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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF TRAMADOL HYDROCHLORIDE LOADED TRANSFEROSOMAL GEL BY THIN FILM HYDRATION TECHNIQUE

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Abstract

Objective(s): The current study's goal is to develop and test a tramadol hydrochloride transdermal gel based on vesicular drug delivery approaches.
Materials and methods: Transferosomes were chosen as the colloidal carrier for tramadol hydrochloride transdermal gel preparation. Thin film hydration was used to create transferosomes. The obtained transferosomes were characterised for drug content, vesicular diameter, zeta potential, entrapment efficiency, invitro drug release studies.
Results: T5 (made via thin film hydration and comprising a soya lecithin: Tween 60 ratio of 1:2.5) was deemed the best transferosome formulation due to its 274.2nm mean vesicular diameter, -29.5 mV zeta potential, 93.9% drug content, 97% entrapment efficiency, and 92.7% sustained drug release after 12 hours. The T5 formulation was included into the gel. There was a comparison between plain gel and transfersomal gel. Transfersomal gel was rated superior to the other gels due to its higher drug concentration (91%), spreadability (18.35 g.cm/sec), pH (6.9), and sustained drug release profile over 12 hours.
Conclusion: By comparing transferosomal gel with plain gel transferosomal gel indicated better results than plain gel.

Introduction:-

In recent years, the research landscape has turned toward the creation of new forms of drug delivery systems with the goal of high therapeutic activity as well as patient compliance. Many drug delivery systems with increased therapeutic action are being developed, yet some problems with some delivery systems are not being overcome.

Orally delivered drugs are subjected to a hostile environment in the GI tract, where most pharmaceuticals deteriorate in changing pH settings, face solubility issues, and, most importantly, experience first-pass metabolism. The disadvantages of parenteral preparation include the inability to reverse drug, hypersensitivity reactions, infection and emboli risk, and cost. Some drugs have a bitter taste, and taking such a bitter medication, as well as the pain associated with the needle in parenteral delivery, make patients less obedient [(1)].

Due to a range of advantages with this strategy, much attention has been concentrated on the development of topical medicine delivery during the previous few decades. An average adult's skin has a surface area of around 2 m^2 and a total weight of 3 kg; it receives approximately one-third of the blood circulating throughout the body. The

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application of a medicine to the skin for a localised impact is referred to as topical drug delivery, whereas transdermal drug delivery systems (TDDS) use the skin as a potential conduit for the transport of pharmaceuticals with systemic activity. TDDS is one of the systems with high patient satisfaction. Some potential advantages of the transdermal route over other conventional routes include the avoidance of first-pass metabolism, the predictable and extended duration of activity, the utility of short half-life drugs, improving physiological and pharmacological response, avoiding drug level fluctuation, inter- and intra-substance interactions, and inter- and intra-substance interactions [2,3].

However, it has a number of disadvantages, including the possibility of local irritation, erythema, itching, and restricted permeability in the stratum corneum. The stratum corneum's permeability, which limits drug transport and frequently renders this route of administration unsuitable for medical use [4], is a major hurdle to dermal and transdermal drug delivery. The epidermis' top layer is made up of keratinized, flattened remnants of previously actively dividing epidermal cells that are water-resistant and function as a strong flexible membrane. Many technologies and systems, including electrophoresis, iontophoresis, chemical permeation enhancers, microemulsions, sonophoresis, and vesicular systems such as liposomes, Niosomes, ethosomes, and transferosomes, have been investigated to overcome this barrier, and one of the most promising techniques is to formulate novel vesicular carriers for sustained drug delivery through skin [5-10].

These transfersomes all appear to be promising. Transfersome is a novel type of vesicular drug delivery device. In 1991, Gregor Cevc coined the term transfersomes and the underlying concept. A transfersome, in the broadest sense, is a highly flexible and stress-responsive complex aggregate having an aqueous core surrounded by a lipid bilayer complex.

Transfersome is a trademarked name for the patented medicine delivery technique developed by the German business IDEA AG. A transfersome carrier is an artificial vesicle that functions similarly to a cell vesicle or a cell in exocytosis, making it suitable for controlled and potentially targeted medication administration. The name derives from the Latin word "transferred," which means "to convey across," and the Greek word "soma," which means "body." An ultra-deformable vesicle with an aqueous core surrounded by a complex lipid bilayer is the best sort of transfersome. Other vesicular methods have had problems with transdermal drug delivery, such as limited skin permeability, vesicle breaking, drug leakage, and vesicle aggregation and fusion. To solve all of the aforementioned concerns, a novel type of vesicular carrier called as a "transfersome" that is capable of transdermal distribution of both low and high molecular weight drugs has been developed. Transfersomes are a type of synthetic vesicle that is more pliable than liposomes. When applied to the skin non-occlusively, transferosomes have been found to improve transdermal drug delivery [12-16].

Materials And Methods:-

Tramadol hydrochloride was acquired in India from GVK bioscience pvt ltd. HIMEDIA Laboratories Pvt. Ltd. supplied the soya lecithin. Mumbai Limited SD fine-chem supplied the tween 60, chloroform, and ethanol. Mumbai, India, Limited [17].

Preparation Of Tramadol Hydrochloride Transferosomes By Thin Film Hydration Technique:

The weighed amounts of soya lecithin and surfactant were placed in a round bottom flask and dissolved in a 2:1 mixture of chloroform and ethanol. Rotary evaporation was used to create the thin film for 15 minutes at 60°C, 600 mm/hg pressure, and 100 rpm. Vaccum was applied until a film formed. Tramadol hydrochloride was dissolved in 10 mL of a 6.8 pH phosphate buffer heated to 50°C. The film was then hydrated with the hot buffer and rotated for 45 minutes to create the vesicles. Following that, transferosome vesicles were examined with a projection microscope.

The transfersomal suspension was refrigerated at 4^0C. Six formulations were developed using different soya lecithin concentrations and by varying soya lecithin: surfactant ratios [17-18].

Composition of transferosomes is given in a table1:

Six formulations were prepared using different surfactants by varying the concentrations of soya lecithin: Tween 60 ratio.

Table 1:- Composition of transferosomal formulations:

Formulation no	Surfactant: Lipid ratio	ethanol: Chloroform ratio (ml)	Tramadol hydrochloride (mg)
T1	1:0.5	1:2	50
T2	1:1	1:2	50
T3	1:1.5	1:2	50
T4	1:2	1:2	50
T5	1:2.5	1:2	50
T6	1:3	1:2	50

Results And Discussion:-

Tramadol hydrochloride loaded transferosome using thin film hydration method optical microscopy:

The morphology of six formulations was determined using optical microscopy (S3700N, Hitachi, Japan). Under the microscope, photomicrographic photographs of the preparation were captured using a digital SLR camera [19].

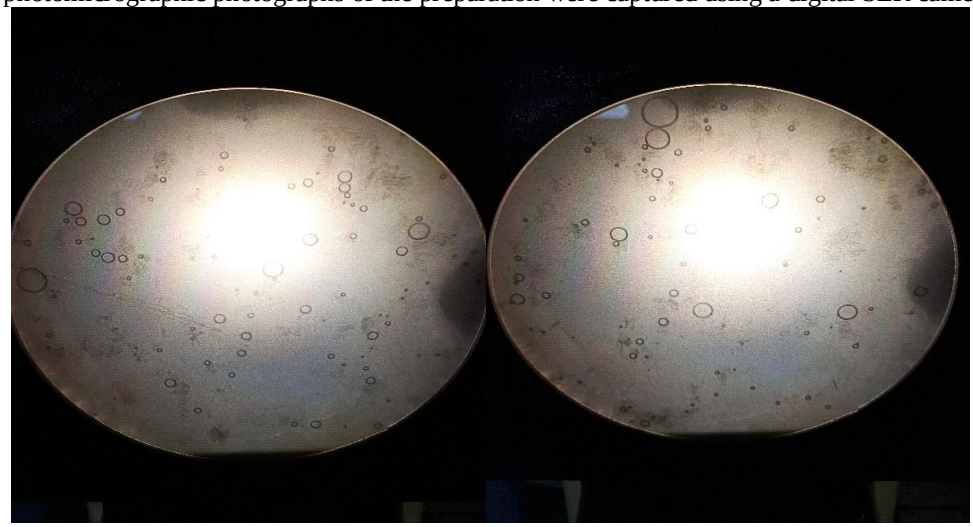

Fig 1:- Photomicrographic images of T5 formulation of Tramadol hydrochloride loaded transfersomes prepared by thin film hydration technique.

Drug content:

The prepared six formulations were evaluated for drug content.

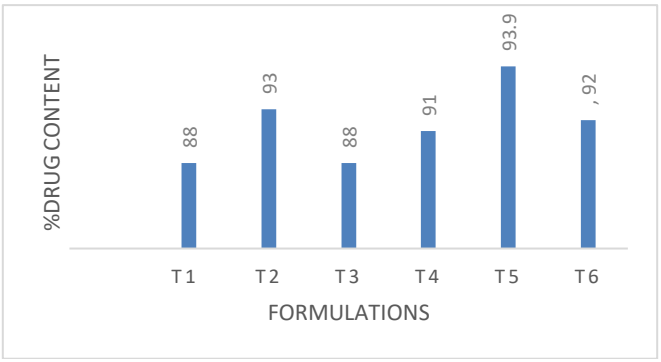

Fig 2:- Comaparision of drug content among six formulations of tramadol hydrochloride loaded transferosomes prepared by thin film hydration technique.

T1, T2, T3, T4, T5, and T6 formulations had drug concentration of 88%, 93%, 88%, 91%, 93.9%, and 92%, respectively. The maximum drug concentration was observed in formulation T5 with a 1:2.5 ratio of surfactant to phospholipid of 97%.

Entrapment efficiency:
All the formulations were evaluated for drug entrapment efficiency using cooling ultracentrifuge (Eltek/Mumbai) [20].

The percentage of drug entrapment efficiency of T1, T2, T3, T4, T5, and T6 formulations was discovered to be 73.3%, 52%, 68.0%, 67.1%, 97% and 72.9% accordingly. The ratio of surfactant to phospholipid utilised to prepare formulation T5 had the highest percentage of entrapment efficiency. Entrapment efficiency was greater in transferosomes produced with a 1:2.5 ratio of soya lecithin to Tween60. Entrapment efficiency reduced as lipid concentration increased, which could be ascribed to the fact that increasing surfactant ratio above a particular limit/concentration can disturb the regular linear shape of vesicular membranes.

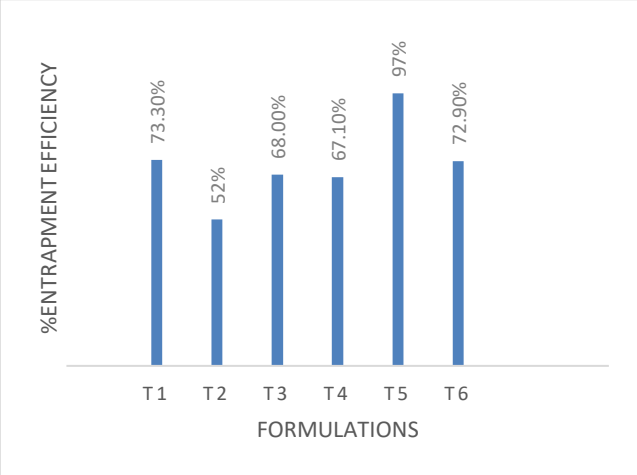

Fig 3:- Comaparision of drug entrapment efficiency among six formulations of tramadol hydrochloride loaded transferosomes by thin film hydration technique.

Comparison Of In Vitro Drug Diffusion Of Tramadol Hydrochloride Loaded Transfersomes:
All Six formulations were evaluated for in vitro drug diffusion studies using Franz diffusion cell. In vitro drug release studies were conducted for a time period of 12 h as shown in Fig 4.

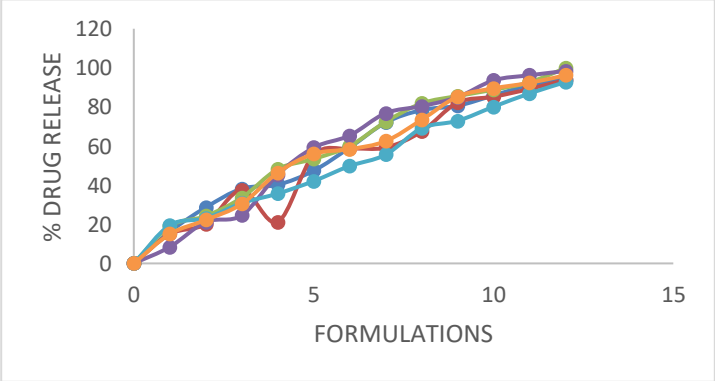

Fig. 4:- Comparison of in vitro drug diffusion among six formulations of Tramadol hydrochloride loaded transfersomes prepared by thin film hydration technique

When compared to other formulations, the T5 formulation with a 1:2.5 ratio of Tween 60 to soya phospholipid demonstrated a sustained release profile of 92.71% up to 12 h. The results of transfersomal formulations showed that the rate of drug release was proportional to the percentage of drug entrapment efficiency. T5 formulation outperformed other transferosomal formulations in terms of prolonged drug release. As a result, it was further improved to be the best transfersomal formulation [21].

Vesicular diameter:
Zeta sizer was used to measure the vesicular diameter of the six produced formulations (Malvern Instruments Ltd). The experiment was carried out at a temperature of 25ºC using double distilled water as the dispersion medium.

The six compositions were all in the nano size range. T1, T2, T3, T4, T5, and T6 formulations had mean vesicular diameters of s, respectively. T5 formulation had the smallest vesicular diameter of all formulations, measuring 271.3 nm.

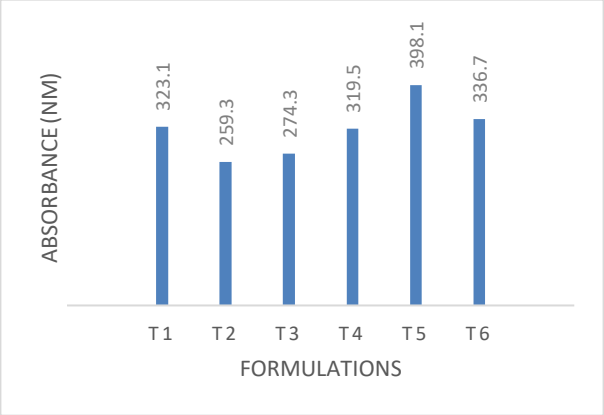

Fig. 5:- Comparison of mean vesicular diameter of six formulations of Tramadol hydrochloride loaded transfersomes prepared by thin film hydration technique

Zeta potential:
The created six formulations were characterised for zeta potential value to determine the formulations' stability. The experiment was carried out at a temperature of 25ºC with a dispersion of double distilled water.

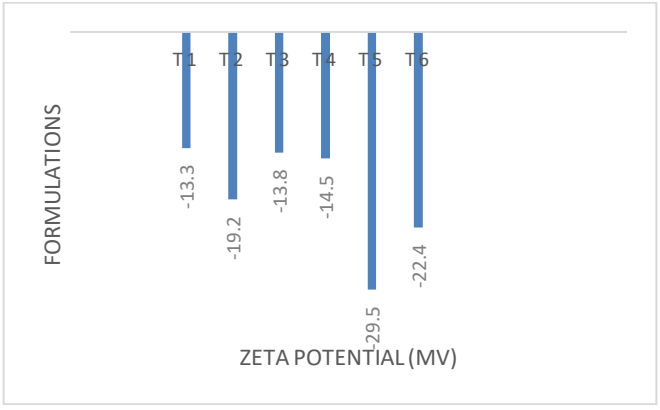

Fig. 6:- Comparison of zeta potential values of six formulations of Tramadol hydrochloride loaded transfersomes prepared by thin film hydration technique.

According to the findings, all formulations were stable. T1, T2, T3, T4, T5, and T6 formulations had zeta potential values of−13.3 mV, −19.2 mV, −13.8 mV, −14.5 mV, −29.5 mV, and -22.4 mV, respectively. T5 formulation had the highest level of stability among all formulations.

Formulation Of Transferosomal Gel:
Plain gel (PG) and nano-based gels (T5G) were prepared by simple dispersion technique and evaluated visually for clarity.

Table 2:- Composition Of Different Formulations Of Gel.

INGREDIENTS	PLAINGEL	T5 FORMULATION
Tramadol hydrochloride	50mg	5ml
Carbopol	0.25g	0.25g
Guar gum	0.05 g	0.05 g
Propylene glycol	5ml	5ml
Methyl paraben	0.2ml	0.2ml
Propyl paraben	0.1ml	0.1ml
Triethanol amine	q. s	q. s
Distill water	10ml	10ml

Evaluation Of Transferosome Loaded Gel:

Clarity:

Plain gel (PG) and nano-based gels (T5G) were prepared by simple dispersion technique and evaluated visually for clarity and the results are shown in Table 3.

The results clearly indicated that all formulations were clear

Table 3:- Clarity results of PG and T5G formulations.

Formulations	Clarity
Plain gel	++
T5 gel	++

pH measurement:

The pH values of the formulated plain gel (PG) and nano-based gels (T5G) were determined, and the findings are shown in Table 4.

Table 4:- PH evaluation of PG and T5G formulations.

Formulations	pH
Plain gel	6.8
T5 gel	6.5

Homogeneity:

All gel formulations were confirmed to be homogeneous and aggregate-free.

Grittiness:

All of the formulations were found to be devoid of specific matter and grittiness, which is required for any topical medication.

Drug content:

The percentage concentration of PG and T5G formulations was assessed. The drug content percentages of PG and T5G formulations were determined to be 91.2% and 94.8%, respectively, indicating that T5G formulation had the greatest drug content of 94.8%.

Spreadability:

The spreadability of the formulated plain gel (PG) and nano-based gels (T5G) was examined, and the findings are shown in Table 5. T5G formulation has the highest spreadability of 183.50 g.cm/sec.

Table 5:- Spreadibility results of PG and T5G formulations.

Formulation	Spreadability
Plain gel	14.37 g.cm/sec
T5 gel	18.31 g.cm/sec

Ex-vivo diffusion studies:
Drug release studies was done on animal skin to see how much drug is releasing.

After 5 and 12 hours, the cumulative drug release of PG and T5G formulations was determined to be 99.8% and 92.7%, respectively. The larger drug concentration and greater entrapment efficiency of the T5G formulation resulted in a more prolonged release compared to other formulations.

The kinetics parameters were determined using several plots, and it was discovered that the best formulation (FT5) used zero order release with a non-fickian diffusion mechanism.

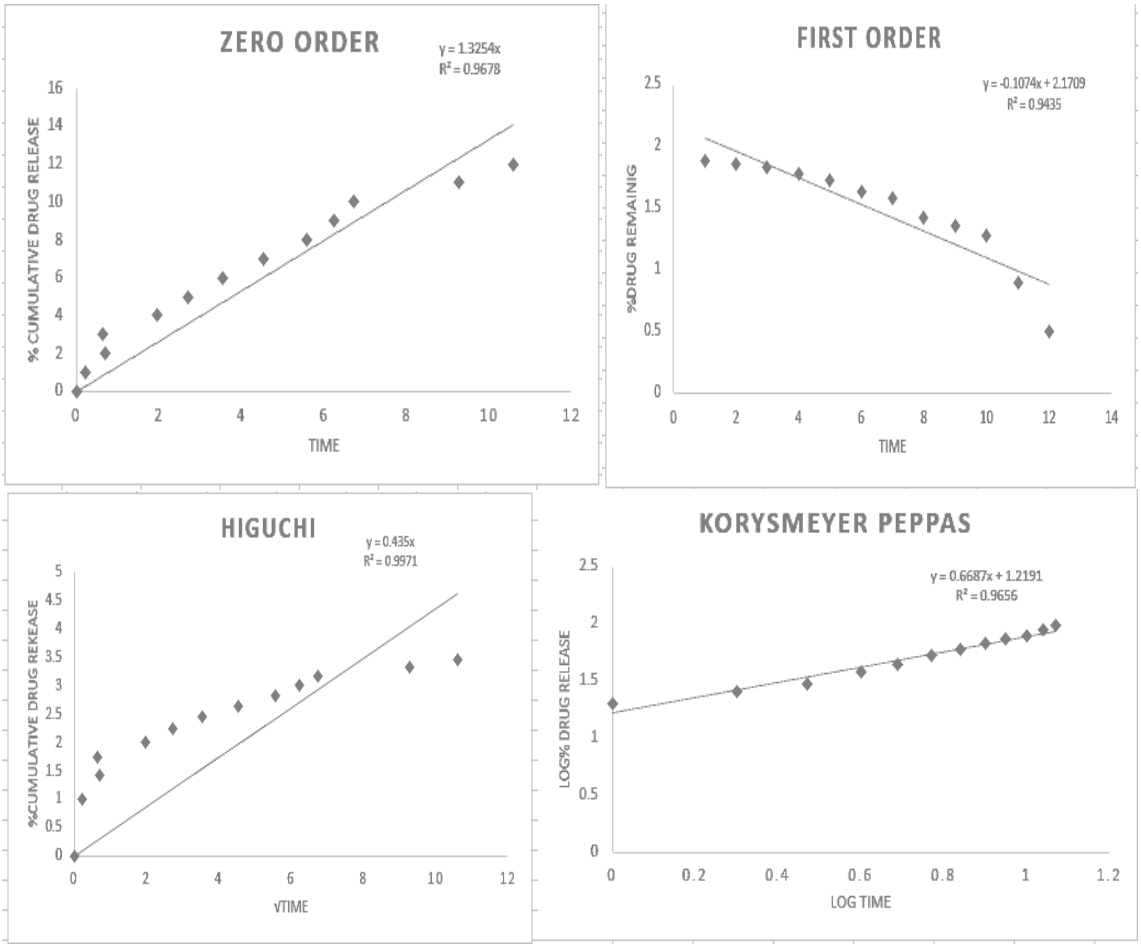

Table 6:- Kinetic parameters determined from the in-vitro drug release kinetics plots.

Formulation	Zero order	First order	Higuchi	Peppa's	n-value
T5G	0.9678	0.9435	0.9971	0.9656	0.811084

Conclusion:-

Six transfersome formulations were created using thin film hydration procedures and changing the surfactant to phospholipid ratios. All formulations were examined for drug content, entrapment efficiency, and in vitro diffusion studies, as well as vesicular diameter and zeta-potential. T5 formulation with surfactant: phospholipid 1:2.5 ratio was shown to be the optimum formulation. During the transfersomes preparation process, many factors such as surfactant: phospholipid ratio, hydration temperature, and heating temperature were tuned. The best transfersomes (T5) formulations were dispersed in 1% Carbopol gel base using a simple dispersion process. The gels were tested for clarity, pH, drug content, spreadability, viscosity, and in vitro diffusion. When compared to simple gel and transferosomal (GT5) gels, transfersomal gel produced the greatest results.

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