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EVALUATION OF TRANSDERMAL GEL OF LISINOPRIL DIHYDRATES

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Abstract:
Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. Various new technologies have been developed for the transdermal delivery of some important drugs. The goal of the present study was to formulate and evaluate the potential use of transfersomal vesicles as a transdermal drug delivery system for the poorly soluble drug, Lisinopril Dihydrate. It was investigated by encapsulating the drug in various transfersomal formulations composed of various ratios of tween-80 prepared by thin film hydration method. The prepared formulations were characterized for entrapment efficiency (EE %), drug content, in-vitro skin permeation studies. The vesicles were spherical in structure as confirmed by Transmission Electron Microscopy. The EE% of Lisinopril Dihydrate in the vesicles was in the range of 87.16%. The result revealed that Lisinopril Dihydrate in all of the formulations was successfully entrapped with uniform drug content. The optimized Lisinopril Dihydrate -loaded transfersom was used to prepare Lisinopril Dihydrate -loaded transfersomal gel with the aid of HPMC K100 M, Eudragit L100 as the gelling agent. The Optimized Lisinopril Dihydrate -loaded transfersomal gel had a pH, Viscosity, Extrudability, Homogeneity, Drug Content, Spreadability and Ex vivo permeation studies. It is evident from this study that transfersomes are a promising prolonged delivery system for Lisinopril Dihydrate and have reasonably good stability characteristics. This research suggests that Lisinopril Dihydrate loaded transfersomes can be potentially used as a transdermal drug delivery system. According to this report, Transfersomal Gel is a promising long-term delivery mechanism for Lisinopril Dihydrate and has reasonably good stability. This study suggests that Transfersomal gel Lisinopril Dihydrate may be used as a transdermal drug delivery tool for fungal skin infections.

Key words: *Lisinopril Dihydrate, Transfersomes, Soya phosphatidyl choline and Tween 80.*

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1. INTRODUCTION:

NOVEL DRUG DELIVERY SYSTEM

[1]For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables, as drug delivery systems are the primary pharmaceutical products commonly seen in the market, even though these drug delivery system ensure a prompt release of drug, it is necessary to take this type of drug several times a day to achieve as well as to maintain the drug concentration with in the therapeutically effective range needed for the treatment. This results in significant fluctuations in drug level.

In the past two and a half decades several advancements have been made. They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a cell or tissue. Recently pulsatile drug delivery system is gaining importance.

These advancements have led to the development of several novel drug delivery systems that could revolutionalise the method of medication and provides a number of therapeutic benefits.

[2]Novel drug delivery system can be broadly divided into two classes:

1. Sustained release drug delivery system.
2. Controlled release drug delivery system.

Controlled release drug delivery system can be classified into four categories:

1. Rate-Preprogrammed drug delivery system.
2. Activation-Modulated drug delivery system.
3. Feedback-Regulated drug delivery system.
4. Site-Targeting drug delivery system.

[1] RATE-PREPROGRAMMED DRUG DELIVERY SYSTEM

In this system, the release of drug molecules from the drug delivery system has been preprogrammed at specific rate profiles. This was achieved by system designing which controls the molecular diffusion of drug molecules in and/or across the barrier medium with in or surrounding the delivery system. (e.g.) implants, transdermal system[3].

[2] ACTIVATION – MODULATED DRUG DELIVERY SYSTEM

The release of the drug molecule from this delivery system is activated by some physical, chemical or biochemical process and/or facilitated by the energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input.

Based on the nature of the process applied or the type of energy used, these activation modulated drug delivery system can be classified in to three categories:

1. Physical–e.g.: Osmotic pressure activated drug delivery system- osmotic pump[4], iontophoresis activated drug delivery system
2. Chemical- e.g.: pH activated drug delivery system[6]
3. Biochemical-e.g.: Enzyme activated drug delivery system[7]

[3] FEED BACK –REGULATED DRUG DELIVERY SYSTEM

The release of the drug molecule from the delivery system is activated by a triggering agent, such as biochemical substance in the body and regulated by its concentration viz. some feed back mechanisms. The rate of drug release is then controlled by the concentration of triggering agent detected by a sensor in the feed back regulated mechanism. E.g. bio-responsive drug delivery system, glucose triggered insulin delivery system[8].

LIMITATIONS OF NOVEL DRUG DELIVERY SYSTEM

Though there are so many advantages in this system there are few factors thatlimit its usage.

1. Variable physiological factors such as gastro intestinal pH enzyme activities, gastric and intestinal transit rates, food and severity of patients disease which often influence drug bioavailability of conventional dosage forms may also interfere which the precision of control release and absorption of drug from this system.
2. The products which tend to remain intact may become lodged at some sites. Ifthis occurs slow release of drug from the dosage form may produce a high- localized concentration of drug, which causes local irritation.
3. Drugs having biological half-life of 1 hr or less are difficult to be formulated as sustained release formulations. The high rate of elimination of such drugs from the body needs an extremely large maintenance dose which provides 8- 12 hrs of continuous therapy.
4. These products normally contain a large amount of drug. There is a possibility of unsafe over dosage, if the product is improperly made and the total drug contained there in is released at one time or over too short time of interval.
5. If it is once administered it may be difficult to stop the therapy for reasons of toxicity or any

other.

6. It may be unwise to include potent drugs in such systems.

TARGETED DRUG DELIVERY SYSTEM (TDDS)

THE CONCEPTS OF TARGETING

- Targeted drug delivery as an event where, a drug-carrier complex/conjugate, delivers drugs exclusively to the pre-selected target cells in a specific manner.
- Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at pre-identified target in therapeutic concentration, while restricting its access to non-target normal cellular linings,thus minimizing toxic effects and maximizing therapeutic index.

RATIONALE OF DRUG TARGETING

The site specific targeted drug delivery negotiates an exclusive delivery to specific pre-identified compartments with maximum intrinsic activity of drugs and concomitantly reduced access of drug to irrelevant non-target cells. The targeted delivery to previously in-accessible domains, e.g. intracellular sites, virus, bacteriaand parasites offers distinctive therapeutic benefits.

The controlled rate and mode of drug delivery to pharmacological receptor and specific binding with target cells; as well as bioenvironmental protection of the drug en route to the with of action are specific features of targeting. Invariably, every event stated contributes to higher drug concentration at the site of action and resultantlower concentration at non-target tissue where toxicity might crop-up. The high drug concentration at the target site is a result of the relative cellular uptake of the drug vehicle, liberation of drug and efflux of free drug from the target site.

Targeting is signified if the target compartment is distinguished from the other compartments, where toxicity may occur, and also if the active drug could be placed predominantly in the proximity of target site.

MATERIALS AND METHODS:

LIST OF EQUIPMENTS

Electronic Balance Sartorius
Magnetic Stirrer Remi
Rotary Flash evaporator Roteva
UV- Visible Spectrophotometer Lab india
Ultra Sonic Processor Vibronics
pH meter Elico
Differential Scanning colorimetry Hitachi
Laser particle counter Spectrex
Scanning electron microscopy Hitachi
FT-IR BRUKER

LIST OF MATERIALS

Lisinopril Dihydrate Provided by SURA LABS, Dilsukhnagar, Hyderabad.
Carbopol 934P Purchased from Merck Limited, Mumbai (India)
HPMC K4M Purchased from Merck Limited, Mumbai (India)
Triethanolamine Purchased from Merck Limited, Mumbai (India)
Propylene glycol Purchased from Loba Chemie Pvt Ltd. (Mumbai, India)
PEG 400 Purchased from SD Fine- Chem Limited, Mumbai

7. METHODS

Analytical Method Development

Identification and Characterization of Drug

Preparation of reagents:

Preparation of 0.2M NaOH Solution

Dissolved 4g of Sodium hydroxide pellets in to 1000mL of Purified water and mixed

Preparation of pH 6.8 Phosphate buffer

Dissolved 6.805 g of Potassium dihydrogen phosphate in to 800mL of purified water and mixed added 112mL of 0.2M NaOH solution and mixed. Diluted to volume 1000mL with purified water and mixed. Than adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

a) Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 6.8 phosphate buffer UV spectrum was taken using Lab India Double beam UV/VIS spectrophotometer (Lab India UV 3000+). The solution was scanned in the range of 200 – 400 nm.

b) Construction of standard graph

100 mg of Lisinopril Dihydrate was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 2, 4, 6, 8 and 10 µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}) i.e., 210 nm.

Organoleptic properties:

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of Lisinopril Dihydrate Melting point

The melting point of Lisinopril Dihydrate was determined by capillary tube method according to the USP. A sufficient quantity of Lisinopril Dihydrate powder was introduced into the capillary tube to give a compact column of 4-6 mm in height.

The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Lisinopril Dihydrate in the tube passed into liquid phase**.**

Determination of Lisinopril Dihydrate Solubility

Determination of solubility of drug by visual observation. An excess quantity of Lisinopril Dihydrate was taken separately and adds in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

PREPARATION OF TRANSDERMAL GEL

All methods of preparation of Transdermal gel are comprised of two steps.

0.1% w/w Lisinopril Dihydrate Transdermal gels were prepared by using different Concentrations of polymers such as Carbopol 934P, and HPMCK4M.

The formulation data for the preparation of Lisinopril Dihydrate Transdermal gels using Carbopol 934P and HPMCK4M in different ratios is shown in Tables.

Procedure: Accurately weighed amount of Polymers (Carbopol 934P and HPMC K4M in four different ratios was placed in known amount of distilled water (Twelve different formulations were prepared using varying concentrations of Carbopol 934P and HPMC K4M. After complete dispersion, the polymer solution was kept in dark for 24 hours for complete swelling. Accurately weighed amount of Lisinopril Dihydrate was dissolved in a specified quantity of suitable solvent. The drug solution was added slowly to the aqueous dispersion of polymer with the help of high speed stirrer (500 rpm) taking precaution that air did not entrap. Finally, the remaining ingredients were added to obtain a homogeneous dispersion of gel.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Lisinopril Dihydrate	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Carbopol 934P (gm)	0.5	1	1.5	2	-	-	-	-
HPMC K4M (gm)	-	-	-	-	0.5	1	1.5	2
Triethanolamine (ml)	2	2	2	2	2	2	2	2
Propylene glycol (ml)	10	10	10	10	10	10	10	10
PEG 400 (ml)	5	5	5	5	5	5	5	5
Distilled water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

8. RESULTS AND DISCUSSION:

Organoleptic properties

Table: Organoleptic properties

S NO.	Properties	Observed Results
1	State	Solid
2	Colour	White to off-white powder
3	Odor	Odorless
Melting point determination		
4	Reported Melting Point	Observed Melting Point
	148 °C	147.5°C

Solubility studies

Table: Solubility studies of drug in different solvents

S NO.	Solvents	Solubility of Lisinopril Dihydrate
1	Water	Insoluble
2	Methanol	Slightly soluble
3	Acetonitrile	Slightly soluble
4	Dimethyl formamide	Soluble
5	pH 6.8 Phosphate Buffer	Soluble
6	Ethanol	Soluble

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

Analysis of drug:

A. UV scans:

The lambda max of Lisinopril Dihydrate was found to be 210 nm.

B. construction of calibration curve:

Table: Standard graph of Lisinopril Dihydrate

Concentration (µg/ mL)	Absorbance
0	0
2	0.228±0.10
4	0.424±0.05
6	0.636±0.12
8	0.811±0.09
10	0.999±0.03

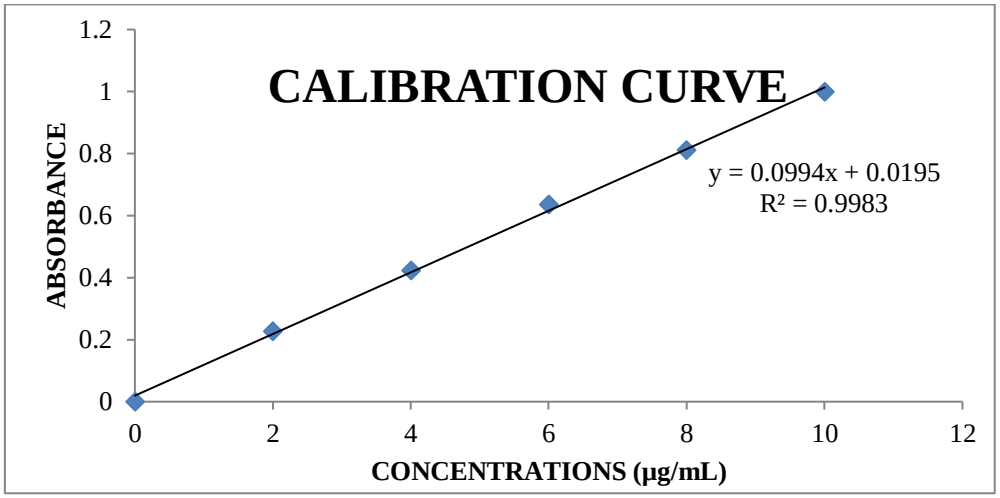

Figure: Standard calibration curve of Lisinopril Dihydrate

Standard graph of Lisinopril Dihydrate was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Lisinopril Dihydrate showed good linearity with R^2 of 0.998, which indicates that it, obeys "Beer- Lamberts" law.

GEL EVALAUTION PARAMETERS

Polymer	Formulation	pH	Viscosity (cp)	Extrudability	Homogeneity	Drug Content	Skin Irritation test
HPMC K15	F1	6.5	52325	+	Satisfactory	93.29±0.01	No
	F2	6.2	53425	+	Satisfactory	95.56±0.05	No
	F3	5.9	54360	+	Satisfactory	96.06±0.09	No
	F4	5.8	55417	++	Excellent	98.90±0.012	No
Carbopol	F5	6.6	50368	+	Satisfactory	92.19±0.01	No
	F6	6.4	51117	+	Satisfactory	95.22±0.18	No
	F7	6.0	51392	+	Satisfactory	96.05±0.04	No
	F8	6.1	51871	+	Satisfactory	96.21±0.06	No

Viscosity (cp)

The viscosity of the gel at different r.p.m was stated. The viscosity was found to decrease with the increase in the r.p.m. i.e., the shear rate showed with the non-Newtonian flow. This behavior might be due to its low flow resistance when applied at high shear conditions. The results showed that in Table, as the concentration of HPMC K15 increased from 0.5 %, 0.1%, 1.5% to 0.2 %, the viscosity was increased as the r.p.m. increased there was a decrease in viscosity.

Homogeneity: The developed gel was tested for homogeneity by visual observation, and the gel was found to be homogenous.

Table: Physical evaluation of Lisinopril Dihydrate Transdermal gel

Polymer	Formulation	Colour	Spreadability (g.cm/sec)
HPMC K15	F1	White to off white	0.456±0.01
	F2	White to off white	0.320±0.12
	F3	White to off white	0.258±0.09
	F4	White to off white	0.229±0.01
Carbopol	F5	White to off white	0.570±0.05
	F6	White to off white	0.590±0.09
	F7	White to off white	0.578±0.06
	F8	White to off white	0.490±0.03

Spreadability

Spreadability is important for patient compliance, and it also helps in the uniform application of the gel to the skin. A good gel spreads easily and quickly spread on the skin. The Spreadability of the optimized gel was found to be 0.229±0.01gm.cm/min.

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 colour, and appearance.

Four topical gel formulations were prepared by varying the concentration of polymer. For all the formulations pH was determined and the results were shown in Table. From the above results it was found that, pH of all gels formulations was in the range 6 to 7 which lies in the skin normal pH range. The minimum pH of the gels should be less than neutral i.e., 7.0.

***Ex vivo* permeation studies of Transdermal gel:**

Polymer	HPMC K15				Carbopol			
Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	40.62±0.01	34.89±0.09	35.96±0.11	30.99±0.04	37.20±0.16	41.98±0.02	32.01±0.02	28.92±0.16
2	45.10±0.05	40.92±0.02	41.60±0.08	38.06±0.13	42.95±0.06	46.93±0.05	40.53±0.16	34.64±0.10
4	71.91±0.09	46.06±0.05	48.14±0.05	45.36±0.00	60.41±0.02	55.54±0.09	45.20±0.19	40.05±0.05
5	76.82±0.13	53.86±0.04	55.30±0.02	56.12±0.05	67.56±0.09	63.63±0.11	49.16±0.10	44.13±0.02
6	80.86±0.10	69.11±0.03	70.82±0.09	60.79±0.02	74.99±0.17	70.15±0.18	56.99±0.03	53.92±0.15
8	94.01±0.04	75.70±0.01	78.14±0.10	75.66±0.09	89.82±0.10	90.83±0.16	62.82±0.05	60.46±0.06
10		82.59±0.08	85.97±0.09	80.90±0.15	92.88±0.11	93.25±0.12	74.61±0.09	64.58±0.02
11		97.05±0.10	90.36±0.02	95.36±0.10		95.14±0.10	80.79±0.04	75.11±0.06
12			93.75±0.04	98.22±0.12			95.26±0.11	90.62±0.02

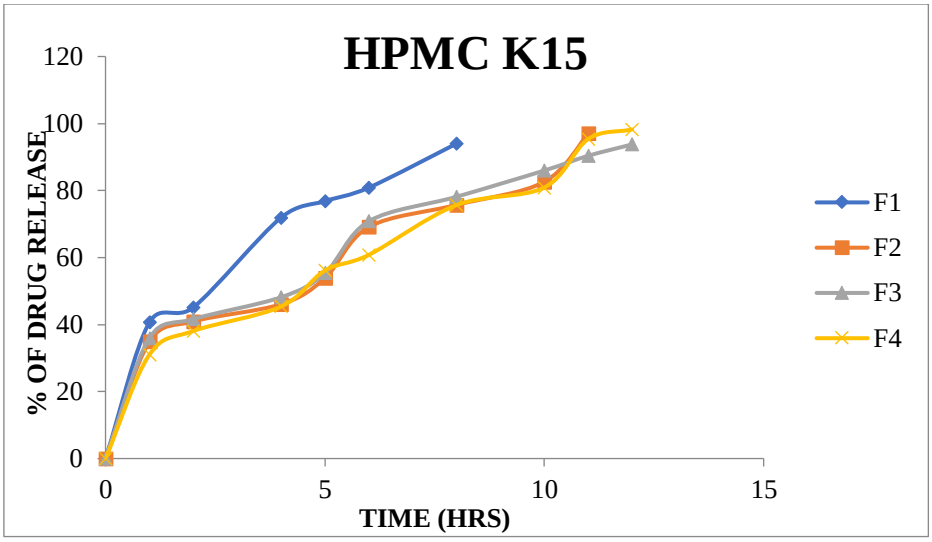

Figure: *Ex vivo* permeation studies for Transdermal gel with different concentrations of HPMC K15

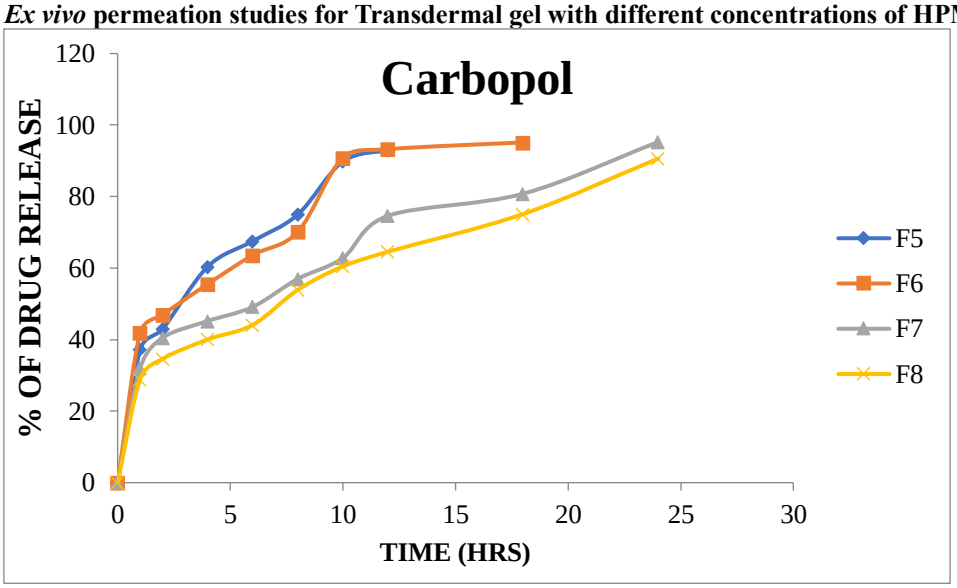

Figure: *Ex vivo* permeation studies for Transdermal gel with different concentrations of Carbopol.

F4 optimized 2 % HPMC K15 gel highest drug release (98.22 % for 12 hours), good Homogenity, highest drug content, Proper viscosity. Hence it was considered as optimized formulation.

Table: Release kinetics of optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
30.99	1	1.000	1.491	0.000	1.839	30.990	0.0323	-0.509	69.01	4.642	4.102	0.540
38.06	2	1.414	1.580	0.301	1.792	19.030	0.0263	-0.420	61.94	4.642	3.957	0.685
45.36	4	2.000	1.657	0.602	1.738	11.340	0.0220	-0.343	54.64	4.642	3.795	0.847
56.12	5	2.236	1.749	0.699	1.642	11.224	0.0178	-0.251	43.88	4.642	3.527	1.114
60.79	6	2.449	1.784	0.778	1.593	10.132	0.0165	-0.216	39.21	4.642	3.397	1.244
75.66	8	2.828	1.879	0.903	1.386	9.458	0.0132	-0.121	24.34	4.642	2.898	1.744
80.9	10	3.162	1.908	1.000	1.281	8.090	0.0124	-0.092	19.1	4.642	2.673	1.969
95.36	11	3.317	1.979	1.041	0.667	8.669	0.0105	-0.021	4.64	4.642	1.668	2.974
98.22	12	3.464	1.992	1.079	0.250	8.185	0.0102	-0.008	1.78	4.642	1.212	3.430

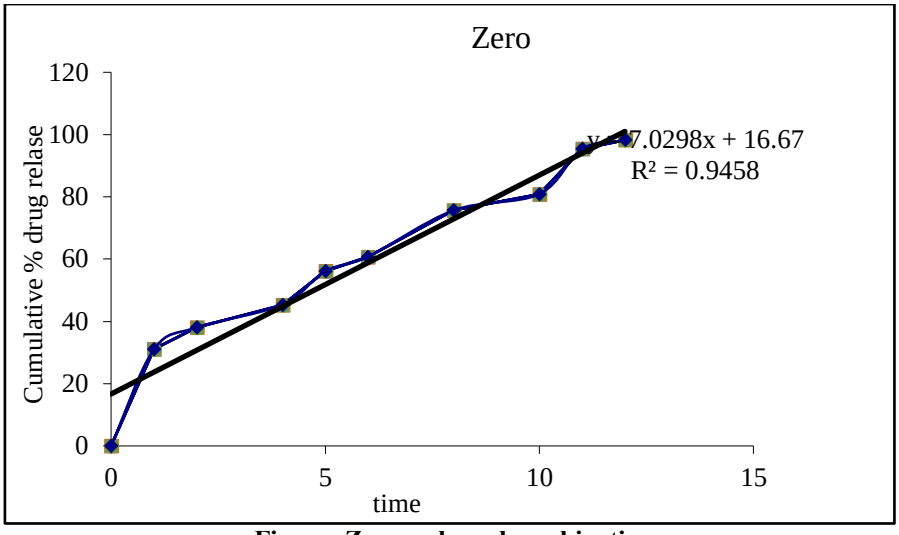

Figure: Zero order release kinetics

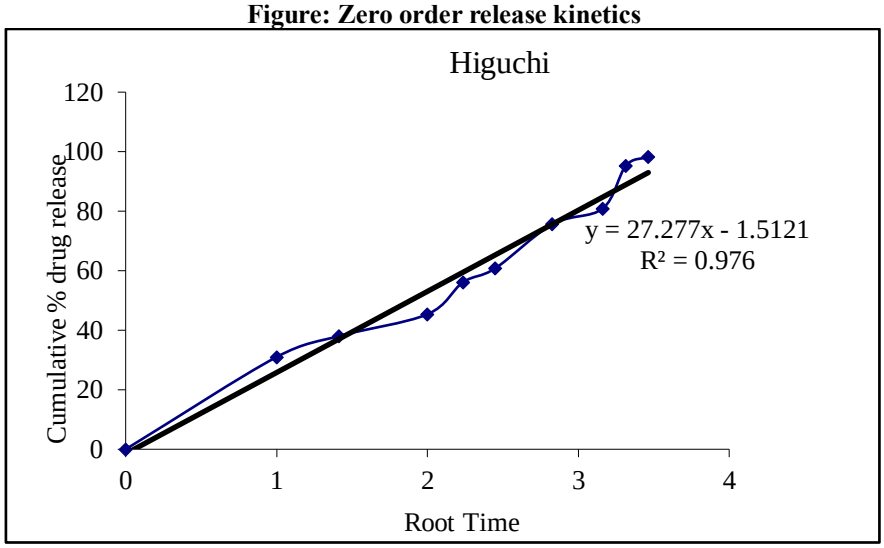

Figure: Higuchi release kinetics

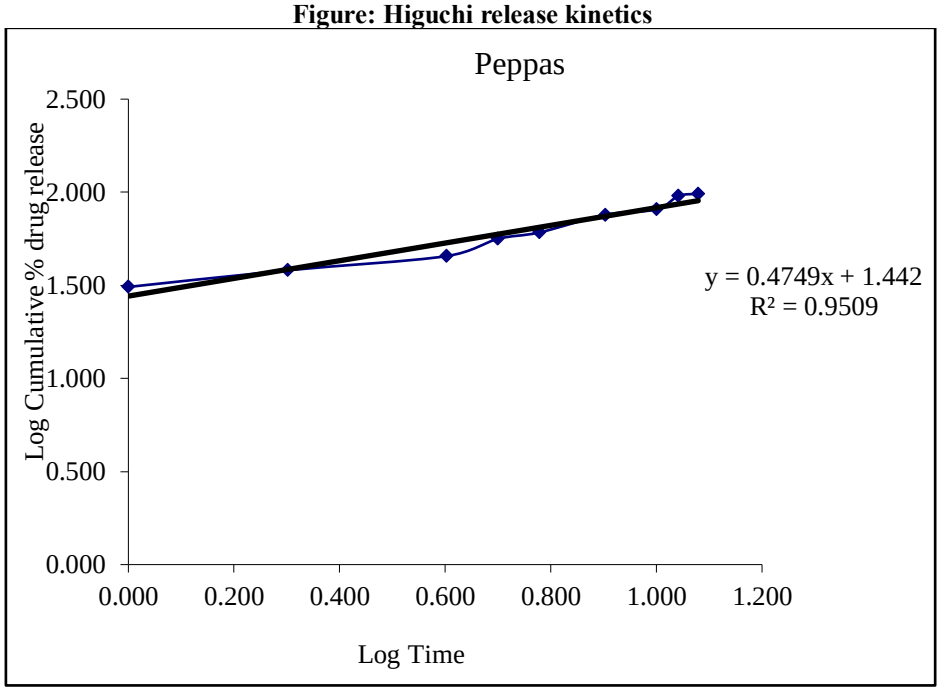

Figure: Peppas release kinetics

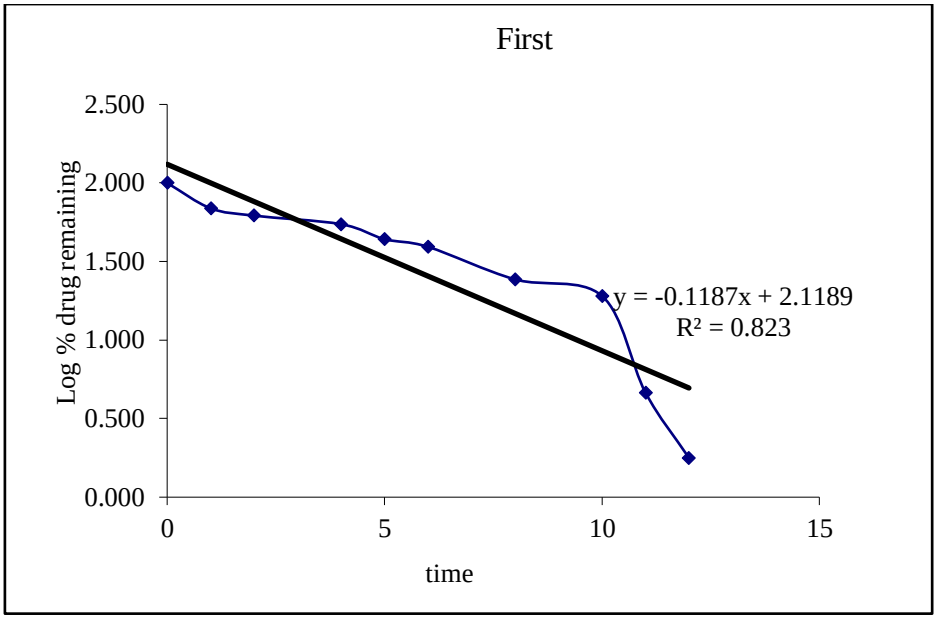

Figure: First order release kinetics

The prepared F4 optimised 2 % HPMC K15 Transdermal gel s were subjected to the drug release kinetics and release mechanism. The formulations were studied by fitting the drug release time profile with the various equations such as Zero order, First order, Higuchi and Korsmeyer pappas. The optimised formulation F4 optimised 2% HPMC K15 Transdermal gel was analyzed for the drug release mechanism. The best correlation coefficient value (0.976) indicates the best release mechanism (Higuchi).

FTIR

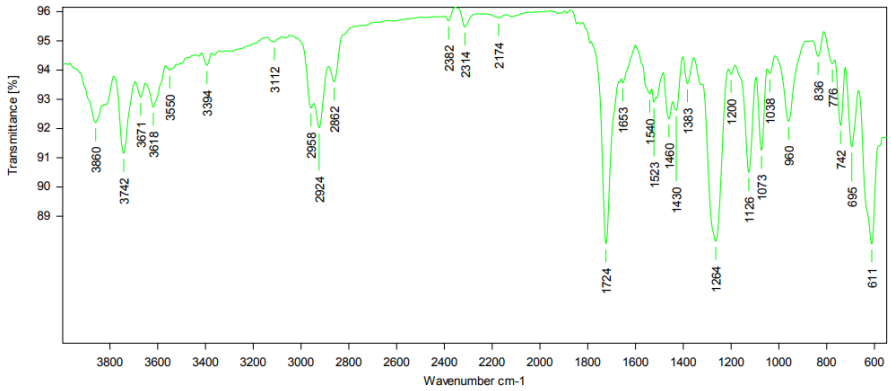

Figure: Lisinopril Dihydrate Pure drug FTIR

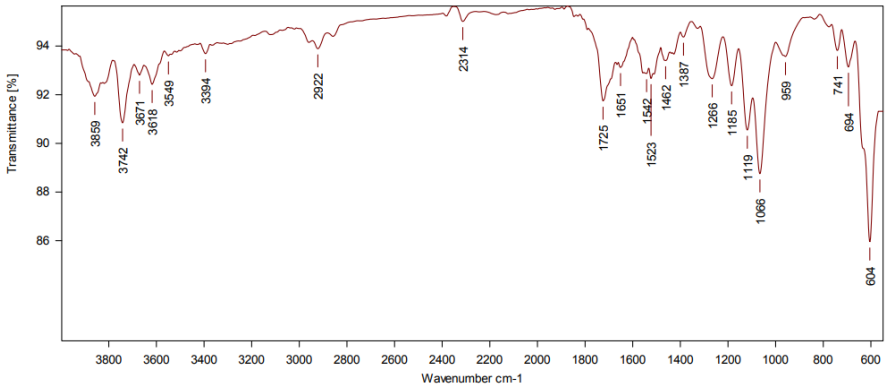

Figure: Optimized formulation FTIR

There is no incompatibility of pure drug and excipients. There is no disappearance of peaks of pure drug and in optimized formulation.

Infrared studies were carried out to confirm the compatibility between the polymers, drug, and selected excipients. From the spectra it was observed that there was no major shifting, as well as, no loss of functional peaks between the spectra of the drug and Transdermal gel . This indicated no interaction between the drug and other excipients.

DIFFERENTIAL SCANNING CALORIMETRY

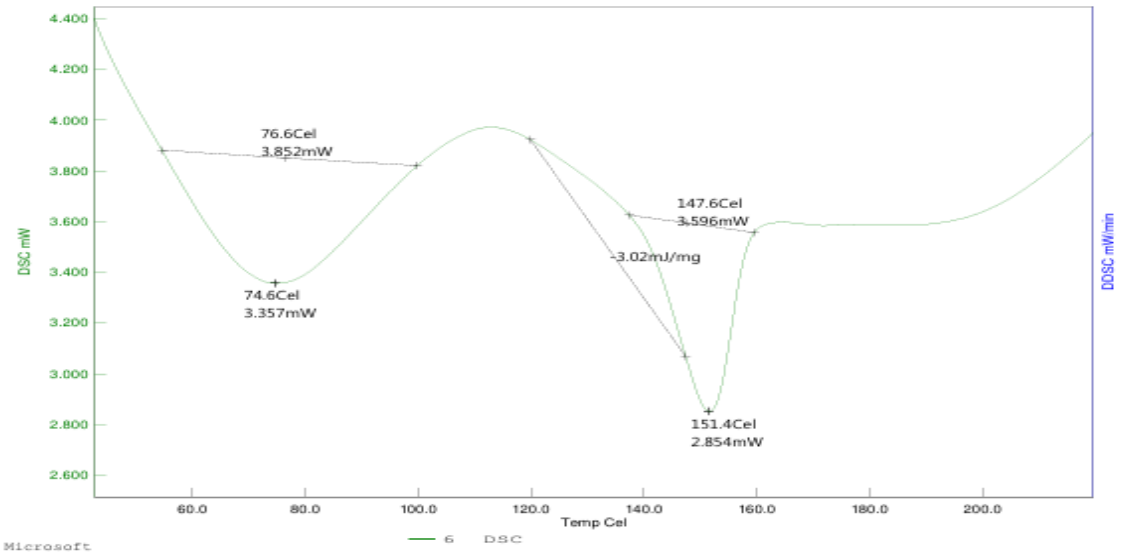

Figure: Lisinopril Dihydrate Pure drug DSC

Differential Scanning Calorimetry enables the quantitative detection of all processes in which energy is required or produced (endothermic or exothermic phase transformation). DSC curves obtained for pure drug is shown in figure. Pure powered **Lisinopril Dihydrate** showed a melting endotherm at 151.4 C.

Stability Study

The stability study of the Transdermal gel was performed as per ICH guidelines. Freshly prepared formulations were divided into groups and kept at specified storage conditions as per ICH guidelines. The sample was withdrawn periodically and tested for various evaluation parameters. The results of the stability study are tabulated in table respectively.

Table No: Stability Study of F4 Transdermal gel

Formulation	**F4**			
Storage Condition	**25°C ± 2°C / 60 % RH ± 5 % RH**			
Time interval (days)	0	30	60	90
Colour	White to off white	White to off white	White to off white	White to off white
Homogeneity	+++	+++	+++	+++
pH	5.8	6.0	6.0	6.1
Viscosity (cP)	55417	54120	54012	52059
Spreadability (g.cm/sec)	0.229±0.01	0.226±0.05	0.225±0.02	0.224±0.06
Extrudability	++	++	++	++
Drug content uniformity (%)	98.90	98.82	98.72	98.60
+++ Excellent, ++ Good, + Satisfactory, - Poor, -- Fail				

There was not much more variation in the properties of Transdermal gel F4 under stability study as the formulation retained all the properties when stored at specified storage conditions over a while, indicating that the Transdermal gel was very much stable.

Table No: *Ex vivo* permeation studies of Transdermal gel

Stability Study *Ex vivo* permeation studies of Transdermal gel				
Storage Condition	**25°C ± 2°C / 60 % RH ± 5 % RH**			
Time interval (days)	**Initial**	**30**	**60**	**90**
Time (hrs)	**F4 optimized**	**F4 optimized**	**F4 optimized**	**F4 optimized**
0	0	0	0	0
1	30.99±0.01	29.15±0.15	28.56±0.10	28.25±0.02
2	38.06±0.12	37.92±0.05	37.50±0.15	37.42±0.10
4	45.36±0.06	44.66±0.20	44.25±0.01	44.18±0.16
5	56.12±0.09	55.81±0.14	55.36±0.11	55.29±0.20
6	60.79±0.02	60.10±0.06	59.01±0.21	58.96±0.14
8	75.66±0.01	75.01±0.02	74.90±0.19	74.82±0.05
10	80.90±0.10	80.15±0.11	80.05±0.06	80.00±0.12
11	95.36±0.15	95.22±0.18	95.14±0.02	95.11±0.05
12	98.22±0.04	98.15±0.02	98.10±0.04	98.06±0.09

Stability study of Transdermal gel containing Lisinopril Dihydrate gel was done to see the effect of temperature and humidity on Transdermal gel during the storage time. Transdermal gel were evaluated periodically (0, 30, 60 and 90 days) for *Ex vivo* permeation studies. Stability study results show that there was no significant change in *Ex vivo* permeation studies of the formulation shown in Table.

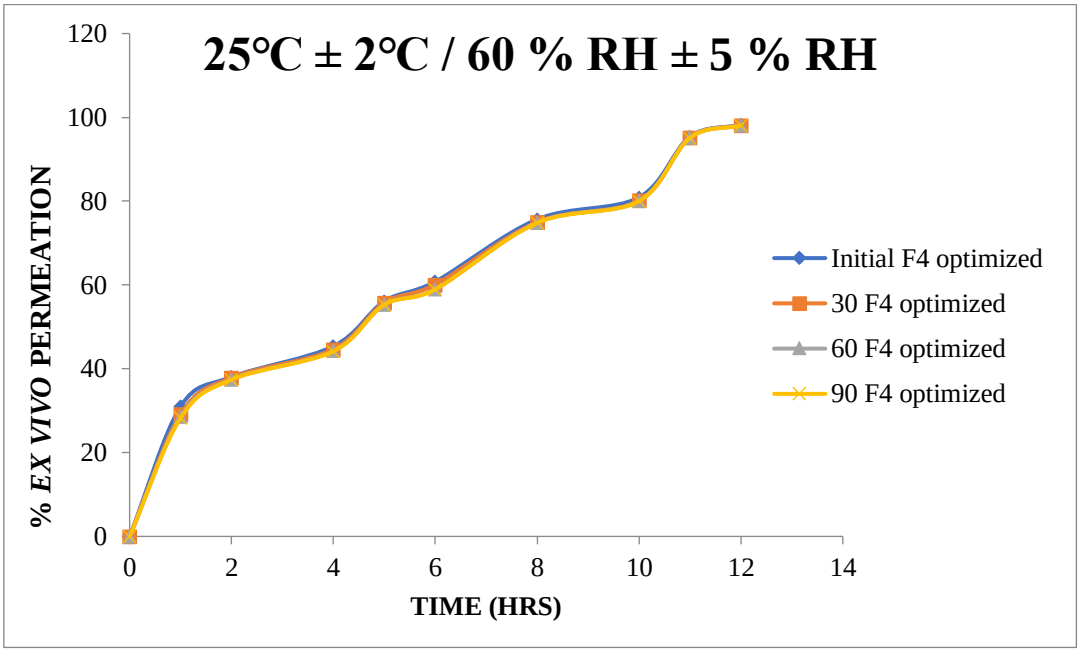

Figure: *Ex vivo* permeation studies for Transdermal gel with Stability studies

CONCLUSION:

It is concluded from the study that Transdermal gel formulated using HPMC K100 M, Carbopol, Propylene Glycol, Triethanolamine, along with the pure drug Lisinopril Dihydrate can be used to improve the site specificity, increase the transdermal flux and prolong the release of the drug. Lisinopril Dihydrate could be entrapped into Transdermal gel for penetration into skin pores much narrower than the vesicle diameter. The optimized Transdermal gel formulation F4 containing 2% Lisinopril Dihydrate showed promising results having maximum drug release (98.22%) when compared to other formulations with concentrations of drug being the only variable factor. Similarly the Transdermal gel formulation (F4, 2% HPMC) showed better results having maximum drug content (98.90%) and cumulative percent drug release (98.22%). Transdermal gel can alternatively be used as carriers for other transdermal drug delivery system as they possess simple scale up and can also act as a penetration enhancer by itself with easy production. Finally it is confirmed that Transdermal gel formulation of Lisinopril Dihydrate is therapeutically effective for the treatment of high blood pressure and can be developed successfully as a commercial product to improve the drug. The stability study was conducted on optimized Lisinopril Dihydrate Transdermal gel formulation. It was observed that there was no any significant change in Colour, Homogeneity, pH, Viscosity (cP), Spreadability (g.cm/sec), Extrudability and Drug content.

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BIBILOGRAPHY:

1. Remington 'The science and practice of pharmacy' 20th edition, VOLI: 903-905, 2001.
2. Y.W. Chien, Drug Development And Industrial Pharmacy 1983, 9:447-520, 1291-1330.
3. F. Teewes, Drug Development And Industrial Pharmacy 1983,9: 1331-1357.
4. J. M. Class., R.L.Stephan and S. C. Jacobson, Int. j. Dermatol, 19:519.
5. H.Sezahi and M. Hashida, Crc, Critical Reviews In "Therapeutic drug Carrier Systems", 1984, 1:1.
6. T.A Horbett, B.D Ratner, T.Kost and M.Sigh In " Recent Advances InDrug Delivery System" Plenum Press, New york. 1984, 209-220.
7. Joseph R. Robinson., Vincent H.L. Lee, "Controllrd Drug Delivery",2nd edition, revised and expanded, 1987: 596-597.
8. S. P. Vyas, R.K. Khar. "Targeted and Controlled Druig Delivery Novel Carrier Systems", I edition, CBS Publishers, New Delhi, 2002:39-40, 42-46.
9. Welling pG, Dobrinska MR, In Robinson JR, Lee VHL, eds:"Controlled Drug Delivery", II edition, Marcel Dekker, Newyork.1987: 253.
10. Gregoriadis G, "Targeting of drugs", Nature. 1977: 407-411.
11. Gregoriadis G. In Gregoriadis C, Senior J, Trout A, eds: "Targeting ofdrugs", Plenum, New york. 1982: 155.
12. Tretise A, D.M. Brahmankhar, Sunil B. Jaiswal, "Biopharmaceutics and Pharmacokinetics", 2001: 360-363.
13. Wirth M, Hamilton G and Gabar F, "J.Drug Target", 6, 1998: 95-104.
14. Subheet Jain, Dipankar Bhadra, N. K. Jain. (2001)"Advances in Controlled and Novel Drug Delivery" 1st edition, CBS Publishers, New Delhi, 427.
15. Christophers, e.; Walff, H. H; Laurence, E.B. (1974) "The formation of epidermal cell columns", J. Invest. Dermatol., 62: 556-564.
16. Christophers, E.91988) In: The Skin of vertebrates, Spearman, R. I.C. ; Riley, P.A; (Eds.0, Academic Press, London, 137-139.
17. Juliano, R. L. (1980) "Drug Delivery Systems". Oxford universitypress. New york, 15.
18. Prausnitz, M. R. ; Allen, M. G. (1998) J. Pharm. Sci., 87(8): 925
19. Chowdary, K. P. R.; Naidu, R. A. S. (1995)"Transdremal drug delivery; areview of current status", Indian Drugs, 32(9): 414-422.
20. Barry, B. W. (1991)"LPP theory of Skin penetration enhancement", J.Control. Rel., 15: 237-248.
21. Williams, A. C.; Barry, B. W (1992)"Skin absortion enhancers", Crit.Rev. Drug Carr. Sys, 9, 305-353.
22. Bellantone, N. H.; Francoeur, M. L.; Rasadi, B. (1986)"Enhanced Percutaneous absorption via iontiphoresis, Evaluation of an invitro syatem and transport of model compounds", Int. J. Pharm., 30:72-80.
23. Banga, A. k.; Chien, Y. W. (1998)"Iontophoretic delivery of drugs, fundamentals, developments and biomedical applications", J.Control.Rel., 7: 1-24
24. Sounderson, J.E; Coldwell, R. w.; Hsio, J.; Dixon, R. (1987)"Noninvasive delivery of a novel iontscopic catecholamine iontophoretic. Versus intravenous infusion in dogs". J. Pharm. Sci, 76;215-218.
25. Weaver, J. C.; Chizmadzhevy. (1996),"Electroporation", In: Polte, C.;Postow, E. (Eds), "Biological effects of electromagnrtic fields", CRC,Press, Boca Raton, NY, 247-274.

26. 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.
27. Runyan, W. R.; Bean, K.E. (2990)"Semi conductor integrated circuit processing technology", Addition-Wesley, New york.
28. Kulkarni, R.g.; Jains; Agrawal G. p. ; Chourasia M. ; Jain N. K. (2000)"Advances in transdermal drug delivery systems", PharmaTimes, 32(5): 21-24.
29. Schreier, H.; Bouwstra, J. (1994)"Liposome and niosomes as topicaldrug carriers: drmal and transdermal drug delivery", J. Control. Rel.,30: 1-15.
30. Cevc, G.; Blume, G.; Schatzlein, A. (1997)"Transfersomes- medicated transepidermal delivery improves the regiospecificity and biological activity of corticosteroids invivo", J. Control. Rel.,45:211-226.
31. Cevec, g.; Blume, g. (1992)"Lipid Vesicles Penetrate into intack skin owing to the transdermal osmotic gradients and hydration force", Biochem, Biophys Acta., 1104: 226-232.
32. Schatzlein, A.; Cevec, G. (1998)"Non-uniform cellular packing of the stratum corneum and permeability barrier function of intact skin: a high resolution Confocal Scanning Laser Microscopy study using higly deformable vesicles (transfersomes)", Brit. J Dermatol., 138:583-598.
33. Cevec, G. (1993b)"Lipid hydration, In: Hydration of biological macromolecules", Westhof, E. (Ed.), Macmillan Press, New york, 338-351.
34. Cevec, G. (1996)"Transfersomes, liposomes and other lipid suspensions on the skin, Permeation enhancement, vesicles penetration and transdermal drug Delivery", crit. Rev. Ther. Drug Carrier Syst., 13: 257-388.
35. Cevec, G. (1992b)"Lipid properties as a basis for the modeling and design of liposome membrane", In: Liposome technology, 2nd ed., Gregoriadis G., b(Ed.), CrC Press, Boca Raton, FL, 1-43.
36. Panchagnula, R. (1997) "Trandermal delivery of drugs" Ind JPharmacol., 29; 140 – 156.
37. Cevc, G.(1993a) " Phospholipids Hand book" , Marcel Dekker, Newyork, Basel, Hongkong, 215 – 240.
38. Cevc, G (1991b) "Isothermal lipid phase transition" , Chem. Phys .Lipids, 57; 293 -299.
39. Cevc.G.; Grabauer, D.; Schatzlein,A.; Blume, G. (1993) "ultra high efficiency of drug and peptide transfer through the intact skin bymeans of novel carriers, Transfersomes", In : Bain, K.R.; Handgkraft, AJ; Prediction of percutaneous penetration, vol 3 b, STS publishing, Cardiff, 226 – 234.
40. Schubert, R., Beyer, K., Wolburg, H.and Schmidt,K.H., Biochemistry,1986, 25, 5263.
41. Holfer, C.,Goble, R., World.J.Surg, , 2000, 24, 1187.
42. Poul , A., Cevc, G., Vaccine Research, 1995, 4, 145.
43. Poul , A., Bachhawat, B.K., Vaccine Research, 1998, 16, 188.
44. Poul , A., Cevc, G., Eur.J.Immunol, 1995, 25, 3521.
45. Schatzlein , A., Cevc, G., Brit.J.Dermatol, 1998, i38, 583.
46. Holfer, C.,Goble, R., Anti Cancer Res., 1999, 19, 1505.
47. Cevc, G., Blume,G., J.Control .Release, 1997, 45, 211.
48. Jain, S.,Jain, N.K.,In, proceeding of 28 Th conference of CRS, U.S.A ,2001, 5207.
49. Cevc, G., Crit,Rev Ther.Drug Carrier Syst., 1996, 13, 257.
50. Cevc, G., Blume,G.,Biochem.Biophysic.Acta., 2001, 1514, 191.
51. Maghraby , E,I,., Williams,M., Barry,B.W., J.Pharm .Pharmacol.,1998, 50, 146.
52. Cevc, G., Biochemistry, 1987, 26, 6305.
53. Cevc, G., Crit,Rev Ther.Drug Carrier Syst., 1996, 13, 257.
54. Jain, S.,Sapra,R.and Jain., In, proceeding of 25 Th conference of CRS, U.S.A , 1998, 32.
55. Guo , J., Ping.Q., Int., J.Pharm . 2000, 194, 201.
56. Jain, S.,Jain, N.K.,Drug Deliv.Tech , 2002,2, 70.
57. Jain, S.,Bhadra,D.and Jain.N.K., Drug Develop.Ind.Pharm., 2003, inpress.
58. Hukriede, A., Bungener, L., Daemen, T.and Wilschut,J., Meyhods ofEnzymol, 2003, 373, 74.
59. Babizhayev, M.A., Arch.Biochem.Biophys., 1988, 266, 446.
60. Blume, G. and Cevc., Biochem.Biophys.Acta, 1993, 1146, 157.