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Formulation and Evaluation of Topical Gels with Solid Dispersions of Tolperisone HCl Drug.

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ABSTRACT-

Formulation and development of a most effective product from poorly soluble drugs is one of the most challenging tasks in pharmaceutical industries. Solid dispe rsion is an efficient solubility enhancement method to overcome the solubility problem.Solid Dispersion of Tolperisone Hydrochloride was prepared by Solvent Evaporation Method and Co-Evaporation Method. Standard solution of Tolperisone Hydrochloride was prepared with0.01N NaOH and methanol for spectrophotometric methods at 283nm. The interaction of several excipients and the drug sample used in the formulation were investigated for FTIR. Prepared solid dispersion was then analyzed for various parameters like Saturation solubility studies, Permeation studies and in-vitro drug release studies. Finally, the solid dispersion prepared was used to formulate Tolperisone gel formulations with the help of Carbopol 934and HPMC with other ingredients with formula and methods. The aim of the work is an attempt to made formulation and evaluation of Tolperisone Hydrochloride solid dispersion incorporated topical gel by Solvent Evaporation Method with the aid of solid dispersion. Solid Dispersion incorporated topical gel are thermodynamically stable. Among the solid dispersion the formulation which shows the highest release was selected to incorporate with Carbopol 934 and HPMC base to form gel. The in vitro and in-vivo study for optimized Tolperisone Hydrochloride solid dispersion incorporated gel FG1 was compared with marketed gel, revealed a significant increase in skin permeation profile and anti-inflammatory effects for optimized gel. The percent inhibition value of optimized gel after 12 hours of administration was found to be 5.22% as compared with 5.41% for marketed gel. It can be concluded that optimized carbopol gel containing Tolperisone Hydrochloride solid dispersion have great potential for topical delivery. This research target is to promote the dissolution and solubility of SM by employing a technique called solid dispersion and then incorporating the formula of solid dispersion into a topical gel that can be used for wound healing.

There were alot of drugs in the category of rejection of use because of low oral bioavailability and the main factors that are responsible for these are poor drug dissolution /solubility, less permeation through epithelia of the gastrointestinal tract that are responsible for less bioavailability. Therefore, the key property that governs the dissolution, absorption and in vivo efficacy of any therapeutically active substance is the aqueous solubility. Drugs that have very low aqueous solubility have very low rate of dissolution and thus face oral bioavailability problems.

Key word- Tolperisone Hydrochloride **,**Solid Dispersion incorporated topical gel, Carbopol, HPMC

INTRODUCTION

SKIN:

Skin is considered as the largest organ of the body that made up to 10% of the body mass and interacts it to the external environment. It serves as a protective barrier between the body and external environment. The surface area of skin 1.5 to 2.0 sq. meters whereas the thickness lies between 0.5 – 3mm. Skin conditions are prevalent across different cultures, ages and socioeconomic statuses, making one of the most widespread medical issues worldwide.[1]

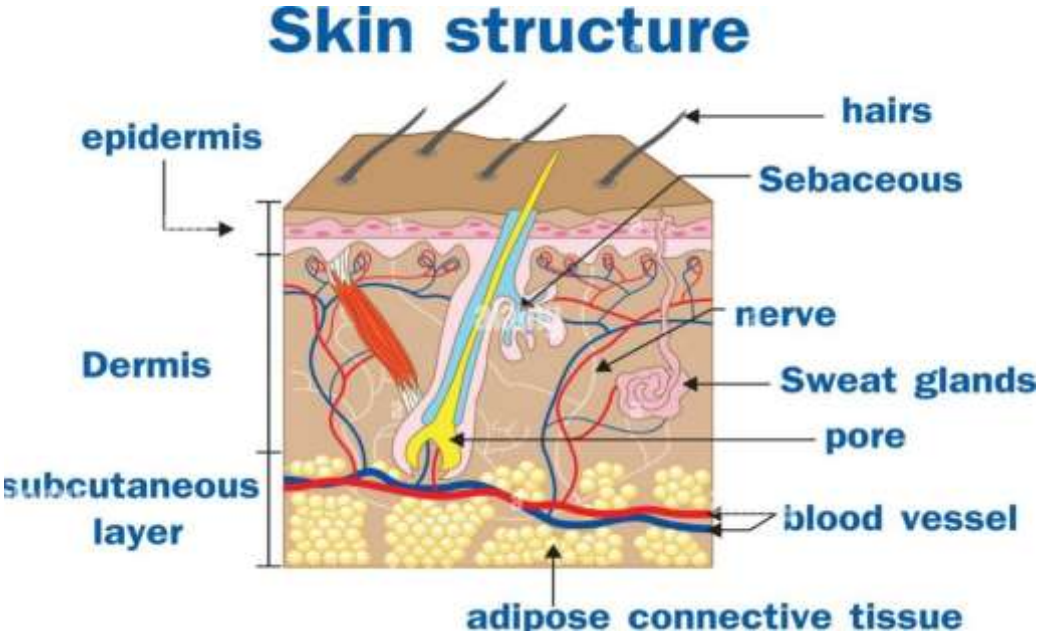
The skin composed of 3 layers:

- Epidermis
- Dermis
- Sub-cutaneous tissue

Apart from these, skin also have associated appendages like hair follicles, sweat ducts, apocrine glands. Accidently or deliberately, a lot of agents are applied to the skin for beneficial or deleterious results. In historical times, the use of topical products was noticeable and the data showed that in 1940's people used topical anti-infective and hormonal agents. Later in 1980's the modern transdermal patch technology was established.[2]

The main areas of use of dermal preparations are:

- Local effects
- To transport drug to the skin (like- Nicotine patches for skin)
- To make effects of the preparation on the surface of skin to target deeper tissues (Sunscreens, Cosmetics and Anti-infectives).
- To neglect the problems associated with the stomach emptying, pH, deactivation of enzymes, and first pass metabolism.
- To avoid the first pass metabolic effects of skin.
- Vitamin D synthesis: The skin synthesizes vitamin D when it is exposed to sunlight.
- Absorption: The skin can absorb certain substances such as medications, cosmetics and chemicals.
- Excretion: The skin eliminates waste products such as: water, salts, and small amounts of nitrogenous waste.
- Sensation: The skin is responsible for sensing different types of stimuli such as: touch, temperature, pressure, and pain.
- Immune defense: The skin serves as a barrier against infections and contains immune cells that help defend against pathogens.[3]



(Gross structure and functions of the skin)

It is necessary to focus on that the homeostatic, protective, and sensing functions of the skin are united and overlapping. A clear illustration of this is for a chemical compound the barrier properties of skin resists its entry (by stratum corneum), metabolism bypasses the stratum corneum (in epidermis), and then to pay attention to the damage caused by its entry (inflammatory mediators released in epidermis) and the removal of this chemical compound with the supply of dermal blood and distribution in the body organs that are responsible for elimination of this chemical entity either by metabolism from liver or by excretion with kidney. The regulation of heat happens with help of the subcutaneous fat pad, physiological regulation of blood flow to affect, for example, the loss of heat by vasodilation and its cooling by perspiration.[4]

SOLID DISPERSION

There are a lot of techniques for poorly water soluble drugs to enhance their dissolution rates are micro-ionization, inclusion complexion with cyclodextrins, conversion into amorphous drugs as well as the formation of solid dispersions with hydrophilic carriers. Out of these, solid dispersion is the technique that is used widely to increase the intrinsic solubility, dissolution and although results in the oral bioavailability of poorly water soluble drugs. Chiou and Riegelman developed the solid dispersion formulation.

Traditionally, solid dispersion was recognized as the dispersion includes one or more active ingredients in a matrix or inert excipient but the condition is this is that the active ingredients could exist in finely crystalline, solubilize and amorphous form. As it is easy to prepare, easy to optimize and reproducibility, it is the most commonly used method by the formulators. Solid dispersion systems are in practice because they increase dissolution rate and bioavailability of water insoluble drugs. In case of solid dispersions, in inert hydrophilic carriers a drug may exist as an amorphous form to form solid solutions. Upon exposure with aqueous media the carrier get dissolve to release the drug as fine colloidal particles. As a result, this deduced the particle size and increase the surface area that helps in improvement of the dissolution rate and oral absorption. Moreover, no energy is needed to break

the crystal lattice of the drug at the duration of dissolution process. If hydrophilic carriers surrounds the drug, it will increase the wettability and solubility of the drug.

Types of Solid Dispersion

Binary solid dispersion: It has a drug and a polymeric carrier.

Ternary solid dispersion*:* It has a drug, polymeric carrier and a surfactant. The most common surfactant used is Polysorbate 80 which plays a crucial role in dissolution of the solid dispersion to enhance the dissolution of poorly soluble drugs in case of both ternary and binary solid dispersion. In spite of this, the dissolution of ternary solid dispersion is somehow faster than binary, this is due to Polysorbate 80 which enhanced the wettability and solubilized the non –molecularity and the drug's crystalline fraction and one clear illustration of this is Ofloxacin.

Polymers like Polyethylene Glycol (PEG), Polyvinyl Pyrrolidone (PVP), polyvinyl pyrrolidone-vinyl acetate copolymer are used to formulate surface solid dispersion by fusion technique to enhance its solubility. It is the process which helps in the deposition of the drug on the surface of the certain material which changes the dissolution characteristics of the drug. Deposition of drug on the surface of inert carrier results in the deduction of particle size that helps in the therapy or treatment that leads to faster dissolution of drug.

Method of preparation

Various methods for the preparation of solid dispersions are:

a) Solvent evaporation method
b) Modified solvent evaporation method
c) Melting method
d) Melt-solvent method
e) Kneading method
f) Co-grinding method
g) Co-precipitation method
h) Co-precipitation with super critical fluid
i) Spray drying method
j) Gel entrapment method

TOPICAL GEL

There are a lot of pharmaceutical dosage forms in pharmaceutical company out of which the topical gel plays a crucial role because of it's a lot of benefits like therapeutic effects and myriad of limitations has minimized like systemic effects. Gelling agent like a polymer is the main ingredient of the topical gels because of their inertness, safety and biocompatibility, good adhesion to mucus membrane of permeation of drug membrane and as well as biodegradable. In formulation, swelling, syneresis, and rheological properties are the characteristics that polymer should have to enhance solidifying stiffness of the system. Commercially there are plethora of gelling agents for the formulation of topical gels such as Carbomers and Semi-Synthetic Cellulose as well as cellulose derivatives. The example of central acting skeletal muscle relaxant is 1,2,3 Carisoprodol by blocking pain sensation between brain and nerve. Because of short life of Carisoprodol in oral dosages it causes a lot of fluctuations and ultimately results in drowsiness, GI irritation and so on.

DEFINITION: Gels are defined as semi-solid dispersion systems which may contain suspension of small molecules dispersedin a suitable vehicle by using a gelling agent.

Benefits of gels:

- Greater surface area.
- Applicable for all skin types like dry or oily skin.
- Target only specific area.
- Easy absorption.
- Plumping effect on skin.

- Leaves no residue.
- Keeps skin hydrated.
- Greasiness low or non-greasy, can be removed by rubbing easily.
- Excellent adherence property.
- Biocompatible.
- Eco-friendly.

MATERIALS AND METHODS

Materials:

The following materials that were either AR or best possible LR (Laboratory Reagent) or best possible grade available used for the formulation of solid dispersion gel are: Materials used for Research Work

S.No.	Material Used	Company Name
1.	Tolperisone Hydrochloride	Nice Chemicals Pvt. Ltd
2.	PVP	S. D. Fine Chemicals Ltd.
3.	β-Cyclodextrin	S. D. Fine Chemicals Ltd.
4.	Carbopol	HI Media Laboratories
5.	TEA	GSK Pharmaceuticals
6.	Glycerol	Loba Chemicals Pvt. Ltd.
7.	Methyl Paraben	HI Media Laboratories
8.	HPMC	Loba Chemicals Pvt. Ltd.

Instruments used for research work:

S. No.	Instrument Name	Company Name
1.	Electronic Digital Balance	Shimadzu, Japan
2.	Magnetic Stirrer	Genuine Equipment Manufactures, Coimbatore
3.	Brook Field Viscometer	Brook field Engineering Labs.
4.	FT-IR	Shimadzu, Japan
5.	Dissolution Test Apparatus	Electro Lab, Mumbai, India
6.	Double Beam UV/VIS Spectrophotometer	ELICO, Mumbai, India

7.	Digital pH meter	Digi sum Electronics, Hyderabad

Methods:

Preformulation Studies[77]: Preformulation study is the first step in the development of dosage forms of a drug substance. It is the study of physical and chemical properties of drug particles alone and combined with different excipients. The study is useful to find out any interaction between drug and excipients and also useful in developing stable and bioavailable dosage forms. The drug samples obtained were examined for its appearance and color and results are recorded.

Appearance of drug:

The drug samples obtained were examined for its appearance, color, and results are recorded.

UV Spectroscopy:

Preparation of Standard Solution:

For spectrophotometric method, the standard sample was prepared as follow. Tolperisone Hydrochloride standard was taken in 50 mg and made the value 100ml with 0.01N NaOH, sonicated for 10 minutes, filtered the solution and took 2 ml of filtered solution and made the volume 100ml with 0.01 N NaOH. For the spectrophotometric method 2, in the above method for standard preparation, 0.01N NaOH was replaced with methanol.

FTIR Spectroscopy: The interaction of several excipients and the drug sample utilized in the formulation were investigated with FTIR. For compatibility tests, the FTIR spectra of pure Tolperisone, polyvinyl pyrrolidone, cyclodextrin, physical mixtures of drug and PVP, and pure Tolperisone were examined.

Preparation of Standard Curve of Tolperisone with 0.01N HCl (pH is 1.2):

A 100ml volumetric flask was filled with precisely weighed 100mg of Tolperisone, which was then dissolved in a little amount of 0.1N HCl. Its principal stock solution had a 1000 g/ml concentration. A volumetric flask of 100ml was filled with 0.1N HCl, which had a concentration of 100g/ml, and 10ml of primary stock solution was pipette out and transferred there. 10ml were pipette out of the second stock solution and diluted to 100ml with 0.1N HCl. From the third stock solution, aliquots equivalent to 2-10 g/ml (2,4,6,8,10 ml) into a succession of 10 ml volumetric flasks, and the liquid was topped off to 10ml with 0.1N HCl. Using a UV-Visible Spectrophotometer, the absorbance of this solution is determined at 254 nm. Concentration (gm/ml) was plotted on the X-axis and absorbance on the Y-axis was used to generate the calibration curve.

Preparing Tolperisone Solid Dispersion:

Using a Fourier Transform Infra-Red Spectrophotometer, initial tests of compatibility between Tolperisone and carriers were conducted, and compatible excipients were employed in the formulation of the final product. For the study, 1% of the tolperisone was employed. Cyclodextrin and Polyvinyl pyrrolidone carriers were used in the ratios of 1:1, 1:2, 1:3 and 1:1, 1:3 and 1:5 to create a physical combination of tolperisone. Solvent evaporation method and co-evaporation techniques were used to create Tolperisone solid dispersions. The drug and carrier were dissolved in methanol with 15 minutes of stirring to create solid dispersion by solvent evaporation, which was then stored in desiccators for 4 days. A #120 sieve was used to filter the resulting solid dispersion.

The drug and carrier were dissolved in methanol and the SD was made by solvent evaporation method. The organic drug solution was then gradually added to the aqueous carrier solution, followed by stirring of 24 hours at 37 degree Celsius with the magnetic stirrer at 300 rpm. A sieve # 120 was used to filter the resulting solid dispersion.

Different batches of Tolperisone Solid Dispersion Formulation:

Sr. No.	**Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1.	Tolperisone Hydrochloride (%w/w)gm	1	1	1	1	1	1
2.	Polyvinyl Pyrrolidone (%w/w), mg	-	-	-	1:1	1:2	1:3
3.	Beta – Cyclodextrin	1:1	1:3	1:5	-	-	-
4.	Water: Methanol	Qs	Qs	Qs	-	-	-
5.	Methanol	-	-	-	10ml	10ml	10ml

RESULTS

PREFORMULATION STUDIES:

Preformulation studies are necessary to understand the physicochemical properties of the drug and other excipients used in the formulation. The results of the various pre-formulation characterizations are given below:

Appearance of drug substance:

The drug sample obtained was appeared as a white crystalline powder having characteristic odor and hygroscopic in nature.

Determination of Melting Point:

Melting point of Tolperisone Hydrochloride was found to be 167-174^{0}C.

Solubility Studies:

- Tolperisone Hydrochloride is very soluble in acetic acid,
- Freely-soluble in water and in ethanol (95%),
- soluble in acetic anhydride,
- slightly soluble in acetone and
- insoluble in diethyl ether

pH: (Limit 4.5-5.5)

Weigh 1.0 gm of tolperisone hydrochloride under examination in 20 ml of water.

Result: 5.09

Identification test:

A. By chemically:

Procedure: Weigh 0.2 gm of tolperisone hydrochloride in 2 ml of ethanol (95%), add 2ml of 1,3 dinitrobenzene solution and 2 ml of sodium hydroxide solution and then heat.

Observation: A red colour develops on heating

B. Chemical method:

Procedure: Weigh 1 gm of tolperisone hydrochloride and dissolve it in 20 ml of water, take 5 ml of this solution and add 2-3 drops of iodine solution.

Observation: A red brown ppt. formed on addition of iodine solution.

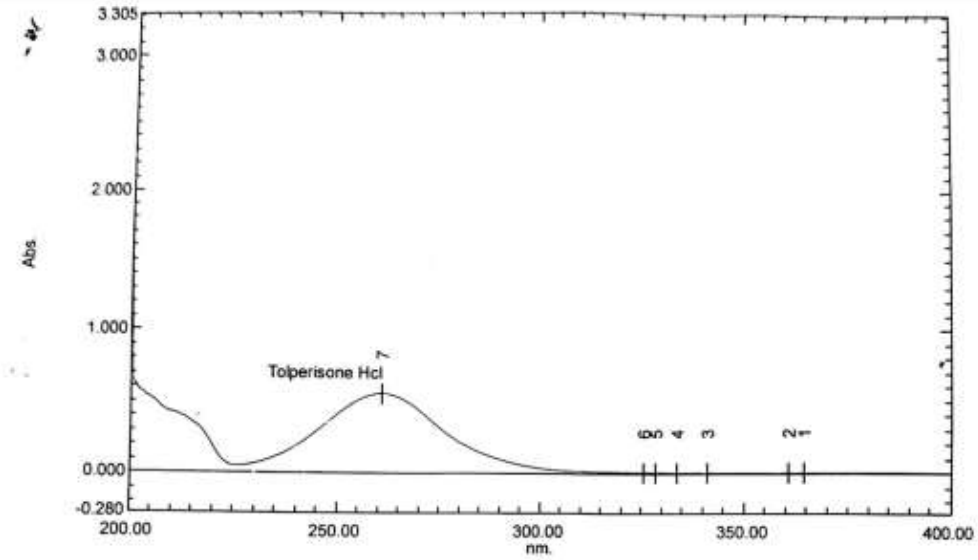
C. Clarity and colourless:

Procedure: Weigh 1 gm of tolperisone hydrochloride under examination and add 10 ml of distilled water.

Observation: The solution was clear and colourless.

UV Spectroscopy:

The UV spectrum analysis of Tolperisone Hydrochloride was carried out using methanol as blank and the λ max of Tolperisone was found to be 283 nm.



[Measurement Properties]
Wavelength Range (nm.): 200.00 to 400.00
Scan Speed: Fast
Sampling Interval: 0.2
Auto Sampling Interval: Enabled
Scan Mode: Auto

[Instrument Properties]
Instrument Type: UV-1800 Series
Measuring Mode: Absorbance
Slit Width: 1.0 nm
Light Source Change Wavelength: 340.0 nm
S/R Exchange: Normal

[Attachment Properties]
Attachment: None

[Operation]
Threshold: 0.0010000
Points: 4
InterPolate: Disabled
Average: Disabled

[Sample Preparation Properties]
Weight:
Volume:
Dilution:
Path Length:
Additional Information:

No.	P/V	Wavelength	Abs.	Description
1	ⓟ	364.40	0.002	
2	ⓟ	360.80	0.002	
3	ⓟ	341.20	0.003	
4	ⓟ	333.60	0.005	
5	ⓟ	328.40	0.006	
6	ⓟ	325.40	0.007	
7	ⓟ	260.80	0.559	

DISCUSSION

In the present study, an attempt was made to develop and evaluate solid dispersion incorporated topical gel of Tolperisone Hydrochloride as skeletal muscle relaxant to treat this problem in a better way. In usual way, Tolperisone Hydrochloride have only 17% oral bioavailability due to hepatic first pass effect. Thus, formulated Tolperisone Hydrochloride solid dispersion incorporated topical gel prevents or avoids first pass metabolism as their absorption directly takes place through skin which results in better bioavailability facilitated by solid dispersion.

CONCLUSION

The conclusion drawn from the present investigation is given below:

- Preformulation Studies of Tolperisone Hydrochloride were performed. From the FT-IR, the interference was observed, and found that Tolperisone Hydrochloride did not interfere with the polymers used.
- Among the solid dispersion, formulation which showed highest release was selected for further development as a gel formulation incorporating Carbopol 934 and HPMC.
- Through various evaluations including swelling index, in-vitro release studies, spreadability, viscosity, homogenization and saturation solubility, the FG1 formulation containing Tolperisone Hydrochloride and β-Cyclodextrin solid dispersion incorporated into Carbopol 934 gel was chosen for both in vitro and in- vivo studies.

- Comparisons were made between the optimized FG1 gel and a marketed gel through in vitro skin permeation study, in vivo anti-inflammatory effects, and skin irritation study. The results showed a significant increase in skin permeation and anti-inflammatory effects for the optimized gel compared to the marketed gel.
- The percent inhibition value for the optimized gel after 12 hours of administration was 5.22%, slightly lower than the 5.41% observed for the marketed gel.

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