GELLIFIED EMULSION OF GLUCOSAMINE SULPHATE FOR
TRANSDERMAL DRUG DELIVERY

SYNOPSIS FOR
M.PHARM DISSERTATION

SUBMITTED
TO
RAJIV GANDHI UNIVERSITY OF HEALTH SCIENCES
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BY
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ANNEXURE-II

PROFORMA FOR REGISTRATION OF SUBJECTS FOR P.G. DISSERTATION

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| 2 | COURSE OF STUDY AND SUBJECT                        | M.PHARM  
PHARMACEUTICS |
| 3 | DATE OF ADMISSION                                 | 28/06/2010 |
| 4 | TITLE OF THE TOPIC                                 | “GELLIFIED EMULSION OF GLUCOSAMINE SULPHATE FOR TRANSDERMAL DRUG DELIVERY” |
6. BRIEF RESUME OF INTENDED WORK

6.1 NEED FOR THE STUDY

Transdermal drug delivery (TDD), the delivery of drugs across the skin is gaining wide acceptance among patients. It is a viable administration route for potent, low molecular weight therapeutic agents susceptible to first pass metabolism. Advantages of TDD include non-invasiveness, prolonged drug levels in the blood stream, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug administration\(^1\).

The transdermal route ranks with oral treatment as the most successful innovative research area in the drug delivery, with around 40\% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system\(^2\).

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Topical formulations apply a wide spectrum of preparation, both cosmetic and dermatological to their healthy or diseased skin.

Drugs administered topically for their action at the site of application or for systemic effects. For the most part, pharmaceutical preparation applied to the skin are intended to serve local action and as such are formulated to provide prolonged local contact with minimal systematic drug absorption.

The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of risk and inconveniences of intravenous therapy and of the varied condition of absorption like \(pH\) changes, presence of enzymes, gastric emptying time are other advantages of topical preparations. The topical drug delivery system is generally used where the other system of the drug administration fails. Emulgel is emulsion, either of the oil-in-water or water-in-oil type, which are gelled my mixing with gelling agent\(^3\).

In developing a transdermal delivery system, two criteria are considered: one is achieving adequate flux across the skin and the other is minimizing the lag time in skin permeation. One strategy of overcoming this constraint is the incorporation of various skin
permeation enhancers into the vehicle. Another strategy is a choice of an appropriate vehicle that corresponds to the drug being used for the dermal route of administration\textsuperscript{4}.

Emulsions, vehicle extensively used to deliver various drugs to the skin have a high ability to penetrate the skin. In addition, the formulator can control the viscosity, appearance and degree of greasiness of cosmetic or dermatological emulsions. Gels for dermatological use have also several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emolient, non-staining, compatible with several excipients, and water soluble or miscible.

Osteoarthritis is characterized by progressive degradation and loss of articular cartilage. Osteoarthritis is the most common arthritic disease and its incidence increases with age. As population demographics changes to include more elderly individuals, this disease will have a serious impact in multiple ways. Along with the cost for health care and lost work time, individuals with osteoarthritis suffered from pain and disability. Currently, there is no specific treatment to prevent or retard the cartilage degradation in osteoarthritis. Present treatments used for osteoarthritis provide only symptomatic relief from the pain. Glucosamine sulfate, which has received attention as a putative agent that may retard cartilage structural degradation in osteoarthritis, has been investigated in several osteoarthritis trails\textsuperscript{6}.

The oral bioavailability and half life are 26% and 150 minutes respectively, therefore the concept of transdermal drug delivery has greater importance over oral route.

Thus, based on the above-mentioned information and considering the cutaneous route as an alternative and on various instances, as a complement of other routes of administration, the present investigation is aimed to formulate gellified emulsion for the topical delivery of glucosamine sulfate\textsuperscript{5}.  

6.2 REVIEW OF LITERATURE

- Formulation of chlorphenesin emulgel using 2 types of gelling agents. Hydroxy propyl methyl cellulose and Carbopol 934 was developed. The prepared emulgels were evaluated for their physical appearance, rheological behavior, drug release, antifungal activity, and stability. It was found that the emulsifying agent concentration had the most pronounced effect on the drug release from the emulgels. Rheological studies revealed that the emulgels exhibited a shear-thinning behavior with thixotropy. Stability studies showed that the physical appearance, rheological properties, drug release, and antifungal activity in all the prepared emulgels remained unchanged upon storage for 3 months\(^7\).

- The study was conducted to evaluate the permeation of diclofenac acid and its salts from emulgel. Emulgel was prepared by dispersing carbomer 974 in purified water and adding triethanolamine to adjust the viscosity. Their penetration performances were evaluated using two-chamber side-by-side diffusion cells containing excised rat skin and the drug concentration in the receptor compartment was determined by HPLC. The partition coefficient of the drugs between stripped skin and emulgel (Ks) was also determined and a positive relationship was found between Ks and the cumulative amount of drug permeated over a period of 8 h with a correlation coefficient (r) of 0.974. So it was concluded that Diclofenac salts were more suitable for emulgel preparation than diclofenac free acid\(^8\).

- The emulgel of ketorolac trometamol was prepared using isopropyl myristate, isopropyl palmitate, Tween 80, oleic acid, transcutol, propyl glycol, glycerin, water. \textit{In-vitro} release behaviour of the drug from different microemulsion and emulgel formulations was evaluated. The developed emulgel appeared promising for dermal and transdermal delivery of ketorolac trometamol, which would circumvent most of the problems associated with drug therapy\(^9\).
Gellified emulsion for sustained delivery of itraconazole was formulated. The prepared formulations were evaluated on the basis of pH, spreadability, viscosity, drug content, in vitro drug release and stability studies. The microbial assay and skin irritation studies on rabbit was also performed. It was concluded that emulsion based system was more effective and safe system for sustained delivery of itraconazole.

The study was aimed at developing a topical formulation of lapachol, a compound isolated from various Bignoniaceae species and evaluating its topical anti-inflammatory activity. The influence of the pharmaceutical form and different types of emulsifiers was evaluated by in-vitro release studies. The formulations showing the highest release rate were selected and assessed through skin permeation and retention experiments. It was observed that the gel formulation provided significantly higher permeation and retained (3.9-fold) of lapachol as compared to the cream formulation. Moreover, lapachol gel presented significant antiedematogenic and antinociceptive activities when used topically. Hence, these results suggest that the topical delivery of lapachol from gel formulations can be an effective medication for topical injuries.

Formulation of microemulsion vehicles – o/w liquid microemulsion and microemulsion gel and their effect on the in vitro permeation of diclofenac, indomethacin and pentacaine through excised hairless rat skin was studied. Microemulsion gel was found to be more advantageous for transdermal application of diclofenac and indomethacin in comparison with liquid microemulsion and commercial preparations used as standards. It can be concluded that bicontinuous gel-like microemulsion dispersed system was suitable as a vehicle for indomethacin, diclofenac and pentacaine in term of the solubilization capability, rheological properties and the influence on transdermal permeation.

An emulgel formulation was developed for a local anesthetic agent and a topical steroidal anti-inflammatory agent in combination using sepigel as the gelling agent. The effect of concentrations of oil, surfactant and gelling agent on the in vitro drug release pattern was investigated using $2^3$ factorial design. The optimized emulgel formulations were
characterized for appearance, color, pH, homogeneity, viscosity and spreadability. The rheological property of emulgels showed shear thinning behaviour with thixotropy. The drug release from the optimized emulgel formulation was found to follow the diffusion controlled Higuchi model. Stability studies were conducted at different temperatures and humidity conditions that indicated the formulations to be stable under accelerated conditions. No erythema or irritation was observed during the skin irritation studies on rabbits. The result obtained was considered as a step forward for the prolonged topical delivery of drugs in combination for the treatment of various skin disorders\textsuperscript{10}.

- The study was conducted to evaluate and compare the \textit{in vitro} and \textit{in vivo} transdermal potential of w/o microemulsion and gel bases for diclofenac sodium. The effect of dimethyl sulfoxide (DMSO) as a penetration enhancer was also examined. To study the \textit{in vitro} potential of these formulations, permeation studies were performed with Franz diffusion cells using excised dorsal rat skin. To investigate their \textit{in vivo} performance, a carrageenan-induced rat paw edema model was used. This study demonstrated that incorporating drug into microemulsion enhanced drug penetration through rat skin \textit{in vitro} and \textit{in vivo}\textsuperscript{11}.

- Topical administration of meloxicam, microemulsion gels and lipogels containing either ethyl oleate or oleic acid as an oil phase were prepared. In addition, Hydrogel and hydroalcoholic gels containing carbopol 940 as a gelling agent were also prepared and evaluated. The results indicated that topical preparation of meloxicam could be an effective topical dosage form beside its oral dosage form (Mexicam\textregistered tablet) in inflammatory condition with the possibility of less systemic side effects\textsuperscript{12}.

- Hydrogel-thickened nano-emulsion system (HTN) with powerful permeation ability, good stability and suitable viscosity was investigated for topical delivery of active molecules. HTN was prepared to deliver an oily mixture of 5\% camphor, 5\% menthol and 5\% methyl salicylate for topical therapy of arthritis, minor joint and muscle pain using soybean oil as the oil phase, soybean lecithin, Tween 80 and poloxamer 407 as the surfactants, propylene glycol as the cosurfactant, carbomer 940 as a thickening agent\textsuperscript{13}. 

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Glucosamine sulphate as a putative agent that may retard cartilage degradation in osteoarthritis was investigated. The effect of glucosamine in an in vitro model of cartilage collagen degradation in which collagen degradation induced by activated chondrocytes is mediated by lipid peroxidation reaction. Lipid peroxidation in chondrocytes was measured by conjugated diene formation. Protein oxidation and aldehydic adduct formation were studied by immunoblot assay. Antioxidant effect of glucosamine was also tested on malondialdehyde formation on purified lipoprotein oxidation for comparison. Finally it was concluded that in an in vitro cartilage collagen degradation in which collagen degradation induced by activated chondrocytes is mediated by lipid peroxidation reaction, glucosamine decreased collagen degradation by inhibiting advanced lipoxidation reaction and thus prevents the oxidation and loss of collagen matrix from Labeled chondrocyte matrix.6

The influence of the vehicle on the release and permeation of fluconazole, a topical antifungal drug dissolved in Jojoba oil was evaluated. Series of Cutina lipogels (Cutina CPA [cetyl palmitate], CBS [mixture of glyceryl stearate, cetearyl alcohol, cetyl palmitate, and cocoglycerides], MD [glyceryl stearate], and GMS [glyceryl monostearate]) in different concentrations as well as gel microemulsion were prepared. In-vitro drug release in Sorensen's citrate buffer (pH 5.5) and permeation through the excised skin of hairless mice, using a modified Franz diffusion cell were performed. The results of in vitro drug release and its percutaneous absorption showed that the highest values from gel microemulsion were assured14.

6.3 OBJECTIVES OF THE STUDY

The aim of the present work is:
Formulation of Glucosamine sulphate emulgel using various emulsifying and gelling agents in different combinations and ratios by suitable methods.

Evaluation of the transdermal formulations for its physico-chemical properties like visual appearance, viscosity, pH, spreadability, uniformity, drug content etc.

*In vitro* drug release permeation studies through the suitable membrane models using Franz-Diffusion cell.

Comparative drug release profile and steady-state flux between the optimized emulgel and hydrogel formulation.

To predict the shelf life of the formulation by conducting stability studies as per the ICH guidelines.

### 7. MATERIALS AND METHODS

#### 7.1 SOURCE OF DATA

1. Library of M.S. Ramaiah College of Pharmacy.
2. e-library of M.S. Ramaiah College of Pharmacy.
3. The data will be collected from official books such as (IP, BP and USP).
4. Internet source.
5. RGUHS Library, Bangalore (J-Gate Helinet).
7. International and National Pharmaceutical journals.
8. Lab based studies.

#### 7.2 MATERIALS

- Drug: Glucosamine sulphate.
- Polymers like carbopol, Hydroxy propyl methyl cellulose, Tween 80 and Oleic acid etc.

All the ingredients, chemicals and solvents used will be of laboratory / analytical grade procured from reliable sources.
7.3 METHODS OF COLLECTION OF DATA

Data will be collected from the experimental work which includes:

1) PRE-LABORATORY WORK

The drug, solvents and excipients required for the formulation and evaluation of the emulgel will be procured from the reputed chemical suppliers like Merck, Ranbaxy, Qualigens and Himedia etc.

2) LABORATORY WORK

- Formulation of stable emulsion of Glucosamine sulphate using ideal emulsifying agents by suitable methods.
- Formulation of stable hydrogel using appropriate gelling agents.
- Development of emulgel of Glucosamine sulphate for transdermal delivery.
- Evaluation of the developed formulations:
  - Visual appearance test: Colour, clarity and appearance of the formulation.
  - Physico-chemical test: pH of the formulation using pH meter.
  - Apparent viscosity studies to determine the flow behavior of the formulation using Brookfield DV++ Viscometer.
  - Spreadability test.
  - Assay and uniformity content.
  - In vitro drug release permeation studies using Franz-diffusion cell.
  - To study the effect of formulation variables on the drug release studies.
  - Comparative drug release profile of the optimized formulation from emulgel and hydrogel preparation.
  - Stability studies: To conduct the studies for the optimized formulation as per ICH guideline and shelf life prediction.

7.4 DOES THE STUDY REQUIRE ANY INVESTIGATION OR INTERVENTION TO BE CONDUCTED ON PATIENTS OR OTHER HUMAN OR ANIMALS?
7.5 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTE

-NOT APPLICABLE-

8. LIST OF REFERENCES


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