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Preparation and Evaluation of Curcumin Invasomes

Lakshmi PK[1], Mounica V[1], Manoj Kumar Y[1], Prasanthi D[1]

*Corresponding author:

Lakshmi PK

[1]Department of Pharmaceutics, G.Pulla Reddy College of Pharmacy, Hyderabad, India.

Abstract

Curcumin has poor aqueous solubility and has bioavailability problems. Hence in the present study the solubility of curcumin was increased by complexing with cyclodextrin (CD) and Hydroxy propyl β cyclodextrin(HPβCD). This complex is incorporated in to invasomes and then into HPMC gel to prepare as a transdermal formulation.Curcumin cyclodextrin complexes were prepared by physical mixture and co-precipitation method. Different formulations of invasomes containing 0.5, 1.0, 1.5 % of limonene, fenchone, nerolidol individually were prepared using mechanical dispersion technique. Invasomes were characterized for vesicular size, surface morphology, zeta potential, entrapment efficiency and percutaneous permeation.Formulations CHL1 and CHL2 were optimized for further studies. It was found in the study that complex with HPβCD in 1:2 proportion prepared by co-precipitation method was found to bind 90% of curcumin.Invasomal preparation with 0.5% limonene, 4% ethanol was found to enhance permeation by 8.11 times the control.*In vivo* diffusion studies were conducted using franz diffusion cell, *ex vivo* skin permeation studies of CHL1using rat abdominal skin showed cumulative drug permeated (Q_{24})of 70.32 µg/cm^2, steady state transdermal flux of 3.344 µg/cm^2/hr^{-1}, permeability coefficient of 5.35 cm/hr and lag time of 1 hr when compared with control formulation. From the results it was concluded that the solubility of curcumin increased by complexing with HPβCD and invasomal preparation with 0.5% limonene has improved permeation through the skin.

Keywords: - Curcumin, Cyclodextrin, Invasomes, HPMCK4M gel

Introduction

Curcumin known as diferuloylmethane a yellow polyphenol is an extract from rhizomes of *Curcuma longa lin.* This compound has potency against many diseases such as cough, diabetes, anorexia, alzheimer disease, rheumatism, hepatic disorders, antioxidant, anti-inflammatory, anti carcinogenic, hypocholesterolemic, antibacterial, antispasmodic, anticoagulant, anti tumor etc. [1].Although therapeutic properties of curcumin have been the topic of several studies widespread clinical applications of curcumin is limited due to its poor aqueous solubility, degradation at alkaline pH, photodegradation, low systemic bioavailability. Cyclodextrins are 1,4 linked cyclic oligosaccharides produced by enzymatic conversion of starch and contain atleast 6 D - (+) glucopyranose units. -CD'sare insufficient in size for many drugs while γ-CD'sare expensive. Usually β-CD has been used extensively for many studies because of its ready availability, cavity size and use with wide range of drugs. Cyclodextrins are used pharmaceutically for drug complexation, as solubilizers, diluents, bioavailability enhancers for poorly soluble drug [2]. Serum plasma levelswere found to be only 2.25µg/ml by intra peritoneal route and 0.36µg/ml by intravenous route [3, 4]. Curcumin was complexed with γ-cyclodextrin using co-precipitation method to increase the solubility[5]. Anand et al., coated that nanoparticles, liposomes, phospholipid complexes are promising novel formulations which improve the bioavailability [6]. Transdermal route is the alternate pathway for localized or systemic pharmacological effects. Although advantageous in avoiding problems of poorly absorbable drugs and enzymatic degradation, penetration through the stratum corneum (SC) of epidermis an efficient barrier is the major problem. Hence several techniques and carrier systems were developed to cross this barrier.Liposomes,phospholipid vesicles are used as drug carriers. Traditional liposomes can be used only for topical application but they cannot deeply penetrate the skin and are restricted to upper layers of SC [7].Hence a series of vesicular carriers transferosomes® with edge activators, ethosomes with high amounts of ethanol, invasomes with ethanol and terpenes were developed. Elastic vesicles have shown to be superior in enhancing the penetration than conventional gel state and even liquid state vesicles [8]. Terpenes like cineole, citral and limonene are widely used for hydrophilic and lipophilic drugs. Dragicevic-Curic et al., 2009preparedsemisolid liposomal formulation by mixing with carbomer hydrogel to avoid leaky behavior of liposomes on application site [8].Two proposed mechanisms of penetration enhancement of terpenes observed are permeation as intact vesicles and disruption of intercellular lipid lamellae, forming channels[9].

Hence the present study deals with improving the solubility of curcumin by complexing with CD or HPβCD and then incorporating

this complex mixture into vesicular carrier invasomes. This vesicular carrier is then incorporated into HPMC K4M gel. Invasomes are characterized for size, morphology, zeta potential, stability. Invasomal gels are investigated for *ex vivo* permeation studies.

Materials and methods

Materials

Curcumin was procured from Sanat Products Limited, New Delhi, Soya phosphatidylcholine-70 from Sonic-Biochem extractions, limonene, fenchone and nerolidol procured from Alfa aesar, HPMC K4M procured from Sigma labs, HPβCD from Otto Kemi and other analytical reagents.

Complexation of Curcumin

Curcumin was complexed with β CD and HPβCD according to the formula (Table – 1) by Physical Mixture and Co-precipitation method (Zaibunnisa A.H et al., 2011)[5].

Table 1: Preparation and optimization of curcumin–CD complex.

Carrier	Method	Drug: Carrier	Percentage bound
HPβCD	Physical Mixture	1:1	43%
		1:2	61%
	Co-precipitation	1:1	65%
		1:2	**90%**
β CD	Physical Mixture	1:1	24%
		1:2	36%
	Co-precipitation	1:1	43%
		1:2	54%

Preparation of invasomes

Optimized 1:2 co-precipitated complex of Curcumin and HPβCD was loaded in to invasomes by mechanical dispersion technique. Soya Phosphotidylcholine (1 – 3% w/v) was added to ethanol and vortexed for 5 minutes. Curcumin – HPβCD complex and different terpenes (0.5 – 1.5%) were added under constant vortexing, this mixture was sonicated for 5 minutes. Fine stream of Phosphate buffer saline (upto 10%w/v) was added with syringe under constant vortexing. It was vortexed for additional 5 minutes to obtain final invasomal preparation.

Entrapment efficiency

Entrapment efficiency was studied by ultracentrifugation method. 1ml of invasomal suspension was transferred to Ephendroff tubes, centrifuged at 15000 rpm, 4ºC for 15 min in two cycles to separate the unentrapped drug and invasomes. Clear fraction was analyzed for free drug at 430 nm spectrophotometrically. Percentage entrapped is calculated indirectly from the amount of free drug from the formula.

$$Entrapment\ efficiency\ (\%) = \frac{total\ drug - free\ drug}{total\ drug}\ X\ 100$$

Surface morphology

Surface morphology was studied by placing a drop of preparation on a clear glass slide, air dried, coated with gold using sputter coater (Polaron E5100, Watford, UK) and visualized under Scanning electron microscope (Joel 5400, Japan).

Ex Vivo permeation studies

Ex vivo studies were approved by institutional animal ethics comittee. Abdominal skin section of male wistar rat was prepared and permeation studies were performed using Franz diffusion cell. Effective surface area of cell was 2.0 cm^2 and has a receptor volume of 20ml. Donor compartment was applied with invasomal preparation and 20 ml of pH 7.4 phosphate buffer saline maintained at 37ºC was used as receptor medium. Aliquot amounts were withdrawn and replaced by fresh media to maintain sink condition. Samples were analyzed using UV spectrophotometer, steady state transdermal flux (µg/cm^2/hr), permeability coefficient (cm/hr), enhancement ratio were calculated.

Preparation of Gel

Aqueous gel of 2% HPMC K4M was prepared by soaking the polymer overnight, appropriate amounts of propylene glycol was added and mixed until gel was formed. To this gel base optimized invasomal suspension was added such that 500 mg of gel contains 12.5% curcumin.

Speradability studies

Spreadability was determined by measuring the spreading diameter of 1g of gel between 20X20 cm glass plates for 1 min. Mass of upper plate was standardized at 150g. It is calculated by using the formula

$$S = {ML}/{T}$$

Where S is spreadability, M is weight tied on upper glass plate, L is length of glass slide, T is time in sec.

Extrudability

Extrudability was carried out by Pfizer hardness tester. 15g of gel was filled in aluminium tube and plunger was adjusted to hold the tube properly. Pressure of 1 Kg/cm^2 was applied for 30 sec and the mass of gel extruded was measured. This procedure is repeated at three equidistance places of tube.

Skin irritant studies

Skin irritant studies were performed on 3 healthy rabbits. Unbraided skin was cleaned with rectified spirit, control formulation was placed on left dorsal surface and test formulation on right dorsal surface. The formulation was removed after 24 hrs and the

skin was examined for erythema/edema and scored according to primary dermal irritation index classification.

Stability studies

Optimized invasomal gel was sealed in 10 ml glass vial and stored at refrigeration temperature (4 - 8ºC) and room temperature for one month. Entrapment efficiency, physical appearance was determined at regular intervals.

Results and Discussion

Characterization of curcumin complex

Physical mixture, co-precipitation methods using βCD, HPβCD in two ratios 1:1 and 1:2 were used for complex preparation. Complexes prepared by co-precipitation method showed more bonding/ complexing than the physical method. It was found that complexation in 1:1 ratio showed 43, 65% bonding by co-precipitation method with β CD and HPβCD respectively which was more than 24, 43% prepared by physical mixing method. Similarly with 1:2 ratio it was found to be 54, 90% with β CD and HPβCD by co-precipitation method where as only 36, 61% by physical mixing method. Complex prepared by co-precipitation method in 1:2 ratio with β CD showed complexation of only 54%, where as HPβCD showed 90%. Hence co-precipitation method showed more bonding than physical method [5] and more bonding was observed with 1:2 proportion.

Solubility of pure curcumin was found to be $2.98X10^{-11}$M and increased to $1.63X10^{-8}$M in HPβCD whereas only $0.21X10^{-8}$M with βCD. This is accounted because of hydrophilic nature of CD derivative HPβCD which enhanced the solubility of poorly water soluble curcumin when compared to parent CD [10]. Hence curcumin- cyclodextrin complexes prepared by co-precipitation method using HPβCD in 1:2 proportion was optimized.

FTIR spectral studies

Compatibility studies were performed using Fourier Transform Infrared spectrophotometer (FTIR 8400s, Shimadzu, Japan) in the range of 4000 – 400 cm-1 using potassium bromide pellet method. Pure curcumin showed absorption peaks at 3504.46 cm-1 characteristic to hydroxyl (–OH) group, peak at 1601 cm-1 characteristic to C=C of benzene ring, 1506.31 cm-1 characteristic to C=O, C=C, peaks at 1000 – 1260cm-1 for C-O and are found to be near to the absorption bands [11]. The complexed mixture with HPβCD also showed peaks in the region of 3503.84, 1601.39, 1506.73cm-1(figure – 1). Retention of the peak in the region 1601 shows that complexes were not formed with carbonyl group of curcumin and increase in intensity around the region of C-O ether bond shows that complexation was due to this C-O bond of curcumin [5].

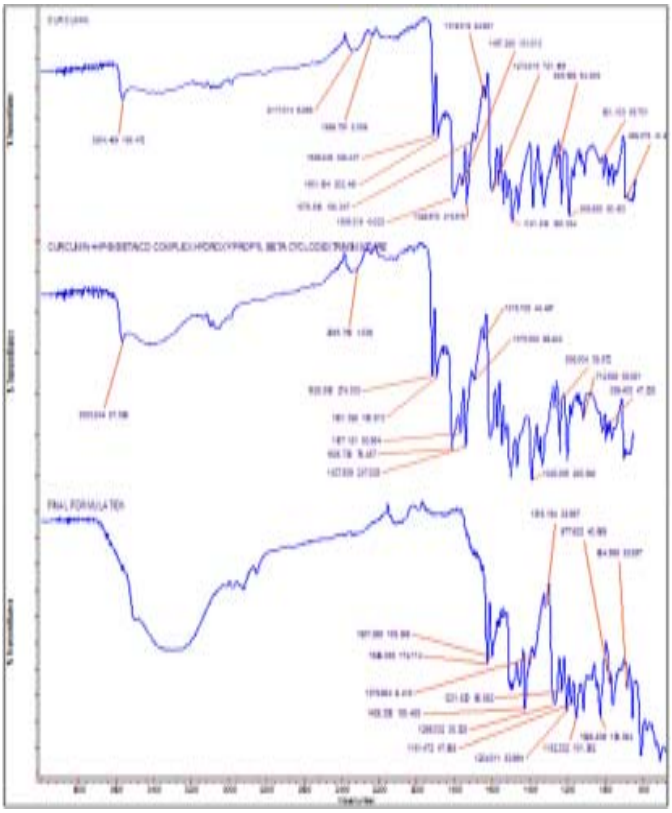

Figure 1: Comparision of FTIR spectra.

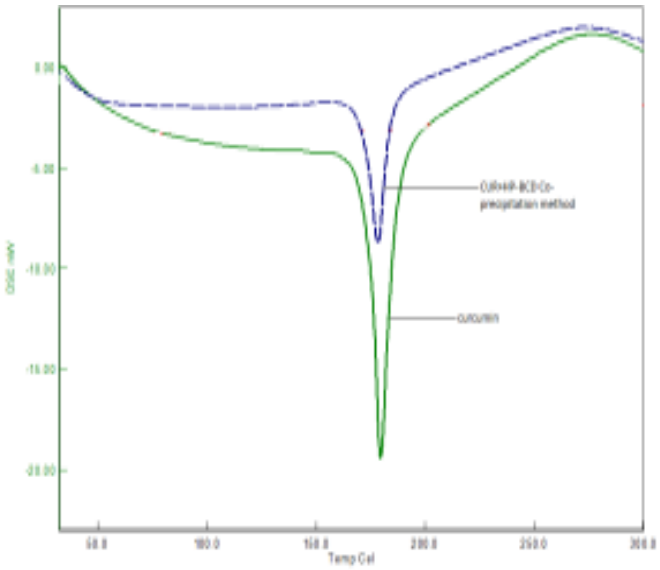

Figure 2: DSC of curcumin alonend curcumin complex

DSC studies

DSC studies were performed and exothermic peaks were observed around the region of 170 – 180ºC [12] this was because of melting of curcumin. The reduced intensity of the peak in complex of curcumin with HPβCD indicates complexation of curcumin (figure–2).

Characterization of invasomes

Entrapment efficiency

Invasomes were prepared by mechanical dispersion method. Preliminary studies were conducted and 1% soya phosphotidylcholine was optimized for further studies as it showed maximum entrapment efficiency. Curcumin-HPβCD was taken as equivalent to 5mg and incorporated into invasomes with different terpenes limonene, fenchone, nerolidol at 3 levels 0.5, 1, 1.5% individually and 4% of ethanol was added to all the formulations(table – 2). Entrapment efficiency of each formulation was calculated and it was found to be maximum inCHL1-93.5±0.08%, 88.4±0.11 in CHF1, 87.4±0.12 in CHL2, 76.8±0.07 in CHF2 and least in CHN3 - 58.4±0.06. Entrapment efficiency with different terpenes was found in the order limonene > fenchone >nerolidol. Limonene showed highest entrapment efficiency which is attributed due to the presence of hydrocarbon group.

Surface morphology

Characterization of invasomes

Vesicular size

Vesicle size was determined using Microtel X100 Leeds & Northrup particle size analyzer, UK and it was observed to be 134.7nm and poly dispersity index was < 0.2 for CHL1.

Zeta potential

Zeta potential was measured at Malvern Instruments Ltd using Zeta sizer and was found to be -33.7mv for CHL1. Negative charge may be imparted due to the presence of ethanol [7,12].

In vitro studies

In vitro diffusion studies were carried out using dialysis membrane to evaluate release from invasomes. Release profile for 24 hrs study is shown in figure 3.Three terpene formulations CHL1, CHL2, CHF2 showed good release rate of 22.31±3.0, 20.89±2.8, 15.25±1.9
respectively. In previous studies 1% terpene formulations showed better release [13] but the results show that 0.5% limonene showed good release than 1% formulation this may be attributed to presence of ethanol in the formulations. These three formulations were selected for *ex vivo* studies. Although CHF1 showed good entrapment efficiency of 88.4 ± 0.11 because of its release rate compared to CHF2 it was not selected for further studies.

Ex vivo skin permeation studies

Ex vivo studies were approved by IAEC. Permeation studies were conducted using excised male wistar rat abdominal skin and were performed usingFranz diffusion cell. Cumulative drug permeated was found to be 70.32±1.98 for CHL1, 60.58±2.61 for CHL2, 51.8±3.02 for CHF2 which was found to be more than control 22.89±2.08. D. D. Verma et al., observed increase in permeation with increase in ethanol [14],many literatures discusses the increase in permeation with terpene loaded vesicles when compared with liposome vesicles. Increased permeation in formulation with terpenes than conventional liposomes (control) may be attributed to synergistic effect of ethanol and terpenes as formulation CE prepared without terpenes also showed increase in permeation of 40.32±2.76 [7](table – 2).

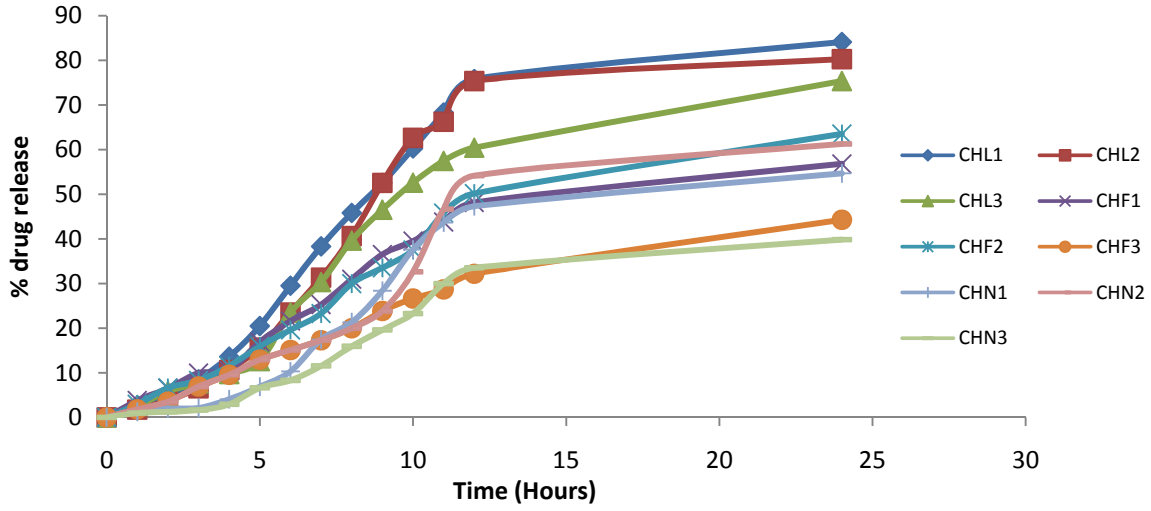

Figure 3: Release profile of prepared invasomal formulations.

Penetration parameters like steady state transdermal flux and permeability coefficient were calculated. Control formulation showed flux of 0.41±0.14 µg/cm^2/hr, maximum flux was observed with CHL1 3.34 ± 0.08 and increased flux of 3.02 ± 0.07 with CHL2 and 2.28 ± 0.16 with CHF2.

$$SSTF = \frac{Amount\ of\ drug\ permeated}{time} Xcrossectional\ area$$

$$K_p = {}^{JSS}/_{CV}, JSS = \frac{dM}{S}dt$$

JSS – steady state flux, dM – amount of drug permeated, S –unit of cross section, t – time, CV – total concentration in the donar compartment, K_p– permeability coefficient.

Permeability coefficient was found to be 5.35±0.03 $X10^{-3}$ with CHL1, 4.83±0.07$X10^{-3}$, 3.66±0.06$X10^{-3}$ with CHL2 and CHF2, where as only 0.32±0.04$X10^{-3}$ with control and 0.98±0.09 CE (with out terpenes).

Table 2: Formulation and Evaluation results of Invasome preparations

Formulation code	Limonene (%)	Fenchone (%)	Nerolidol (%)	Entrapment efficiency ± SD	Release rate µg/cm²/hr$^{1/2}$	Cumulative drug permeated (Q_{24})µg/cm²	SSTF µg/cm²/hr	Permeability Coefficient (X10^{-3} cm/hr)	Enhancement ratio	Lag time hrs
Control	-	-	-	ND	ND	22.89± 2.08	0.41± 0.14	0.32± 0.04	1	3.6 ± 0.12
CE	-	-	-	ND	ND	40.32±2.76	1.73±0.19	0.98±0.09	4.2	2.4±0.5
CHL1	0.5	-	-	**93.5 ± 0.08**	**22.31 ± 3.0**	70.32± 1.98	3.34± 0.08	5.35± 0.03	8.11	1 ± 0.2
CHL2	1	-	-	**87.4 ± 0.12**	**20.89 ± 2.8**	60.58± 2.64	3.02± 0.07	4.83± 0.07	7.33	1.2± 0.1
CHL3	1.5	-	-	82.2 ± 0.06	19.34 ± 2.4	ND	ND	ND	ND	ND
CHF1	-	0.5	-	88.4 ± 0.11	14.26 ± 1.0	ND	ND	ND	ND	ND
CHF2	-	1	-	**76.8 ± 0.07**	**15.25 ± 1.9**	51.8± 3.02	2.28± 0.16	3.66± 0.06	5.55	1.9± 0.6
CHF3	-	1.5	-	68.7 ± 0.13	10.33 ± 2.0	ND	ND	ND	ND	ND
CHN1	-	-	0.5	76.5 ± 0.08	12.98 ± 2.8	ND	ND	ND	ND	ND
CHN2	-	-	1	64.8 ± 0.12	14.86 ± 2.7	ND	ND	ND	ND	ND
CHN3	-	-	1.5	58.4 ± 0.06	8.79 ± 2.7	ND	ND	ND	ND	ND
CNT G	-	-	-	-	-	7.98± 1.86	0.28 ±0.03	0.45±0.02	1	4.2±0.2
CHL1G	-	-	-	-	-	52.8± 2.32	2.21 ±0.27	3.53±0.08	7.78	2.5 ±0.1
CHL2G	-	-	-	-	-	42.32± 2.52	1.77 ±0.08	2.84±0.04	6.25	2±0.05

Curcumin – Hydroxy propyl β cyclodextrin complex – 5 mg (5% w/v), Soya lecithin – 1%, Ethanol – 4% in all formulations except control, L-limonene, F-Fenchone, N- nerolidol, ND- not determined, SSTF - Steady state transdermal flux.

Enhancement ratio was calculated by comparing the formulations CHL1, CHL2, CHF2 with Control. CHL1 was found to enhance by 8.11 time and only 7.33, 5.55 times with CHL2, CHF2 respectively. T. Subongkot et al. also reported enhancement of 6.8 – 8 folds in ultradeformable vesicles compared to liposomes [9]. Lag time decreased with the use of terpenes when compared with control from 3.6±0.12 for control to 1±0.2, 1.2±0.1, 1.9±0.6 for CHL1, CHL2, CHF2 respectively owing to increased permeation effect of terpenes. Permeation enhancement of present study are in controversy with other authors but are according to the results of work of A. F. El-kattan et al., 2001 [16] where limonene showed high entrapment with lipophilic drugs. The increase in the permeation observed with limonene may be due to its lipophilicity and low boiling point [17] and lipophilic nature of curcumin.

Organoleptic characterization of gel

The optimized invasomal suspension CHL1, CHL2 was incorporated in to 2% HPMC K4M which was optimized by preliminary trials. Prepared gel was inspected under black and white background and was found very clear and without any aggregates.

The pH of the gel was determined using digital pH meter LI 127 Elico. 0.5g of gel was dispersed in 100 ml of pH 7.4 Phosphate buffer and checked for its pH. It was found to be 6.9, 7.0 for CHL1, CHL2 respectively.

Spreadability and Extrudability were performed as mentioned earlier and spreadability was found to be 27.07cm, 24.96cm for CHL1, CHL2 respectively, and extrudability was found to be excellent.

Viscosity was measured using LV DV-II+Pro Brookfield programmable viscometer with spindle 64, and was found to be 3982±2cp, 3896±1cp with CHL1, CHL2 respectively.

Ex vivo studies of gel

Ex vivo studies were conducted for prepared gels and were compared with control. Release profile is shown in figure 4. Cumulative drug permeated was found to be 52.8±2.32, 42.32±2.52µg/cm^{2}for CHL1G, CHL2G but with control it was just 7.98±1.86µg/cm^2. Steady state transdermal flux was found to be 2.21±0.27, 1.77±0.08µg/cm^2/hr for CHL1G, CHL2G respectively and 0.28±0.03 µg/cm^2/hr for control. Permeability coefficient was 3.53±0.08X10^{-3}, 2.84±0.04X10^{-3} for CHL1G, CHL2G and 0.45±0.02X10^{-3} cm/hr. Enhancement ratio was found to be 7.78, 6.25 times for CHL1G,CHL2G. Lag time decreased from 4.2±0.2 for control to 2.5±0.11, 2±0.05 hrs for CHL1G, CHL2G respectively. Drug permeation, flux, enhancement ratio and lag time was observed to be high for gel preparation with CHL1G

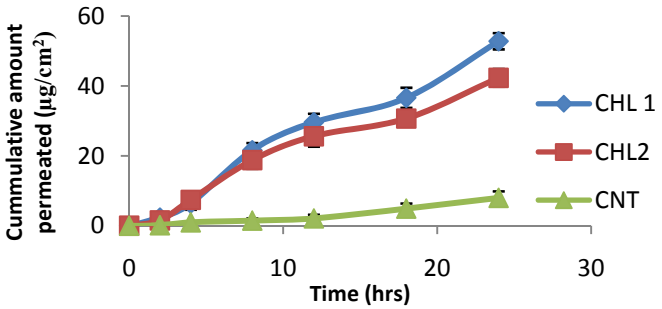

Figure 4: *Ex vivo* permeation studies

Statistical analysis

The results obtained were analyzed statistically using one way ANOVA (Tukey's multiple comparison test) and is depicted in (table 3).Results of control and CHL1 were significant (p<0.001) in SSTF, Q_{24}, permeability coefficient, enhancement ratio and lag time, CHL1 and CHL2 were significant (p<0.001) in permeability coefficient and enhancement ratio but Q_{24}, SSTF and lag time were not significant (p>0.05). CHL1 and CHF2 were significant (p<0.01) in permeability and enhancement, Q_{24} and SSTF but lag time was not significant (p.0.05). Comparing CHL2 with control showed significance of p<0.001 for SSTF, Q_{24}, permeability coefficient, enhancement ratio, lag time. CHL2 and CHF2 are significant in permeability, enhancement (p<0.001), Q_{24} and SSTF were not significant. Comparing CHF2 with control Q_{24}, permeability coefficient, enhancement ratio showed significance of p<0.01, SSTF with significance of P<0.005 and significance of p<0.01 in lag time.

SSTF, Q_{24}, permeability coefficient, enhancement ratio and lag time were observed to be significant to p<0.001 in CHL1G and CHL2G with control but lag time was not significant in CHL2G. SSTF, Q_{24}, permeability coefficient, enhancement ratio were significant but lag time was not significant (p>0.05) when comparing CHL1G, CHL2G.

From this analysis it is observed that terpenes shows significant effect on permeability coefficient and flux was influenced by permeability enhancer. Least lag time was observed with CHL2G

Table 3: Statistical analysis by ANOVA (Tukeys multiple comparison test)

Parameters			Cumulative amount permeated (Q_{24})	SSTF	Permeability coefficient	Enhancement ratio	Lag time
Control vs Other formulations		CNT vs CHL1	***	***	***	***	***
		CNT vs CHL2	***	***	***	***	***
		CNT vs CHF2	***	*	***	***	**
		F value	61.26	17.88	9640	18610	23.94
Comparision with in formulations	Invasomes	CHL1 vs CHL2	NS	NS	***	***	NS
		CHL1 vs CHF2	**	*	***	***	NS
		CHL2 vs CHF2	NS	NS	***	***	NS
		F Value	61.26	17.88	9640	18610	23.94
	Gel	CNT vs CHL1G	***	***	***	***	NS
		CNT vs CHL2G	***	***	***	***	*
		CHL1G vs CHL2G	***	***	***	***	NS
		F value	1.031e+006	191731	488463	3.565e+006	5.922

n = 2; *** (p<0.001); ** (p<0.01); * (p<0.005); NS – non significant (p>0.05)

Table 4: release kinetics of prepared invasomes and gel.

Formulations		Zero order	First order	Higuchi	Peppas		Release mechanism
		r^2	r^2	r^2	r^2	n	
Invasomes	CHL1	0.990	0.9068	0.952	0.982	0.434	Fickian diffusion
	CHL2	0.996	0.7341	0.936	0.923	0.471	Fickian diffusion
	CHF2	0.995	0.8202	0.939	0.969	0.472	Fickian diffusion
Gel	CHL1G	0.992	0.9078	0.962	0.982	0.454	Fickian diffusion
	CHL2G	0.986	0.7641	0.926	0.943	0.431	Fickian diffusion

Release kinetics of optimized 0 order kinetics, fickian n<0.5

Release kinetics

Release kinetics was observed by fitting the data in to Zero order, First order, Higuchi's, Korsemeyer peppas equations and was found to follow zero order release with Fickian diffusion mechanism.Table-4

Skin irritation studies were performed on depilated rabbit and was assessed and scored according to primary dermal irritation index classification. Gel formulation CHL1G was applied on to depilated skin and was confirmed that there was no sign of erythema or edema.

Stability studies

Stability studies of optimized formulation was carried out by sealing the formulation in 10 ml glass vial and refrigerated at 4 - 8ºC and at room temperature for 1 month. Drug content was determined and there was a decrease of only 10 % of entrapped drug after 1 month when stored at refrigeration. But when stored at room temperature the loss was upto 50%. Hence curcumin loaded invasomes are stored at 4 - 8ºC as aggravated temperatures causes leaking by transition of lipid bilayer or chemical degradation of lipids.

Conclusion

Because of its poor solubility, its instability in alkaline pH curcumin is formulated as transdermal formulation. Curcumin was complexed with βCD and HPβCD. Improved solubility and stability was observed with HPβCD prepared by co-precipitation method than physical mixture method. Optimized complex ie., 1:2 proportion complex is incorporated into invasomes with limonene, fenchone, nerolidol as terpenes which acted as phospholipid membrane flexibilizers, penetration enhancers. 1% soya phosphotidylcholine, 0.5% limonene was optimized which showed Q_{24} of 70.32 µg/cm^2, SSTF of 3.34 µg/cm^2/hr^{-1}, permeability coefficient of 5.35 cm/hr, and decreased lag time of 1 hr. formulation CHL1 was found to be better in all characteristics and was incorporated into 2% HPMC K4M gel formulation. Further *in vivo* studies are to be carried out to assess the pharmacokinetics of curcumin invasomal formulations.

Abbreviations

HPMC- Hydroxy propyl methyl cellulose

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