1. RECOMMENDATIONS & SUMMARY GAINS, LIMITATIONS, SCOPE FOR FURTHER WORKS

1.1. SUMMARY GAINS AND CONCLUSIONS

In previous few decades, the concept like proniosomes or proniosomes derived niosomes NDDS have been convey a new aspect in research of pharmaceutical sciences and also widely accepted by the investigator in targeting the specific organ or tissue target for enhanced action of drug. Proniosomes can be easily used as non-invasive via transdermal route and oral route for sustained release of drug. In comparison to conventional liposomal preparation this provesicular system, are more accepted for the reason that it has good chemical as well as physical stability and economical. Proniosomes can also house the extensive range of drugs in its multi compartments arrangement. It has been establish that proniosomes can also be used to target specific tissue or organ in treatment of cancer e.g. haemoglobin and leishmaniasis.

Proniosomal transdermal gel (PTG) of dithranol offers an enormous prospective to diminish the adverse effects of API and amplify the curative value, as a semisolid liquid crystal preparation of nonionic surfactants. Dithranol is hydroxyanthrone, anthracene derivative with an antipsoriatic activity. It interfere mitotic rate and its repair, interfere cyclic nucleotides. Its action leads to inhibit the DNA synthesis in psoriasis. Dithranol is commonly accessible in a variety of marketed preparation for example Drithocreme, Anthraforte, Anthranol and Anthrascal.

Dithranol drug is responsible to cause different skin related troubles e.g. irritation, erythema, peeling and possible formulation difficulties like photosensitivity and high lipophilicity of drug this problem overcome by preparation of proniosomal transdermal gel and these intrinsic drawbacks allied with conventional preparation of dithranol, an effort is made to propose an choice of drug delivery system.

The present research investigation decidedly prove the huge potential of provesicular system in accomplishment of elevated skin permeation flux along with high skin retention of dithranol and with improved pharmacodynamically antipsoriatic activity without any skin irritation.
Provesicular as a carrier of drug delivery systems was given benefits due to controlled and sustained release action. It’s developed a lot of awareness in various scholars and researchers. Especially the areas of transdermal preparation carrier have enormous scope future because this is a non-invasive and provides good local action without cause any side effects. PTG contain equally phospholipids and non ionic surfactant which perform penetration enhancing role along with helpful in mounting drugs permeation.

A successful challenge was finished to build up proniosomal gel for transdermal delivery of dithranol via different grades of surfactant Span and Tween and determine of different characterization such as in vitro, in vivo and ex vivo.

It can be concluded that by following results obtained

- Preformulation study of pure drug was performed by different identification test such as FTIR and DSC of dithranol alone and mixture of drug lecithin, cholesterol and drug excipients mixture showed not any significant interaction therefore it can be concluded that dithranol and other excipients were compatible with each other.

- Optimization PTG of nine formulations were prepared by $3^2$ factorial designs to evaluate the effect of concentration of independent variables such as surfactants (A) and cholesterol (B) for different dependent variables Flux and percentage entrapment (%EE).

- Entrapment efficiency was amplified with raise in concentration of cholesterol. It may be clear the drug lipophilic part predictable to be residence approximately completely inside bilayer of the lipid proniosomes.

- When the concentration of cholesterol increases the flux of vesicle was decreased and lipophilicity was increasing with the cholesterol content.

- Release of dithranol was dependent upon cholesterol concentration. When cholesterol content increases lipid bilayer is more intact as an obstruction for release of drug and preventing leak out of drug through manage flexibility of membrane along dropping the permeation nature of membrane therefore lesser elution of drug from the proniosomes.
The prepared dithranol PTG showed better non irritant and sustained release compared to the commercial preparation with better drug penetration as well as stable. The optimized formulation DNPS6F8 showed better competence for local antipsoriatic preparation.

Skin irritation test was performed for selected formulation DNPS6F8 on Swiss albino mice and compare with marketed formulation DEROBIN ointment 1.125% w/w.

The test proniosomal gel formulation was evaluated for not any significant signs of toxicity were noticed in animals like redness, erythema in animal skin, convulsion, tremor, circling, depression, hypothermia and mortality treated topically with respectively 1000, 1500 and 2000 miligram/kg of BW dose DNPS6F8 Proniosomal formulation. Hence it has observed that formulated Proniosomal gel was safe up to 2000mg/kg. Therefore 1% w/w Proniosomal gel was selected for future use of gel for anti-psoriatic activity.

Dithranol proniosomal transdermal gel showed good stability at the ending of two months at 5± 2°C. Proniosomal transdermal gel formation by using ratio of span 60 with cholesterol 150: 40 (DNPS6F8) shown better deposition in skin and most favorable entrapment PDE has shown potential for delivery of antipsoriatic drug DTH.

In vivo pharmacokinetic and pharmacodynamic study could be affected in order to determine the delivery system for clinical use. Additional long-term stability studies, the prepared PTG of dithranol was not only improving the antipsoriatic activity but also organized the drug availability for skin penetration with less delay time without less staining. Therefore, the prvesiccular system of dithranol was keep significant promise to get better the degree as well as the inception of action of dithranol.

The optimized formulation was able to deal with the most demanding problem of skin-irritation of dithranol with noticeable antipsoriatic activity. The research investigation gives an opportunity for a new research area, the of drug-loaded proniosomal carrier systems was effectively extrapolated for many different topically preparation.
Promising PTG preparation DNPS6F7, DNPS6F8, DNPS6F9, and Test ointment were compared for ex-vivo permeation and deposition study. As a final point the optimized PTG formulation DNPS6F8 was subjected to different test on Swiss albino mice.

The presence of cholesterol, hydrophilic surfactant like Tween produced better entrapment efficiency of vesicles with uniform size. However this entrapment efficiency has quite low in contrast to those prepared by Span. In vitro drug flux was decrease with raise in cholesterol concentration. The outcome showed that as cholesterol concentration increases, at a particular limit, stable vesicles are created and sustained pattern was obtained.

In vitro dithranol release data was shown model for best fitted in higuchi as well as Korsmeyer peppa’s model shown that release of drug was restricted frequently by mechanism of diffusion and drug anomalous transport method.

Consequently from this research it was concluded that the optimized PTG of dithranol showed increase in the antipsoriatic action of drug without any irritation, erythema, peeling at the targeted psoriatic skin when comparison with commercial dithranol cream.

PTG could be a capable transporter for dithranol as well as new API particularly attributable to their easy manufacturing and simplistic develop. This is suggested that PTG should be kept in cooled temperature to attain most excellent stability.

Antipsoriatic activity requires release of drug without any other skin related problems which can be achieved through used PTG of anthralin.

The current research exposed that dithranol-loaded PTG offered an improved and high encapsulation of drug efficiency and transdermal flux. The DTH-loaded PTG showed better pharmacological activity on animal (mice) when compared with the standard marketed cream (dithrocram) therefore important to the conclusion that DTH-loaded proniosomes recommend an appropriate purpose for transdermal delivery for dithranol.
The current researches unambiguously confirm the enormous potential of proniosomes in accomplishment of high skin permeation flux of DTH and with potential optimized formulation devoid of any skin irritation. DTH is the old and gold drug in the treatment of psoriasis. PTG formulations of DTH were prepared with endeavor to supply of the drug via route of transdermal and estimated for their competence.

Various parameters of formulation were accepted for PTG preparation. Nonionic surfactant span 60 with cholesterol and use for gel composition Carbopol 934 was found to be suitable for viscosity, better consistency, homogeneity, spreadability, and Ex-vivo drug diffusion. The relevance of $3^2$ factorial designs establishes to be a useful tool for optimization of DTH-PTG.

As a drug delivery tool, proniosomes preparations are stable and do not need particular circumstances for protection, handling, storage as well as commercial manufacturing. These systems were reducing the toxicity and improve diffusion of drug therefore it fascinated researchers as an alternate approach for release of drug as transdermal form. An extensive diversity of active drugs of diverse curative actions may also be improved by proniosomal drug delivery system in the form of different dosage form. This system on behalf of other non stable processes appears to be a competent carrier of drug with physical and chemical stable with potentially scalable for marketable feasibility.

In this research different types and filling of nonionic surfactant for formulation of proniosomes was assayed with in vitro permeation of dithranol. Proniosomes derived niosomes was opinion to be improved delivery of drug in contrast to vesicular system such as liposomes due to different factors e.g. preparation cost and drug stability etc. These formulations represent similar with liposome and niosomes hence provesicular can symbolize the substitute of vesicular model and capacity to encapsulate numerous drugs inside their multi-environmental arrangement. Proniosomes can be used for different types of drug deliveries such as ophthalmic, topical or dermal, parenteral, oral, vaccine etc.

The result of experiment and related hypothetical analysis has proposed that proniosomal formulations of dithranol permeate from direct transport of drug from vesicles to the skin
or the effect of non-ionic surfactant towards penetration by work as penetration enhancer. These conclusions suggest that in provesicles may play a significant role than already existing marketed preparation. Proniosomal transdermal gel could be developing into a constructive preparation of dithranol, particularly due to easily scale-up, easy manufacturing and capability to adjust dithranol move across dermis. Optimizing the amount of cholesterol and surfactants as excipients drug may be easily encapsulated with lessen dose incidence and adverse effects for better therapeutic action. Dithranol can be productively formulated in proniosomes form. The results of the ex-vivo penetration studies confirmed that about a deep penetration of DTH with localization in skin as compared to existing marketed preparation.
5.2. **RECOMMENDATION**

In this research work entitled “Preparation and evaluation of Pronosomal transdermal gel of dithranol” I have prepared of different proniosomes formulation of dithranol in form of transdermal gel. After that I have performed different optimization technique for evaluation of prepared formulation. Different formulations undergo statistical data analysis with design expert software and determined the regression and ANOVA analysis.

I am recommended that during evaluation prepared proniosomal transdermal gel has shown reasonable Flux and percentage entrapment of dithranol. After in vitro release performance experiment, all formulation undergo towards ex vivo permeation and compare with marketed formulation of test Derobin ointment and it was shown that this formulation have equal flux value. Evaluated and optimized formulation also had shown better in vitro in vivo (IVIVC) correlation. DTH is mainly related to irritation, erythema, and other skin toxicity causing the drug so that it is very necessary step for determine acute dermal toxicity study with animal as on Swiss albino mice. The antipsoriatic activity of prepared optimized formulation was also performed by mouse tail model with slight modification on Swiss albino mice at different concentration of gel of dithranol and recommend that psoriatic cells shown that improved orthokeratotic differentiation in epidermal scales. I had found that DNPS6F8 formulation which was contain specific amount of cholesterol and surfactant Span 60 and markets Derobin ointment had shown approximate equal antidepressant activity in swiss albino mice. In this study the per cent drug retention was found in range 98.59 to 88.43 % after storage of 60 days at low to higher temperature respectively.

- It is recommended that Coacervation phase separation techniques should be used for preparation of transdermal proniosomal gel for better performance.
- It was also recommended that cholesterol and Spam 60 excipients should be used for better transdermal proniosomal gel preparation of anthraline.
• It was recommended that $3^2$ factorial design with design expert software useful tool for statistical determination and experimental optimization.

• It is recommended that 1000mg to 2000 mg/ kg of topically Proniosomal gel formulation anthaline treatment range may be tolerable dose without any acute dermal toxicity related to irritation, redness, erythema etc in antipsoriatic preparation of DTH.

• By the help of proniosomal transdermal gel preparation we are avoiding clearly any invasive or painful treatment which is very necessary in long duration treatment requirement disease i.e. Psoriasis, dermatitis etc.

• Proniosomal transdermal gel preparation may be useful tool for delivery of protein and polypeptdal drugs such as various vaccine deliveries, along with that augmented permeability of skin with safe and effective.
5.3. LIMITATIONS

In this research work entitled “Preparation and evaluation of Proniosomal transdermal gel of dithranol” I was prepared of different dithranol proniosomes in form of transdermal gel but some of limitation also exist in these formulation.

Skin of human body is biggest organ of body which performed largest barrier function of body and deals to many external and environmental factors. Penetration of any drug molecule into body by outer surface of body has tough task because barrier function of skin prevent permeation of active moieties so that this layer work as rate limiting steps in poorly lipophilic drugs.

Preparation of dithranol transdermal gel was passes to different evaluation parameter and various process variables which were dependent and independent in nature and affected of character of final preparation.

Prepared dithranol transdermal gel was also causes skin irritation beyond particular concentration and at higher dose. This may be prescribed that the dose of anthralin was not exceeding above 1 mg in transdermal preparation otherwise different skin immune mediated response or adverse effect reveals.

Some of formulation leak out of active moieties if concentration of cholesterol not proper maintain and release of drug prior to application.

Proniosomal transdermal gel of dithranol was also causing formulation difficulties like photosensitivity and temperature dependence stability at higher temperature most of drug degraded and desired action was not possible but these all intrinsic drawbacks allied with other conventional preparation of dithranol, an effort is made to propose a choice of drug delivery system.

Prepared gel has not shown physical integrity of the formulation if gel will not store or handled as proper manner and guidelines.

Sometimes transdermal gel cannot permeate through skin because size of drug particles in case of vaccine formulation such as a virus particle in vaccine not cross the barrier of
skin and diffuse of such formulation intrepted although it should be suggested that size of drug particle and formulation variables not exceed 500 dalton for proper passive diffusion along with beyyer lipophilic nature of drug.
5.4. SCOPE FOR FURTHER WORKS

On the demand or medical requirement for safely transfer of active drugs in local infectious disease that may be possible by this route.

It is proved that proniosomes delivery system is a more effective than noisome and liposomes, and their additional properties superior over others e.g. formulation, carrying, storage and transportation. We can say that with help of these system ruleout the vesicular preparation with better physicochemical properties of API as well as dosage form.

In old persons as well as adolescent there is major problems were difficulties in swallowing of solid dosage form and patients who are suffered from chronic emesis and nausea, transdermal drug administration are expedient route of application with better patient compliance. This delivery route is trouble-free, effortless, and act or behave as panacea of medication therefore in commercial point of view huge market sector offered for a pharmaceutical industries.

Proniosomal preparation was converted into niosomes before producing its action at targeted site. In most of cases the immune system of body was resposiable for immune generating disease it was mainly containg lot of immune defence cells like langerhans cells which was form a barrier against chemicals and antigen presenting cells present in epidermal viable layer noticed to resposiable for immune response disease.

In Present time huge numbers of cosmetic preparations existing in the market are turn to account as vesicular preparation for carrying cosmetics preparing.

Following key points related to future prospects of proniosamal preparation as gel form and more works could be performed with these type preparation.

- Improvement by topical action lot of novel physical augmentation techniques have been used for dermal route and facilitated or controlled passive diffusion of drugs.

- The clinical development of formulation was required for the enteries of preparations in to market for commercialization of dosage form.
These formulations were used to extended release of drug for their maintaining stable plasma drug concentration and reducing the dosing frequency along diminishes the possible side effects of the medication.

Firstly, in future, proniosomal transdermal preparation may be useful technique for delivery of minute particles of drugs by dermal route and prolong to be used for the right position those drugs which was at present taken through buccal as well as injectable preparation.

Second one is this formulation will be use as penetration for delivery of large molecular size and both hydrophilic and lipophilic drugs for topical or dermal formulation i.e. ointment, creams, gel paste etc.

These prepared systems will be targeted, to specific organ or tissue by enhancement of biochemical reaction or physicochemical action of drugs on targeted site of body.

Proniosomes was facilitating to diffusion or penetration of new drug entities for treatments of life threatening disease without producing any side and adverse effect through stratum corneum barrier layer of skin.

Transdermal route was better site for drug action due to rapid achievement and localization of drug into the skin has beneficial for clinical and preclinical study aspects.

Proniosomal transdermal gel has controlled the release of drug and maintaining dosing frequency requirement and controlled the delivery rates in providing sustained effects of drug for in chronic disease patient profiles.

This research provides a review of important feature concerning with transdermal preparation for esteeming to commercialization of dosage form for external application

The future experiments would investigate the appropriateness of PTG with other local action drugs such as hypertension, heart disease, and Baldness treatment, eczema, dermatitis etc. without cause any side effects and other drawbacks by improved effective intended therapy.