Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 44 No. 3 (2023)

Designing, Optimization and Characterization of Linagliptin Transferosomal Gel to Actively Target Type II Diabetes

Shilpa Chandel[1], Deepak Sharma[2*], Ashok Kumar[3], Mahesh Kumar Yadav[4], Swarnalata Mohapatra[5], Sonam Raj[6], Shuvashree Meher[7]

[1]Associate Professor, Faculty of Pharmaceutical Sciences, The ICFAI University, Baddi, Himachal Pradesh, India
[2]Professor, Institute of Pharmacy, Assam Don Bosco University, Sonapur, Kamrup, Assam, India
[3]Associate Professor, Faculty of Pharmaceutical Sciences, The ICFAI University, Baddi, Himachal Pradesh, India
[4]Assistant Professor, Faculty of Medical Science & Research, Sai Nath University, Chandway, Ormanjhi, Jharkhand, India
[5]Assistant Professor, Koustuv Research Institute of Medical Science, Patia, Bhubaneswar, Odisha, India
[6]M.Pharm Research Scholar, School of Pharmacy, Monad University, Uttar Pradesh, India
[7]Assistant Professor, Centurion University of Technology and Management, Balangir, Odisha, India

[*]Corresponding Author:

Deepak Sharma
Professor, Institute of Pharmacy, Assam Don Bosco University, Sonapur, Kamrup, Assam, India
Email: deepak28aug@gmail.com

Abstract

Transfer somes are especially optimized, designed in ultraflexible lipid molecular aggregates, which are diffuse through human skin. Transfersome is a one type of carrier system which is susceptible for transdermal drug delivery system. It also diffuses through the pores of stratum corneum, which are smaller than its size. Different chemicals are used in this formulation. Soya lecithin, Span 80, methanol are used in analytical grade. Various formulations (F-1 to F-8) of transfersomes was prepared and evaluated for vesicle size and entrapment efficiency. The vesicle size of all transfersomes found between 465.2 and 314.3 nm. According to result, entrapment efficiency was found between 66.35 to 79.76 %. Results showing that formulation (F4) having small vesicle size and higher the entrapment efficiency. Formulation (F4) categorized as designed formulation and incorporated into gel base (F4 1% Carbopol, F4 2% Carbopol and F4 3% Carbopol) and evaluated for Drug content, pH, Spreadability, Viscosity measurements and drug release study. Transfersomes gel released 81.71% in regulated manner in 12 hours. The designed Linagliptin show the ability to formed transfersomal gel overcome the barrier properties and increase the drug release.

Keywords: Linagliptin, Transfersomes, Soya lecithin, Span-80 and Tween-80.

I. INTRODUCTION

Linagliptin is used for the treatment of Type-II diabetes. Type-II diabetes is a disease does not prepare enough insulin. This can cause hyperglycaemia. This drug is a competitive and reversible DPP-4 inhibitor. It also inhibits the enzymes and reduces the glycogen in the liver and increase the insulin release according to glucose. The bioavailability of Linagliptin is very low in orally (29.5%).

Bioavailability is low due to high pass metabolism. Thus used for the transdermal route of administration is more effective than other routes. It avoids the first-pass metabolism and also maintains the plasma drug level for prolonged period of time. In the formulations due to low dosing remain biological activities over a longer period of time without systemic side effects. It is more useful for a person who does not take drugs orally and GI side effects also avoided.

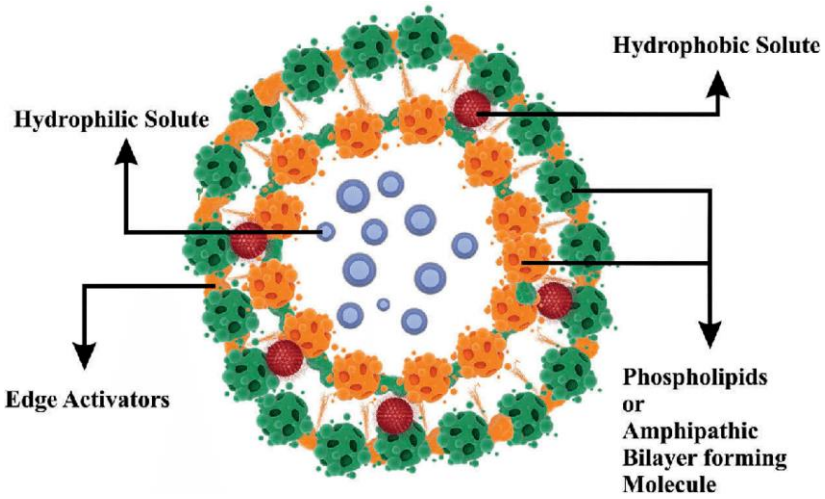


Figure 1: Structure of Transfersomes

Transfersomes are modified vesicular system that are particularly designed to have a one inner aqueous compartment it closed by lipid bilayer. In order to literature review vesicular transfersomes are several orders of magnitudes more elastic than the standard. In few decades vesicular carrier systems like liposomes and niosomes prepared for the transdermal drug delivery system. In initial stage of report liposomes are tested on skin. In various cases, transdermal drug penetration have not achieved properly. To outcome all the discussion, create a new type of carrier system known as "transfersomes". Transfersomes are overcome the skin penetration difficult by squeeze along with intracellular fluids [1, 2]

II. MATERIALS AND METHODMATERIALS

All the chemicals are used in analytical grade. Linagliptin was procured from MSN Pharmachem pvt. ltd, Telangana. Soya lecithin was collected from Himedia, Mumbai, India. Cholesterol and chloroform collected from Merck Limited, Mumbai (India), Span 80, Tween 80 and Methanol obtained from SD Fine-Chem Limited, Mumbai.

METHOD

Linagliptin-loaded transfersomes prepared by Rotary-evaporation sonication method

In this process, thin film is prepared and sonicated the vesicles homogenized by extrusion through a membrane filter. Various mixture of vesicles formed ingredients, that is phospholipids and surfactant are dissolved with volatile organic solvent (chloroform- methanol), organic solvent higher evaporated the lipid transition temperature using a rotary evaporator. Solvent were removed by vacuum for overnight. The deposited lipid films deposited lipid films were humidify with buffer (pH 6.4) by rotation at 60 rpm / min for 1hr at the corresponding temperature. The various resulted vesicles were swelling for 2 hour at room temperature. Preparing small vesicles resulted LMV was sonicated by probe sonicator for 30 min at room temperature. The prepared vesicles were homogenized by manual extrusion method through membrane filter [1, 3, and 5].

III. FORMULATION DESIGN

Table No 1 – Formulation Design of Linagliptin-Loaded Transfersomes

	F1	F2	F3	F4	F5	F6	F7	F8	F9
LINAGLIPTIN (mg)	10	10	10	10	10	10	10	10	10
SOYALECITHIN (mg)	15	30	45	15	30	45	15	30	45
CHLOROFORM:METHANOL	2:1	2:1	2:1	2:1	2:1	2:1	2:1	2:1	2:1
SODIUM DEOXYCHOLATE	6	12	18	---	---	---	---	---	---
TWEEN 80	---	---	---	6	12	18	---	---	---
SPAN 80	---	---	---	---	---	---	6	12	18
SODIUM BENZOATE	1	1	1	1	1	1	1	1	1
DISTILLED WATER	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

IV. PREPARATION OF LINAGLIPTIN LOADED TRANSFERSOMES (Particle Sizes, PDI, Zeta Potential)

The degree of the distribution of transfersomes (particle length and polydispersity index) was determined by using the method dynamic light scattering (Delta Nano C, Beckman counter), and Zeta capability was determined by the use of zeta Sizer Nano ZS (Malvern Instruments, UK) [6,7].

V. ENTRAPMENT EFFICIENCY

The entrapment efficiency was decided by using direct method. Various detergents are used to gap the transfersome membranes using Triton X-100 1 ml of 0.1% (Triton X-100 dissolved in phosphate buffer). Transfersomes preparations and prepare up to 5 ml with phosphate buffer and it was incubated at 37ºC for 1.5 hours. It was complete breakup of the transfersome membrane and to release the entrapped material. The sample vesicle was filtered through a membrane filter (0.25 µm) and the filtrate was determined at 260 nm for Linagliptin. The amount of Linagliptin was determined by calibration curve method [6, 8].

The entrapment efficiency is expressed as: $\boldsymbol{amount\ trapped/total\ amount} \times \mathbf{100}$

Diffusion Study for Linagliptin Transfersomes

***In Vitro* Drug Release-** Franz diffusion cell with cellulose membrane, Extrusion method

In brief, Franz diffusion cells are employed in the in vitro drug release study. A mixed cellulose ester membrane of an average pore size of 0.45 µm is used. The membranes are soaked in the release media (phosphate buffer) at room temperature overnight in order to allow the membrane pores to swell. The aliquots of 1 mL of the receptor medium are withdrawn at appropriate time intervals (such as 0, 0.5, 1, 2, 3, 4, 5 and 6 h), and simultaneously, the receptor medium is replaced by an equal volume of the fresh PBS to maintain the sink conditions. The obtained samples were analyzed for drug content using UV spectrophotometer at 230nm wavelength.[7]

PREPARATION OF TOPICAL TRANSFERSOMAL GEL FORMULATION

Prepared transfersomes were incorporated in to carbopol-934 (1%) gel base in a 1:1 ratio. The carbopol-934 (1%) gel base prepared by soaking 30 min followed by continuous stirring with water. Transfersomes loaded with the drug were incorporated into the gel base by slow stirring until a homogeneous transfersomal gel was achieved. 1% carbopol-934 gel base has a good consistency (gelling characteristic).[6, 7]

VI. CHARACTERIZATION OF LINAGLIPTIN LOADED TRANSFERSOMES

Physical appearance:

The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

P^H of formulation:

pH measurement of the gel was carried out of the formulation was measured by using a digital pH meter (Lab India SAB5000).[8]

Determination of viscosity

Viscosities of the gels were determined by using Brookfield Viscometer (model- RVTP).Spindle type, RV-7 at 100 rpm. 100gm of the gel was taken in a beaker and the spindle was dipped in it and rotated for about 5 minutes and then reading was taken.

Extrudability

It is useful empirical test to measure the force required to extrude the material from the tube. The formulations were filled in a collapsible metal tubes with a nasal tip of 5mm opening tube extrudability was then determined by measuring the amount of gel, extruded the tip when a pressure was applied on tube gel. The extrudability of the formulation was checked and the results were tabulated.[9, 10, 12]

Spreadability: For the determination of Spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1kg weight for 5 min. weight (50 g) was added to the pan. The time in whichthe upper glass slide moves over to the lower plate was taken as measure of spread ability.

$$S = M.L / T$$

M- Weight tied to the upper slide L- Length moved on the glass
T - Time Taken

Homogeneity:

The homogeneity of Linagliptin Transfersomal gels were checked by visual inspection. In this regard the gels were filled into narrow transparent glass tubes and were checked in light for the presence of any particulate or lump.[10, 11, 12]

Drug Content Determination

A specific quantity of developed gels was taken and dissolved in 100mI of respective media. The volumetric flask containing gel solution was shaken for 2hr on a mechanical shaker in order to get complete solubility of the drug. Thissolution was filtered. After suitable dilution drug absorbance was recorder by using UV[13]

VII. RESULTS AND DISCUSSIONS

FORMULATION	Particle Sizes (nm)	PDI	Entrapment Efficiency (%)
F1	465.2	0.668	75.91
F2	425.8	1.268	67.35
F3	432.6	1.153	77.17
F4	**314.3**	**0.168**	**79.76**
F5	404.1	0.277	78.42
F6	387.3	0.309	67.30
F7	329.8	0.698	72.91
F8	505.4	0.385	66.35

Figure 2: Graphical representation of mean vesicle size and of %EE

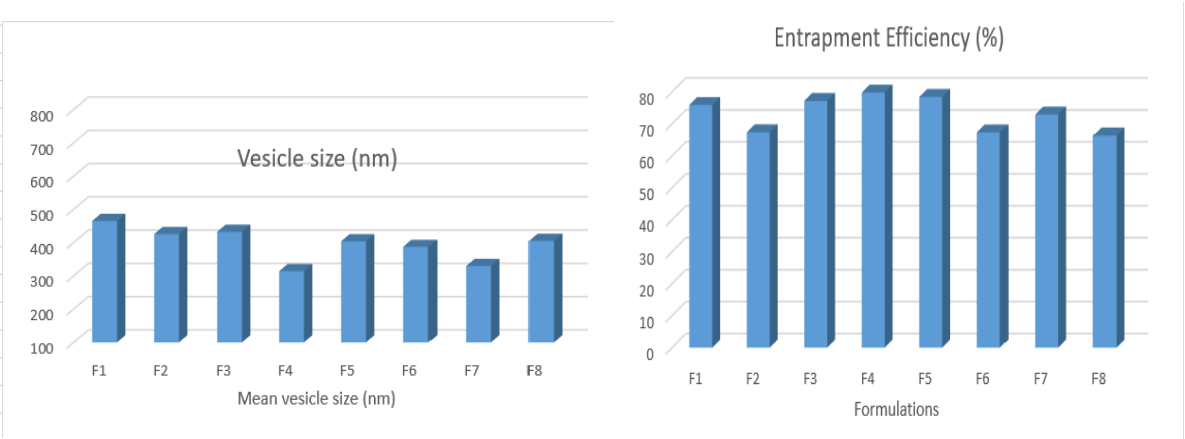
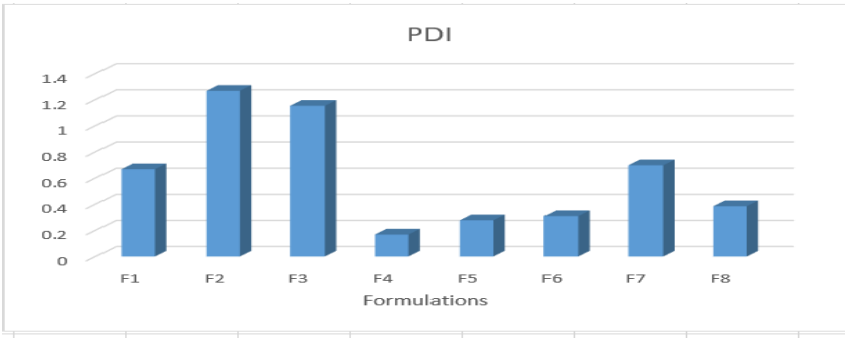


Figure 3: Graphical representation of PD



Determination of In vitro diffusion of Linagliptin Transfersomes

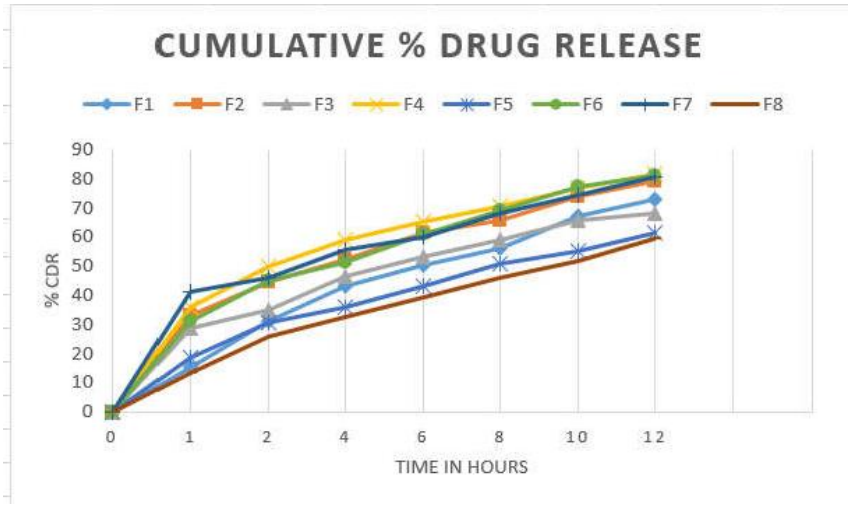


Figure 4: Graphical representation of %CDR of transfersomes

In vitro drug release study of the selected Transfersomes (F1, F2, F3, F4, F5, F6, F7 and F8) was carried out. The Transfersomes exhibited 12 hours sustained release pattern. Fifty percent of the incorporated amount of drugs was found to be released during the first 2 hours, followed by a slowed release of 81.71% of the drug up to 12 hours. The Linagliptin Transfersomes F4 showed a better release profile of 81.71 % by 12 hours. The prolonged release at 12 hours can be attributed to slow diffusion of drug from lipid matrix. The results of *in vitro* drug release are depicted in above Table.

CHARACTERISATION OF OPTIMISED FORMULATION

Vesicle shape and morphology

The transfersomes were subjected to microscopic examination (S.E.M) for characterizing size and shape of the transfersomes. Microscopic examination revealed, spherical small unilamellar vesicles size.

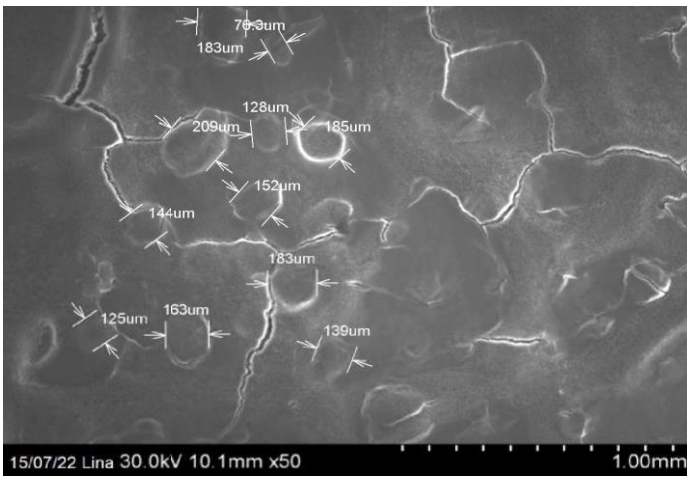
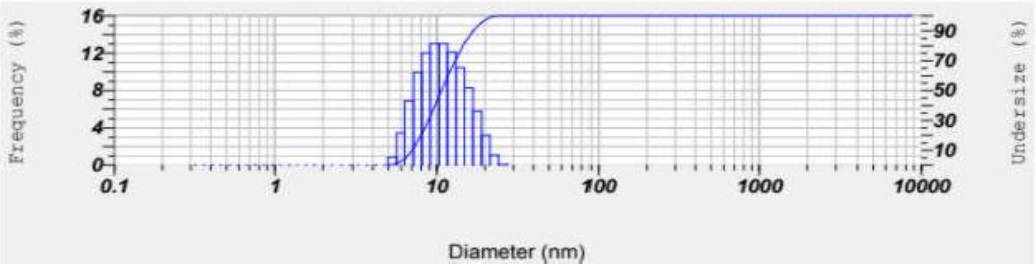


Figure 5: SEM Photograph of Linagliptin Transfersomes (Formulation-4)



Figire 6: Particle Size of optimized formulation F4

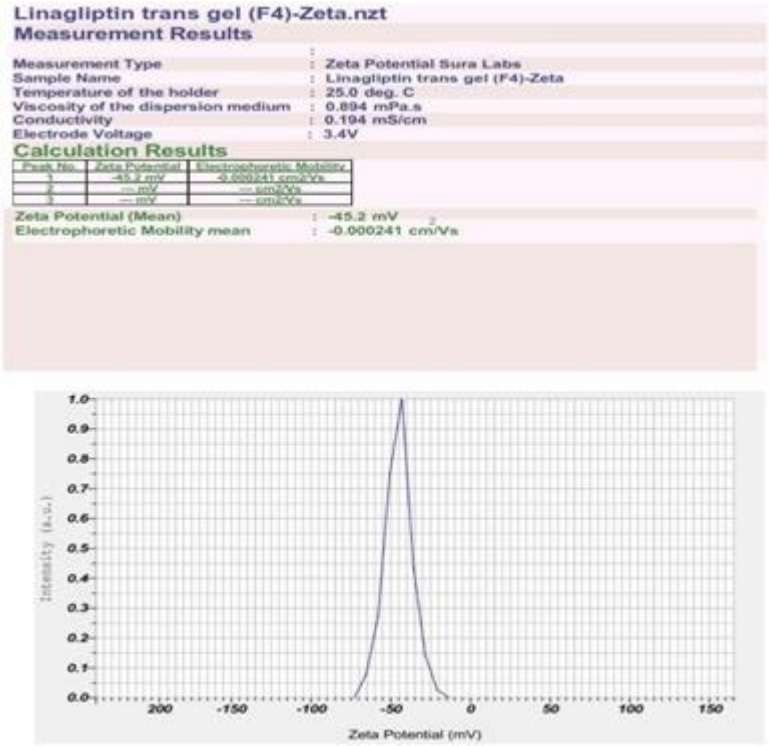


Figure 7: Zeta Potential of optimized formulation F4

CHARACTERIZATION OF LINAGLIPTIN TRANSFERSOMAL GEL

Table no 2: Physical evaluation of Linagliptin Pharmacosomal gel

Formulation	pH	Viscosity (cp)	Extrudability	Homogeneity	Drug Content(%)
F4 optimized 1%carbopol gel	6.11	65154	+	Satisfactory	76.54
F4 optimized 2% carbopol gel	6.07	71797	++	Excellent	85.19
F4 optimized 3% carbopol gel	6.02	70560	+	Satisfactory	77.67

All values are expressed as mean ± SD, (n=3)

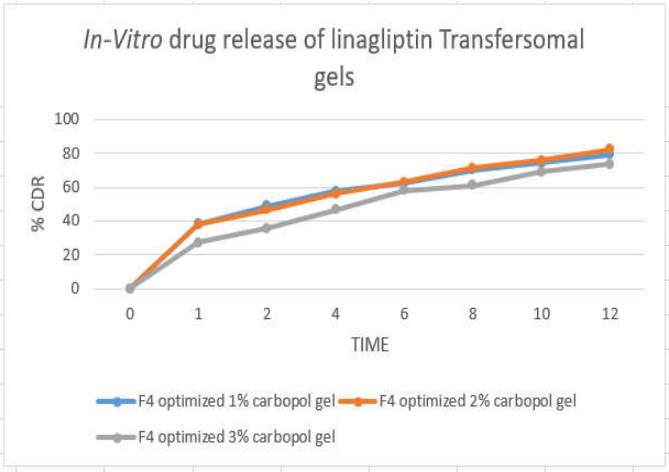
Immediately after the formulations were prepared their physical characteristics of formulations were studied and the data was shown in Table. Thus all the formulations exhibited good characteristics like homogeneity in color, and appearance.

***IN-VITRO* DRUG RELEASE**

Table No: 3 In-Vitro Drug release of Transfersomal gels
All values are expressed as mean ± SD, (n=3)

Time (hrs)	F4 optimized 1% carbopol gel	F4 optimized 2% carbopol gel	F4 optimized 3% carbopol gel
0	0	0	0
1	38.18±0.11	37.82±0.65	27.11±0.41
2	49.06±0.72	46.53±0.36	35.48±0.39
4	57.67±0.88	56.12±0.46	46.57±0.32
6	61.96±0.02	63.02±0.93	57.98±0.42
8	70.10±0.55	71.10±0.58	60.84±0.16
10	74.29±0.57	75.63±0.21	68.93±0.03
12	79.07±0.67	82.24±0.76	73.65±0.25

Figure 8: Graphical representation of In-vitro drug release of transfersomal gels



Formulation	Colour	Spreadability (g.cm/sec)
F4 optimized 1%carbopol gel	White to off white	0.521±0.90
F4 optimized 2% carbopol gel	White to off white	0.413±0.29
F4 optimized 3% carbopol gel	White to off white	0.603±0.19

VIII. CONCLUSION

Total Eight formulations were prepared using varying amount of Soya-phosphatidylcholine, Cholesterol and drug and evaluated for Vesicle size and Entrapment efficiency. Formulation F4 which contain smallest vesicle size and increase in entrapment efficiency, Formulation F4 Sleeted as optimized formulation for further evaluation. The optimized batch of Transfersomes was further incorporated into gel base and evaluated for pH, Spreadability, Measurement of viscosity, Drug content and In-vitro diffusion study. From this study, it was concluded that the optimized batch of Linagliptin, with high EE% and small particle size. Also, the preparation of Linagliptin as transfersomal gel has the ability to overcome the barrier properties of the skin and increase the drug release.

REFERENCES

1. Christophers, E.Walff H. Laurence, E.B.(1974)“The formation of epidermal cell columns”,J.Invest.Dermatol.,62:556-564.
2. Christophers,E.9(1988)In:TheSkinofvertebrates,Spearman,R.I.C.;Riley,P.A;(Eds.0,AcademicPress,Lond on,137-139.
3. Juliano, R.L.(1980)“DrugDeliverySystems”. Oxford university press. New york,15.
4. Prausnitz, M.R.Allen, M.G.(1998)J. Pharm. Sci., 87(8):925
5. Chowdary K. P.R.Naidu, R.A.S. (1995)”Transdermal drug delivery are view of current status”, Indian Drugs,32(9):414-422.
6. Barry, B. W, (1991)”LPP theory of Skin penetration enhancement”, J.Control.Rel., 15:237-248.
7. Williams,A.C.;Barry,B.W(1992)”Skinabsortionenhancers”,Crit.Rev.Drug Carr. Sys,9, 305-353.
8. R Asijia, D Sharma, H Nirmal "Development of proniosomes gel as a drug carrier for transdermal delivery of acyclovir" 2014 Journal of Drug Delivery and Therapeutics, Volume 18 41-51.
9. Bellantone, N. H. Francoeur, M. L. Rasadi, B. (1986)”EnhancedPercutaneous absorption via iontiphoresis, Evaluation of an in-vitro system and transport of model compounds”, Int.J.Pharm.,30:72-80.
10. Banga,A.k.;Chien,Y.W.(1998)”Iontophoreticdeliveryofdrugs,fundamentals,developmentsandbiomedica lapplications”,J.Control.Rel.,7:1-24.
11. Chirag Goda, Madhabi Priyadarshini Behera, Joti Devi, Satish P. Mohitkar, Vivek Dhir, S. Sitamani Marndi, Deepak Sharma"An Innovative Breast Cancer Treatment Using Turmeric Leaf Oil Encapsulated Nanoemulgels" 2023 Rivista Italiana di Filosofia Analitica Junior, 14 (1)775-783.
12. Sounderson, J.E; Coldwell, R. w.; Hsio, J.; Dixon, R.(1987)”Noninvasive delivery of a novel iontscopic catecholamineiontophoretic. Versusintravenous infusionindogs”.J.Pharm.Sci,76;215-218.
13. Weaver,J.C.Chizmadzhevy. (1996),” ”,In:Polte,C.;Postow, E. (Eds), “Biological effects of electromagnetic fields”, CRC, Press, Boca Raton, NY, 247-274.
14. Levy, D. Kost, J. Meshulam, Y; Langer, R, (1989)”Effect of ultrasound on transdermal drug delivery to rats and guinea pigs”, J.Clini. Invest., 83:2074-2078.
15. Deepak Sharma*, Chandra Shekhar Taylor, Arati Tamta, Devesh U Kapoor, Pharmacognostic Study, Phytochemical Screening, Polyherbal Gel Formulation Development And Basic Evaluation Of Hypericum Oblongi folium And Oxalis Corniculata Medicinal Plant Species Of Uttarakhand Region Journal of Clinical Otorhinolaryngology, Head, and Neck Surgery, Vol: 27 Issue: 01, March 2023.
16. Runyan,W.R.;Bean,K.E.(2990)”Semiconductorintegratedcircuitprocessingtechnology”,Addition-Wesley,Newyork.
17. Kulkarni, R.g. Jains, Agrawal G.P.Chourasia, M. Jain N. K.(2000)”Advances in transdermal drug delivery systems”, Pharma Times, 32(5):21-24.
18. Schreier, Bouwstra J. (1994)”Liposome and niosomes as topical drug carriers dermal and transdermal drugdelivery”,J.Control.Rel.,30:1-15