehicle application blood was taken to measure the concentration of Ketamine in the plasma by the use of HPLC with UV detection. The result showed me that there was penetration of Ketamine through the skin into the blood. Another series of tests was performed where blood was taken at 30, 60, and 90 minutes after application of Ketamine with two different concentrations (1% and 4%).

In conclusion, the use of vehicles showed a promising effect on the transdermal delivery of Ketamine in both in vitro and in vivo situations.

The aim of developing Ketamine containing semisolid dosage forms from which the drug reaches the systemic circulation—was achieved, however, further studies should be performed with higher drug concentrations to evaluate the pharmacodynamic correlation between the in vitro and in vivo permeation.

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Publications


If: 2.156


If: 0.636

Abstract
