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Design and Characterization of Transfersomal Patch of Aceclofenac as a Carrier for Transdermal Delivery

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Abstract

Aim: The objective of present investigation has been focused on formulation and characterization of aceclofenac loaded transfersomal transdermal patch as an alternative delivery method for localized drug action to the targeted site. **Methods:** Aceclofenac was encapsulated into transferosome vesicle by thin film hydration technique using different edge activators and characterized for particle size, vesicle morphology by scanning electron microscopy, entrapment efficiency and drug release. Later, the optimized SP2 and TW3 transferosome formulations were selected for patch preparation by solvent casting method. **Result:** Transfersomal vesicles were found to be nanometric range [below 400 nm] with spherical structure. SP2 formulation showed maximum drug release of 86.4 % and entrapment efficiency of 76 % wherein TW3 formulation showed maximum drug release of 92.3 % and entrapment efficiency of 64 %. Vesicles formed with tween 80 are smaller than that with span 80. Based on the *in vitro* permeation studies, aceclofenac loaded transfersomal patch was found to have greater drug permeation than a plain patch of aceclofenac. The results obtained revealed that aceclofenac in all the formulations was successfully entrapped with good uniformity and followed Higuchi's drug release kinetic model with non-fickian mechanism. **Conclusion:** This research work suggested that aceclofenac loaded transfersomal transdermal patch can be a novel alternative approach to oral therapy in the treatment of arthritis.

Keywords
Aceclofenac, Arthritis, Transferosomes, Transdermal Patch, Vesicle.

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INTRODUCTION

A current scenario of novel drug delivery system is shifted towards designing of nanoscale drug delivery which not only increases a therapeutic index but reduce drug toxicity also to achieve controlled and targeted drug delivery [1]. Novel drug delivery system (NDDS) involves combination of polymer science, pharmaceutics and molecular biology to provide an ease and convenience of drug administration, minimize drug degradation, delivery of accurate dose, increase drug bioavailability [2] as compared to conventional delivery system hence, transdermal drug delivery establishes itself as an integral part of novel drug delivery system which is

designed to deliver therapeutically effective amount of drug across the skin for local and systemic effects and could provide sustained drug release [3]. The major challenge of poor dermal permeability, unpredictable drug release and skin irritation in topical transdermal delivery may be resolved using an innovative approach such as iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, microneedles and colloidal drug carrier systems like micellar solutions, vesicular system such as liposome, niosome, ethosome, transfersome as well as nanoparticles dispersion consisting of smaller particles size of 10 - 400 nm range [4].

Encapsulation of drug in vesicular structure is one such newer approach which can be expected to prolong the duration of drug in systemic circulation [5] and thereby reduce toxicity with advantages of improved bioavailability, delay elimination of rapidly metabolized drugs, incorporation of both hydrophilic and lipophilic drugs, decreases dosing frequency, enhanced stability and patient compliance [6]. The vesicular system is highly ordered assemblies which consist of one or more concentric lipid bilayers, when amphiphilic building blocks are confronted with water [7]. Transferosome is one such vesicular drug carrier system composed of phospholipid, surfactant and water for enhanced transdermal delivery. The surfactant here acts as an edge activator which destabilizes the lipid bilayer and increases the deformability of the vesicle and thereby imparts elasticity in the lipid bilayer structure [8]. Transferosome is first generation elastic vesicular carrier that resembles lipid vesicles called liposome in morphology but functionally can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss and thus high deformability gives better penetration of the intact vesicles [9]. Transferosome are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes and act as depot, releasing their content slowly and gradually, thus applied for systemic and topical drug delivery. The transfersomal patch has advantages over transfersomal gel because patch offer application of transferosome under occlusive conditions hence more permeation, lesser amount of active drug and gradual supply rather than a large dose [10].

Nonsteroidal anti-inflammatory drugs (NSAID's) are the most commonly used drugs to reduce pain and inflammation, but their numerous well-described side effects can limit their oral use [11]. NSAID inhibit cyclo-oxygenase-2 enzyme which results in anti-inflammatory action while block cyclo-oxygenase-1 enzyme which protects the lining of the stomach from acid [12]. NSAID when applied topically in the form of transdermal patch, without reaching higher drug plasma concentration penetrate into the skin in amounts sufficient to exert local therapeutic effect and offer the advantage of local enhanced drug delivery to the affected tissues with reduced incidence of systemic adverse events. Aceclofenac is a phenyl acetic acid analog of diclofenac recommended for arthritis treatment to relief pain and inflammation and belongs to BCS Class II with poor water solubility (60 µg/ml). Aceclofenac appear to be well tolerating than conventional NSAID's with lower incident of gastrointestinal adverse effects. Although the drug is rapidly absorbed following oral administration, its bioavailability is relatively low due to first pass effect [13]. Oral aceclofenac administration leads to unfavourable effects especially on the gastric mucosa due to PG inhibition and have reported to cause local irritation, gastrointestinal adverse effect [bleeding, ulceration, perforation] along with other side effects like dyspepsia (7.5 %) abdominal pain (6.2 %) nausea (1.5 %) diarrhoea (1.5 %) ulcerative colitis (0.1 %) and disturbance of platelet function [14].

Therefore, the present investigation deals with the formulation and characterisation of aceclofenac loaded transfersomal transdermal patch.

MATERIALS AND METHODS

Aceclofenac was procured from Empree medicaments [Belagavi, India]. Soya lecithin 30 % purchased from Hi media [Mumbai, India] and chitosan procured from Sigma Aldrich [Mumbai, India]. All other ingredients were of analytical grade.

Development of calibration curve of aceclofenac:

Primary stock solution of aceclofenac was prepared in methanol by dissolving 10 mg drug. From this stock solution 1 ml was withdrawn and diluted up to 10 ml with pH 6.8 phosphate buffer. From this, a series of dilutions were made in the range of 2–12 µg/ml using phosphate buffer and analysed by UV-Visible spectrophotometer [15].

Compatibility studies by FTIR spectroscopy:

Fourier transform infrared spectroscope [FTIR] helps to confirm the identity of drug sample and detect interaction between drug and its excipients. FTIR spectrum of aceclofenac and physical mixture of drug with lipid, surfactant and chitosan were recorded in the scanning range of 400 to 4000 cm^{-1} with resolution of 4 cm^{-1} [IR-Affinity1, Shimadzu, Japan.][16].

Differential scanning calorimetry:
Differential scanning calorimetry (DSC) analysis was performed on DSC-60 detector (Shimadzu, Japan). Approximately 4 mg of aceclofenac drug and physical mixture of drug with other excipients were weighed in an aluminium pan and sealed hermetically. DSC scan was recorded from 30 to 300^0 at a heating rate of 10^0 /min under nitrogen purge [16].

Preparation of aceclofenac loaded transferosome:
Transferosome were prepared by thin film hydration using rotary evaporation. 100 mg drug and mixture of lipid and surfactant in 4 different ratios [Table 1] were dissolved in organic solvent mixture of methanol and chloroform. This mixture is transferred in a clean, dry round bottom flask and organic solvent was carefully evaporated by rotary evaporation [Buchi rotavapor R-3000] under reduced pressure with 60 rpm to form a thin lipid film. The final traces of solvent were removed by subjecting the flask to vacuum overnight. The dried thin lipid film was then hydrated with 10 ml of phosphate buffer solution [pH 6.8] by rotation at room temperature. Resulting vesicles were sonicated for 5 min cycles using probe sonicator [Rivotex] for further vesicles size reduction and stored at 4^0 [17].

Characterization of transferosomes:

Particle size
The mean particle size and polydispersity index (PDI) of transfersomal vesicle were analyzed using dynamic light scattering particle size analyzer [Microtrac A150, Japan] [18].

Vesicle morphology
Shape and surface morphology of transferosome was studied using scanning electron microscopy [SEM] [JSM-T330A, JEOL]. One drop of transferosome suspension was mounted on the slab covered with cleaned glass and observed under scanning electron microscope. Photomicrograph of suitable magnification was obtained [19].

Entrapment efficiency
The concentration of aceclofenac in transfersome formulation was determined by UV analysis after disruption of the vesicles. Transferosome containing aceclofenac was separated from untrapped drug by centrifugation at 14,000 rpm for 30 min. The supernatant was filtered, assayed by UV spectrophotometer and calculated.

***In vitro* drug release for transfersome**
In vitro release of aceclofenac bearing transfersome was determined by simple dialysis method. Transfersome suspension equivalent to 5 mg drug was taken in the dialysis bag and immersed in a beaker containing 100 ml of phosphate buffer (pH 6.8) which was maintained at 32^0 ±2 which is constantly stirred at 100 rpm over a magnetic stirrer. Samples of 2 ml were withdrawn from the receptor compartment at predetermined intervals and immediately replaced with fresh buffer to maintain the sink condition throughout the experiment. All samples in triplicate were collected and analyzed by UV spectrophotometer at a wavelength of 273 nm against phosphate buffer as a blank [20].

Formulation of transfersomal patch:
The promising transfersome formulations were incorporated into transdermal patch by solvent casting method using aluminium foil as a backing membrane. The patch composition and concentration were chosen based on preliminary studies. Transfersomal patch was prepared by using 1% chitosan solution, 50 mg poly vinyl alcohol [PVA] and 1% poly vinyl pyrrolidone [PVP] solution mixture with propylene glycol as a plasticizer. A specified amount of transferosome suspension is then added to the polymer solution with gentle stirring to get a uniform homogenous mixture. The obtained solution was then poured into petridish with aluminium foil as backing membrane and left to dry in an oven at 40^0 until complete evaporation of solvent and then stored in desiccator. Control patch with aceclofenac 1 % w/v was prepared using the same procedure [21].

Characterization of transfersomal patch:
All the transdermal patches were visually inspected for colour, clarity, flexibility and smoothness [22].

Tensile strength
The % elongation and tensile strength of patch was determined by using pulley system designed in laboratory. Force was applied and the force at which patch breaks was measured.

Thickness
Thickness of patch was measured using Vernier calliper. The thickness was measured at three different positions of the patch and average was calculated. This is essential to know the uniformity in thickness of patch as this is directly related to accuracy of dose in each patch.

Folding endurance
The folding endurance was measured manually for all the formulated patches. A strip of patch (2 × 2 cm^2) was cut and repeatedly folded at the same place until it broke. Number of times at which the patch could be folded at the same place without breaking or cracking was observed as an indication of brittleness.

***In vitro* drug permeation studies**
In vitro drug permeation studies of transfersomal patch was performed by Franz diffusion cell using dialysis membrane 150 with receptor compartment. The patch was placed in donor compartment over

the dialysis membrane and receptor compartment filled with buffer [pH 6.8]. The temperature of the diffusion cell is maintained at 32 ±0.5^0. Aliquots of 1 ml were collected at predetermined time interval & replenished with fresh medium. The concentration of aceclofenac present in the patch was determined by UV spectrophotometer at 273 nm [23].

Drug release kinetics studies:

The data obtained from *in vitro* drug release studies of transferosome and its patch formulations were further processed for regression analysis using Pcp Disso-V3 software.

Stability studies:

The optimized transferosome formulations was sealed in glass bottle and kept at 4^0 whereas optimized transfersomal patch was kept at 40^0 ±2, 75% RH in humidity control oven and tested for short term stability studies as per ICH guidelines [24]. Samples were withdrawn at interval 30, 60 days and analyzed for *in vitro* drug release.

RESULT AND DISCUSSION

Calibration curve of aceclofenac

When examined in the range of 200 nm to 400 nm, aceclofenac showed an absorption maximum [λmax] at 273 nm as seen in fig. 1. The calibration curve of aceclofenac in pH 6.8 phosphate buffer was found to be linear with correlation coefficient [R^2] value 0.9998 which indicated that it obeys Beer's law.

Drug excipient compatibility studies by FTIR spectroscopy

FTIR spectrum of pure drug and physical mixture of drug with excipients is shown in fig. 2. Aceclofenac characteristic peaks were observed in the range N-H stretching at 3316, C-H stretching at 2935, C-C stretching at 1479, C=O stretching at 1769, C-Cl stretching at 770 and OH stretching at 2970. From the FTIR spectra it indicated that all the characteristic peaks of the drug were present in the mixture spectra also with minor difference. The similarity in peak proves that there was no chemical interaction between the drug and excipients and hence compatible.

Differential scanning calorimetry (DSC) studies

DSC curve of aceclofenac and drug with other excipients mixture was obtained as illustrated in fig. 3 and fig. 4. Pure aceclofenac exhibited sharp endothermic peak at 152.99^0 which corresponds to its melting point. Encapsulationof aceclofenac in transfersome vesicle does not affect the characteristic peak but showed disappearance of melting endotherm of aceclofenac. The endotherm in the transfersome formulation was slight shift from 152.87 to 150.60 which indicates good interaction between all the components without affecting the final formulation and there is no any other derivative or polymorph was formed. This result indicated that the absence of melting endotherm of aceclofenac suggested significant interaction of aceclofenac with lipid bilayer which leads to enhanced entrapment of drug.

Characterization of transfersome

Aceclofenac loaded transfersome were prepared by thin film hydration technique as this is one of the straight forward, rapid and easy to perform method as compared to other techniques. Transfersome with tween 80 formulations was off-white to yellowish in colour with free flowing nature whereas transfersome with span 80 formulations was dark yellowish in colour with viscous nature.

Particle size

The particle size of transfersome was found to be in the range of 150 to 338 nm with span 80 whereas for tween 80 it was in the range of 60 to 100 nm. Particle size data was shown in Table 1. The vesicles formed with tween 80 were smaller in size than that with span 80. The effect of surfactant HLB value on vesicle size has been noticed, as the HLB value of the surfactant increases, the lipids interaction also increases with decrease in particle size. HLB value of span 80 is 4.3, which have got higher vesicle size whereas HLB value of tween 80 is 15.0, which have got smaller vesicle size. The trend between the HLB value and particle size could be attributed to the increase in surface free energy accompanying increase hydrophobicity of surfactant. The effect of lipid and surfactant concentration on particle size was also checked and in span formulation [SP1 - SP4], the particle size increases as surfactant concentration increased while particle size decreases as lipid concentration increased. Similarly, in tween formulation [TW1 - TW4] the particle size decreases as surfactant concentration increased while particle size increases as lipid concentration increased, this may be due to the aggregation of vesicle.

PDI index indicates the width of particle size distribution. The PDI value for the aceclofenac transfersome varied in the range of 0.5 to 1.5 as tabulated in Table 1 which has shown vesicle were heterogeneously dispersed in population.

Entrapment efficiency

Entrapment efficiency of aceclofenac loaded transfersome formulations was found to be in range of 76 % to 48 % as shown in Table 1. The concentration and type of edge activator used has a very crucial effect on entrapment efficiency. The entrapment efficiency was found to decrease with increase in span 80 concentration whereas

entrapment efficiency was increase with increase in tween 80 concentration. The entrapment of lipophilic drug into lipid vesicles was facilitated by drug distribution coefficient between lipid and aqueous phasesolution. Maximum drug entrapment efficiency was seen in span concentration (76%) as compared to tween (64%).

Vesicle morphology

Transfersome with tween 80 was selected as optimal carrier owing to smaller particle size, good entrapment efficiency and maximum elasticity and hence used for SEM analysis. Shape and surface morphology of transfersome formulation was studied using scanning electron microscopy at various magnifications as shown in fig. 5. The drug loaded transfersome formulation was found to be smooth, spherical in shape with sharp boundaries having internal aqueous space.

***In vitro* drug release for transfersome**

The percent drug release of aceclofenac transfersome was estimated using dialysis bag diffusion technique. The release profiles of aceclofenac from different transfersomal formulations [fig. 6] was biphasic release process, wherein rapid release was observed during the first 6 h which may have resulted from the release of surface-adsorbed drug, followed by a sustained release profile up to 24 h which resulted from the release of remaining drug entrapped in vesicle. Maximum drug release of 86.4 % in SP2 while 92.3 % in TW3 was observed.

Drug release increases with increasing concentration of edge activator in the formulation. Maximum drug release is observed in formulation containing edge activator in concentration of 10-20% because at this concentration the surfactant molecule gets associated with the phospholipids bilayer resulting in better partitioning of the drug and thereby higher drug release from the vesicles as reported by [Abdallah M et al.] and at higher edge activator concentration [> 20 %], release of drug is low may be due to formation of rigid mixed micelles whereas at low edge activator concentration [< 10 %], drug release is also low due to more orderly impact on lipid membrane.

Evaluation of transfersomal patch

Aceclofenac loaded transfersomal patch was prepared by solvent casting method using chitosan, PVA & PVP polymers. Chitosan in patch formulation showed low swelling in water but interpenetrated network of chitosan with hydrophilic polymers such as PVA & PVP showed good uniformity, thickness and tensile strength to the patch. The formulation SP2 and TW3 based on percent drug release are considered as optimal carrier of transfersome formulation which is then incorporated into patch by solvent casting method. The insertion of transfersome into transdermal patch showed smooth and regular surface with uniformly distribution throughout the patch. Plain patch of aceclofenac [1 % w/v] is used as control. The physicochemical characteristics of the patch are shown in Table 2. All the prepared patches were smooth, flexible and uniform in appearance. The thickness of all the patches was found to be in range of 0.1 to 0.2 mm. The folding endurance for transfersomal loaded patch was found to be lesser than 100 which indicated that the patches were flexible and would maintain its integrity with skin. The tensile strength of patches was found in range of 1.2 to 2.9 kg/cm^2

***In vitro* drug permeation studies for transfersomal patch**

In vitro drug permeation studies of transfersomal transdermal patch were performed by using Franz diffusion cell and % drug permeated from the patches were indicated in fig. 7. The *in vitro* drug permeation of aceclofenac was studied for 24 h. 84.6 % of aceclofenac permeated for F1 formulation and 72.1 % of aceclofenac permeated for F2 formulation whereas in plain patch of aceclofenac [i.e F3] formulation 38.3% of aceclofenac was permeated. This result indicates that aceclofenac loaded transfersomal patchis having greater permeation of drug than normal patch of aceclofenac which may be attributes to the fact that the transfersome vesicle can squeeze through the stratum corneum intact. Tween 80 surfactant was more effective for transfersome carrier to load aceclofenac drug as it is having smaller vesicle particle size. Transfersome can pass through the intercellular spaces of the skin cell and the moisture cloud present beneath the stratum corneum can trigger osmo-regulated delivery for transfersome.

Stability Studies

Stability studies were performed for the optimized transfersomeformulationof SP2, TW3 and F1transfersomal patch formulation as per ICH guidelines for 2 months. There were no changes in physical appearance of transfersome formulation when samples stored at 4^0 but sediment was observed at room temperature which disappeared immediately with slight shaking. The values were shown in Table 3 and 4.They were no significant change seen in particle size and drug release of selected transfersome formulation [SP2, TW3] at 4^0 but negligible drug leakage was observed at room temperature after stability studies which indicates

that aceclofenac loaded transfersomal vesicle were stable. Whereas F1 transfersomal patch formulation, they were slight decrease in drug release upon stability.

Drug release kinetics

The data of drug release kinetics is given in Table 5. The best fitted kinetic model for both transfersome formulation as well as transfersomal patch was found to follow Higuchi's order kinetics as seen in fig. 8. The linearity of the plot indicated that the release process was diffusion controlled and n value was in range of 0.5 to 0.7 hence it follows non-Fickian mechanism.

Table 1: COMPOSITION AND CHARACTERIZATION OF ACECLOFENAC LOADED TRANSFERSOME FORMULATIONS

Formulation Code	Composition ratio [PC: S]	Particle size* [nm]	Polydispersity Index	Drug Entrapment Efficiency* [%]
SP1	95:05	165±0.17	1.5	76±1.59
SP2	90:10	198±0.16	0.7	58±1.02
SP3	85:15	338±0.12	1.2	53±1.25
SP4	75:25	220±0.09	2.5	48±2.02
TW1	95:05	80±0.10	1.1	48±1.86
TW2	90:10	72±0.12	0.6	56±1.88
TW3	85:15	76±0.14	0.7	59±1.96
TW4	75:25	73±0.20	0.7	64±2.20

***Data expressed as mean ± SD (n=3)**
Where SP=Span 80, TW=Tween 80, PC= Soya lecithin, S=Surfactant.

Table 2: CHARACTERIZATION OF TRANSFERSOMAL PATCHES

Ingredient/Formulations	F1	F2	F3
Texture	Smooth, Yellowish white in colour.	Smooth, Yellowish white in colour.	Smooth, White in colour.
Folding endurance*	44±1.7	46±2.1	198±2.3
Thickness (mm)*	0.15±0.2	0.13±0.3	0.2±0.2
Tensile strength(kg/cm^2)*	1.9±0.7	1.2±0.8	2.9±0.8

***Data Expressed as Mean ± SD (n=3)**
Where F1= Formulation with tween-80, F2=Formulation with span-80, F3= Plain patch of Aceclofenac.

Table 3: STABILITY STUDY OF ACECLOFENAC TRANSFERSOMAL PATCH

Formulation	*In vitro* drug permeation profile		
	0	30 Days	60 Days
F1	84.6%	81.03%	78.8%

Table 4: STABILITY STUDIES OF ACECLOFENAC LOADED TRANSFERSOMES

Evaluation Parameters	Formulation SP2 at 4^0			Formulation TW3 at 4^0		
	0	30 Days	60 Days	0	30 Days	60 Days
Particle size [nm]*	198±0.05	183±2.5	180±2.4	76±1.6	68.5±1.8	64.9±1.5
In vitro drug release [%]	86.48%	82.6%	78.5%	92.3%	90.4%	86%

***Data Expressed as Mean ± SD (n=3)**

Table 5: *IN VITRO* KINETIC MODEL OF DRUG RELEASE

Formulations	Zero order kinetic model [R^2]	First order kinetic model [R^2]	Higuchi's square root model [R^2]	Korsmeyer Peppas Model [R^2]	Hixson Crowell model [R^2]	Best fitting model
SP1	0.7945	0.8351	0.9541	0.8821	0.7695	Higuchi
SP2	0.7305	0.8935	0.9245	0.5407	0.4796	Higuchi
SP3	0.6863	0.8095	0.8971	0.6841	0.4544	Higuchi
SP4	0.6448	0.6852	0.8771	0.7101	0.6721	Higuchi
TW1	0.6027	0.7014	0.8657	0.5065	0.1068	Higuchi
TW2	0.5697	0.8265	0.8476	0.3779	0.4227	Higuchi
TW3	0.5524	0.7617	0.8209	0.4936	0.0762	Higuchi
TW4	0.5108	0.6067	0.7929	0.4795	0.4187	Higuchi
F1	0.7355	0.7687	0.9333	0.7271	0.4319	Higuchi
F2	0.7005	0.7276	0.9174	0.7088	0.1906	Higuchi
F3	0.8399	0.8497	0.9207	0.8821	0.5721	Higuchi

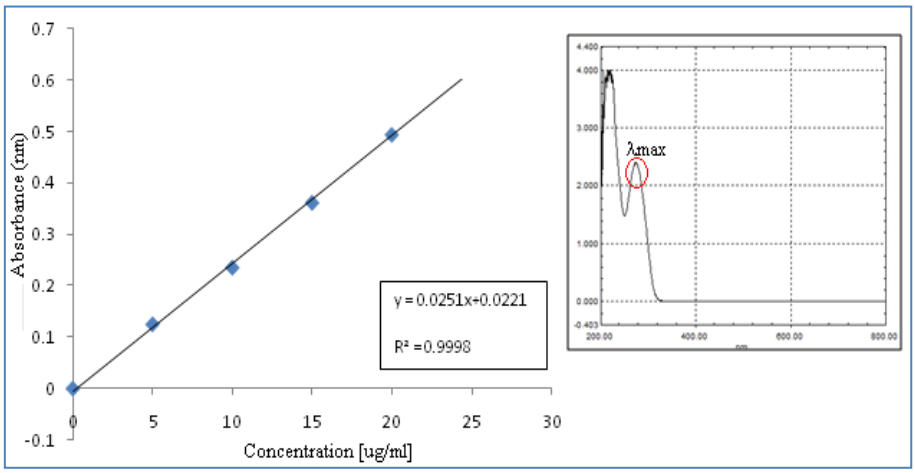

Fig. 1: Calibration curve of aceclofenac

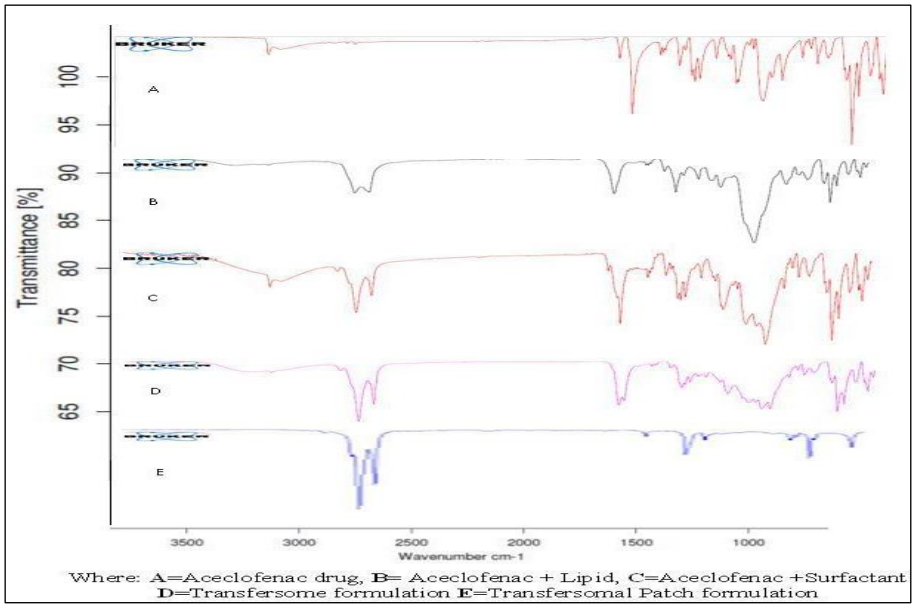

Fig. 2: FTIR spectroscopy

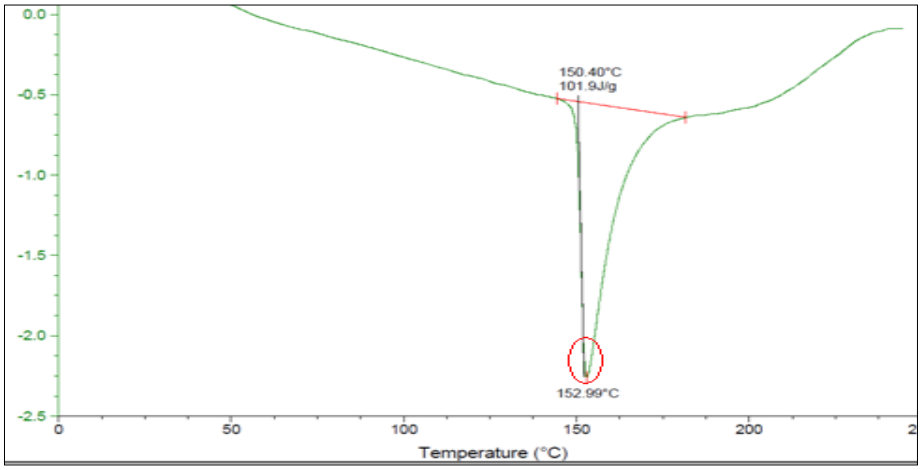

Fig. 3: DSC thermogram of aceclofenac

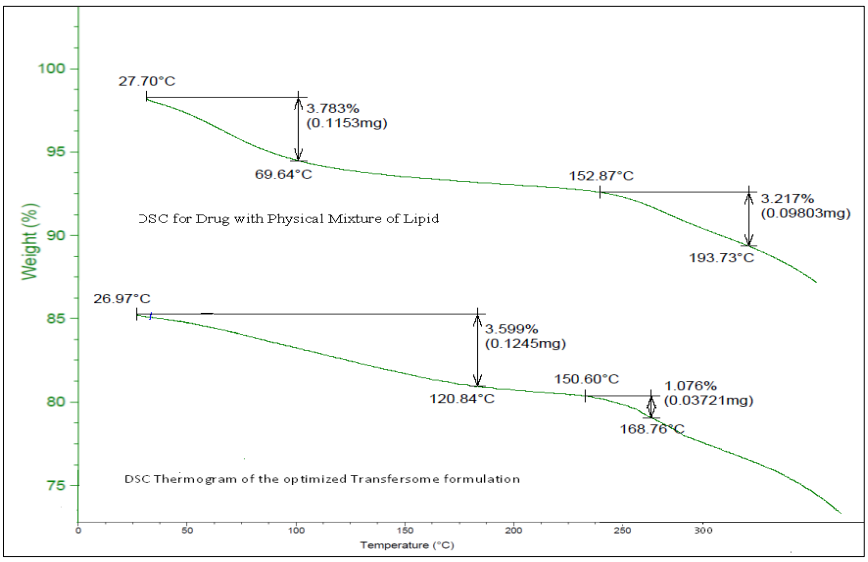

Fig. 4: DSC thermogram of optimized formulations

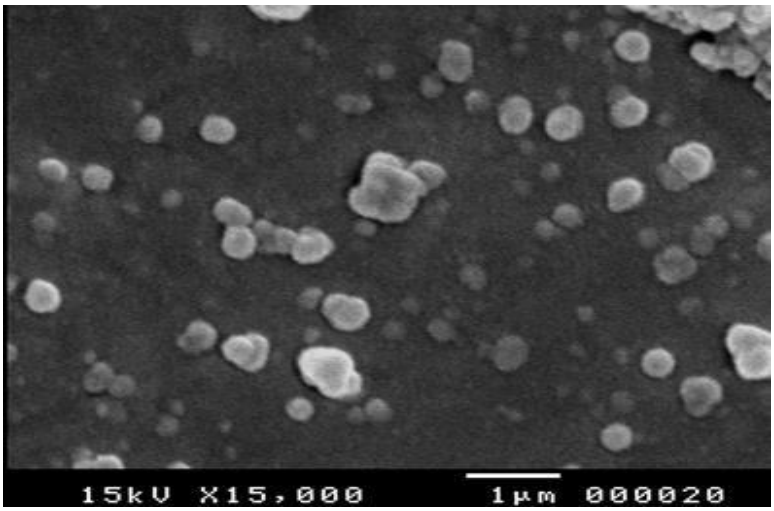

Fig. 5: SEM images of optimized transfersome vesicle.

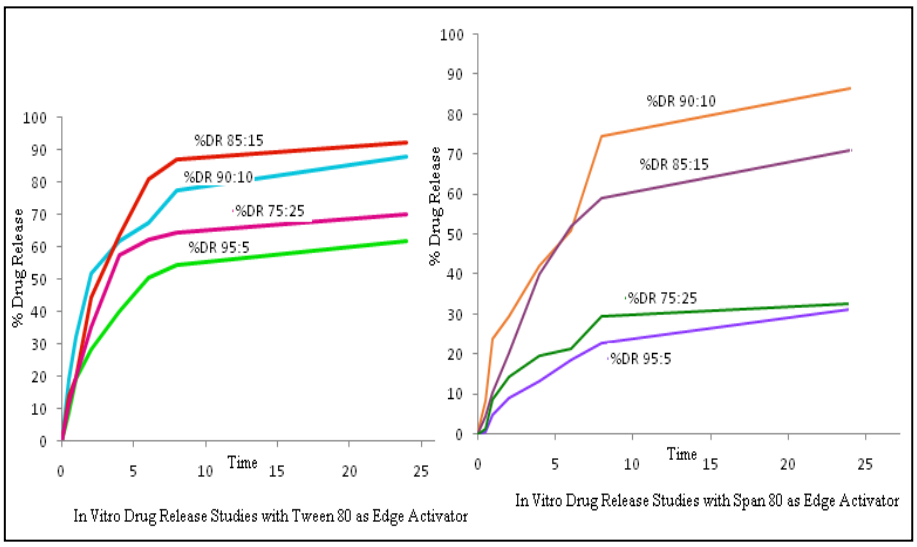

Fig. 6: *In vitro* drug release profile

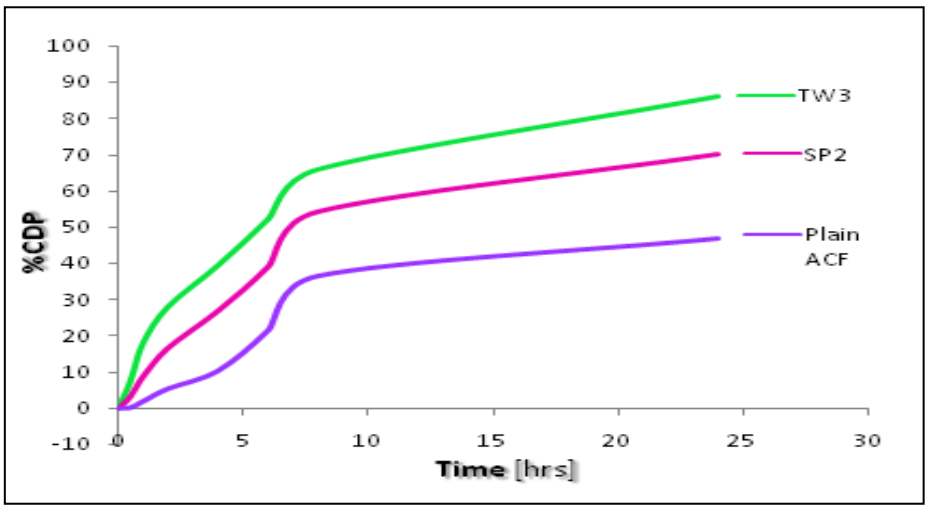

Fig.7: *In vitro* drug permeation studies of patch

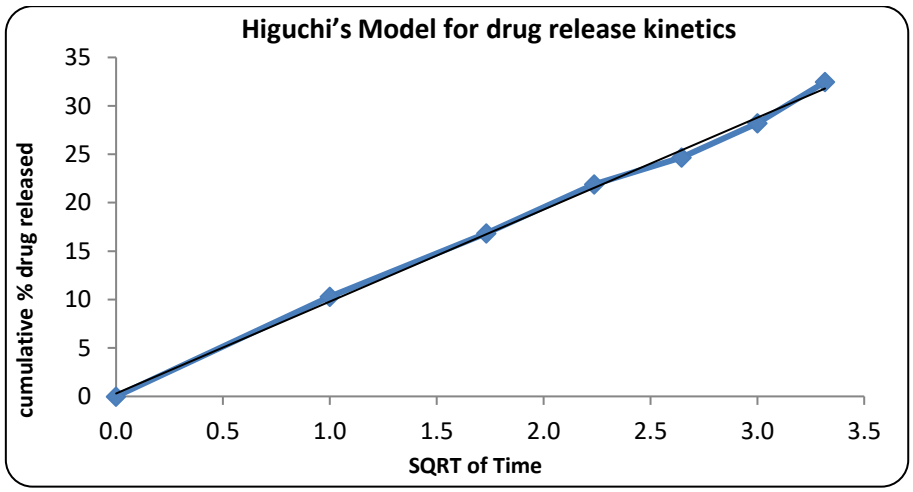

Fig.8: Higuchi's Model for drug release kinetics

CONCLUSION

Aceclofenac loaded transfersomal patch was prepared by solvent casting method using chitosan, PVA & PVP polymers. Chitosan in patch formulation showed low swelling in water but interpenetrated network of chitosan with hydrophilic polymers such as PVA & PVP showed good uniformity, thickness and tensile strength to the patch. Tween 80 surfactant was more effective for aceclofenac loaded transfersome as compared to span 80 with maximum percentage drug release and smaller vesicles size. Transfersomes were uniformly distributed throughout the patch. It was also observed that aceclofenac loaded transfersomal patch is having greater drug permeation than normal aceclofenac patch. Thus, it can be concluded that, drug loaded carrier system of aceclofenac incorporated into patch can be a novel approach for treatment of arthritis through transdermal route in which the drug can permeate through skin and also shows sustained release characteristics.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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