

# Original Research Article

## FORMULATION AND IN VITRO EVALUATION OF DIACEREIN LOADED TRANSFEROSOMAL TOPICAL GEL FOR THE EFFECTIVE TREATMENT OF OSTEOARTHRITIS

### ABSTRACT

**Aim:** The main objective of the current research work was to formulate and evaluate Diacerein-loaded transferosomal topical gel to overcome the drawbacks associated with oral administration of Diacerein in Osteo arthritis treatment.

**Study design:** Transferosomal topical gel

**Methodology:** Transferosomes were developed using different ratios of Phospholipid® 90G as phospholipid and Span-60 as surfactant and cholesterol as fluidity buffer. The selected best formulation of transferosomes was further optimized as a topical gel using different rate controlling polymers such as hydroxyethyl cellulose (HEC), hydroxyl propyl methylcellulose (HPMC) and, carbopol. Transcutol P was used as a penetration enhancer. In vitro diffusion studies of developed formulations were carried out using Franz diffusion cell apparatus.

**Results:** The formulations prepared with Hydroxy ethyl cellulose (TBG1, TBG2, TBG3), HPMC (TBG4, TBG5, TBG6) was shown rapid drug release when compared to formulations prepared with carbopol (TBG7, TBG8, TBG9) are showing controlled drug release. Where the formulation prepared with carbopol with 0.75% concentration has shown acceptable extended drug release for 12 hours with acceptable other physico-chemical properties.

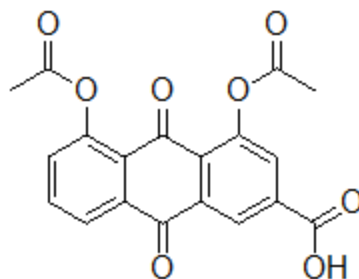
**Conclusion:** It can be concluded that Diacerein-loaded transferosomal gel can be administered topically for the treatment of osteoarthritis with reduced oral side effects.

*Key words: Transferosomes, Topical Gels, Diffusion, Osteoarthritis, Penetration Enhancer*

### 1. INTRODUCTION

Osteoarthritis (OA) is the most commonly occurring rheumatologic problem and type of arthritis with the prevalence of 22%- 39% in India. OA is most commonly affects the joints in the knees, hands, hips, feet and spine. It primarily affects the elderly population. As per the WHO, worldwide 9.6% of men and 18.0% of women over 60 years of age have symptomatic OA [1-6, 23]. Diacerein is an anthraquinone moiety used to treat OA, works by blocking the actions of interleukin-1 beta a protein involved in the inflammation and destruction of cartilage. Chemically Diacerein is 4,5- diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid [7-10].

Figure 1: Chemical structure of Diacerein



Diacerein capsules are available in the market as 50 mg strength with different brand names in different countries, including ART 50®, Artrodar® etc [11-13]. In general, Diacerein is administered orally in the treatment of OA. But the bioavailability of Diacerein through the oral route of administration is very less (40-60%) and the unabsorbed content causes undesirable side effects such as diarrhoea or soft stools. These problems can be overcome through the topical route at the site of OA. The topical formulation has good penetration would provide more therapeutic benefit and lack of diarrhoea when compared to oral administration. Further, the dose required to provide therapeutic action via topical delivery is expected to be less than the oral route [14-16].

Transdermal drug delivery system (TDDS) is the best choice, as it will give consistent systemic drug levels with a controlled and predetermined rate of drug diffusion and hence it reduces the dosing frequency with consequent lower side effects and also improves bioavailability [10-12, 14-16]. However, the permeability of Diacerein across the skin is limited by its impervious stratum corneum. Hence, utilization of transferosomes would be one of the proposals that have been assessed to mitigate this barrier. The main objective of the present research work was to develop the Diacerein loaded transferosomal topical gels and to evaluate the in vitro diffusion ability of prepared formulations [7-18].

## 2. MATERIAL AND METHODS

### 2.1 Materials

Due to the poor production efficiency from plants and chemical synthesis, research groups have directed their attention to the heterologous production of flavonoids in microorganisms such as *Escherichia coli* and *Saccharomyces cerevisiae* using metabolic engineering and synthetic biology but these also have limitations such as reproducibility and handling huge aqueous volumes.<sup>13-15</sup> Hence, search for new plant sources especially non citrus plants is the most viable alternative to identify high Naringenin yielding plant source.

### 2.2 Saturation Solubility Studies

The saturation solubility studies of Diacerein were carried out in different oils such as corn oil, sesame oil, soybean oil, peanut oil, hydrogenated soya bean oil, solvents such as distilled water, Myglyol, Labrafil M 1944 CS, Oleic acid, Transcutol P, Labrafac lipophile WL 1349 (Consists of medium-chain triglycerides of caprylic (C8) and capric (C10) acids), Geliol SC (Consists of a mixture of refined soybean oil, glyceryl distearate (C18) and polyglyceryl-3 dioleate (C18:1)), Capryol 90 (propyleneglycol mono caprylate), Labrafac PG (PG Dicaprolate), PlurolDiisostearique (polyglyceryl -3-diidostearate), Poly ethylene glycol 400 (PEG 400), Propylene glycol (PG), Span 80, Tween 80, Glycerol and in various buffers such as pH 1.2 phosphate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer. Saturated solutions of the drug were prepared by adding an excess amount of drug to 2 mL of each selected vehicle and were agitated on the mechanical shaker for 48 h at 25°C. After reaching equilibrium, samples were collected and centrifuged at 10,000 rpm for 15 min. Further 100 µL of supernatant was collected and suitably diluted with methanol and amount of the drug dissolved was quantified by using UV-Visible Spectrophotometry. Solubility was measured in triplicate in each solvent [19]

### 2.3 Quality by Design (QbD) elements

### 2.3.1 Quality Target Product Profile (QTPP) of transferosomal based gels

Based on the literature review and the current objective of research work, the QTPP for proposed product as follows; topical transferosomal gel with good entrapment efficiency, enhanced drug permeation with same dosage strength in view of oral drawbacks and where the formulation should be stable for 24 months. QTPP is an essential element of a QbD approach and forms the basis for designing of a drug product. The QTPP includes all product attributes that are needed to ensure equivalent safety and efficacy to the innovator drug product (ICH Q8).

### 2.4 Formulation and optimization of Diacerein loaded transferosomal gels

Transdermal administration of drugs is generally limited by the barrier function of the skin. Vesicular systems are one of the most controversial methods for the transdermal delivery of active substances. The reason for using vesicles in transdermal drug delivery is based on the fact that they act as drug carriers to deliver entrapped drug molecules across the skin, as well as penetration enhancers because of their composition [18].

#### 2.4.1 Experimental procedure of preparation of transferosomes

Phospholipon® 90G, unsaturated diacyl-phosphatidylcholine content: 96.5% (PL-90G) was used as phospholipid, Span 60 was selected as surfactant based on the solubility studies. Different formulations of transferosomes were prepared by changing the ratios of drug to total lipid (Phospholipid + cholesterol), ratio of surfactant to total lipid (Phospholipid + cholesterol) and ratio of cholesterol to phospholipids.

Span 60 was heated to 60°C until it was converted to a molten state, required quantity of Diacerein was dissolved in molten state of span 60. Cholesterol and Phospholipid were dissolved in sufficient quantity of solvent mixture (Chloroform: Methanol) taken in round bottom flask of suitable size. API+ Span 60 mixture was added to lipid mixture and mixed well until a homogeneous solution was obtained. Then the solvent was evaporated slowly using a rota flash evaporator at 37°C using vacuum and drying was continued until a thin homogenous film was obtained.

Required quantity of aqueous buffer (7.4pH phosphate buffer) was added to the obtained thin film and mixed well until a homogenous suspension was obtained. Obtained suspension was sonicated with probe sonicator to reduce the size of each vesicle to smaller nano size range and to convert the multilamellar vesicle to monolamellar vesicles [20-21]. Formulation table of transferosomes is given in table 1.

**Table 1: Composition of different formulations of Diacerein transferosomes**

Formulation code	Ratio of drug to total lipid	Ratio of Surfactant to total lipid	Ratio of phospholipid to cholesterol	Solvent (Chloroform:Methanol)
TS1	01:01	01:01	01:01	07:03
TS2	01:01	01:01	01:02	07:03
TS3	01:01	01:01	02:01	07:03
TS4	01:01	01:01	01:03	07:03
TS5	01:01	01:01	03:01	07:03
TS6	02:01	02:01	01:01	07:03
TS7	02:01	02:01	01:02	07:03
TS8	02:01	02:01	02:01	07:03
TS9	02:01	02:01	01:03	07:03
TS10	02:01	02:01	03:01	07:03
TS11	01:02	01:02	01:01	07:03
TS12	01:02	01:02	01:02	07:03
TS13	01:02	01:02	02:01	07:03
TS14	01:02	01:02	01:03	07:03
TS15	01:02	01:02	03:01	07:03

Surfactant used is Span 60; Phospholipid used is (Phospholipon® 90G, unsaturated diacyl-phosphatidylcholine content: 96.5%) (PL-90G)

## 2.5 Evaluation of transferosomes

### 2.5.1 Drug Content

Weight equivalent to one-unit dose was taken and added to 50mL of chloroform: methanol (7:3) and mixed well until a homogeneous solution was formed. Then the solution was sonicated for 30 minutes until the entrapped drug is extracted completely into solvent. Sub dilution was made with 7.4 pH buffer by taking 2mL of above solution and diluting to 200mL. Drug content of each formulation was then estimated by measuring the absorbance against blank at 432nm. Drug content of each formulation was measured in triplicate [20-21].

### 2.5.2 Percentage entrapment efficiency

Entrapment efficiency of each prepared formulation was measured by estimating the free drug concentration by centrifugation method. Weight equivalent to one unit doses was taken in centrifuge tube and added with 20mL of 7.4 pH phosphate buffer and centrifuged at 10000 rpm for 30 minutes to get the clear supernatant with dissolved free drug. Clear supernatant was collected and dissolved free drug was estimated spectrophotometrically at 432nm [20-21]. % Entrapment efficiency of each formulation was calculated by using below formula. Measurement of entrapment efficiency of each formulation was done in triplicate

$$\% \text{ Entrapment efficiency} = \frac{(\text{Total Drug} - \text{Free Drug})}{\text{Total drug}} \times 10$$

### 2.5.3 Vesicle size and Zeta potential

Vesicle size and zeta potential of all the prepared formulations were estimated using Malvern Zetasizer Nano ZS. Each formulation was diluted with 7.4 pH buffer by 100 times before measurement. Each analysis was done in triplicate. Separate method was created in the instrument for the analysis of vesicle size and zeta potential [20-21].

### 2.5.4 Preparation method of transferosomal gels

Best formulation (TS10) was taken and converted to gel formulation by taking different polymers as gelling agents. Hydroxy ethyl cellulose (1-3% w/w), Hydroxy Propyl Methyl Cellulose (1-3%w/w) and Carbopol (0.5-1%w/w) were selected as gelling agents, Transcutol P was selected as penetration enhancer (50mg in each formulation) and propylene glycol was selected as bodying agent (50mg in each formulation). Weight equivalent to one-unit dose of transferosomal formulation was taken added with required quantity of propylene glycol and Transcutol P and mixed under mechanical stirrer until a homogeneous solution was formed. Required quantity of polymer was dispersed in 60% volume of water in separate manufacturing vessel with continuous stirring until a homogenous dispersion was obtained. Then the swollen polymer solution was slowly transferred to drug dispersion and continued stirring for 30 minutes until the drug dispersion and polymer solutions were mixed homogeneously. Volume was made up with batch size with remaining water and continued mixing for another 15 minutes until a homogeneous gel was formed [22, 24]. Formulations of different transferosomal gels are tabulated in table 2.

**Table 2: Compositions of Diacerein transferosomal gels**

Formulation Code	Transferosome	HEC (%w/w)	HPMC (%w/w)	Carbopol 971(%w/w)	Transcutol P (mg)	Propylene Glycol (mg)	Water up to
TBG1	eqvt to unit dose	1	0	0	50	50	1
TBG2	eqvt to unit dose	2	0	0	50	50	1
TBG3	eqvt to unit dose	3	0	0	50	50	1
TBG4	eqvt to unit dose	0	1	0	50	50	1
TBG5	eqvt to unit dose	0	2	0	50	50	1
TBG6	eqvt to unit dose	0	3	0	50	50	1
TBG7	eqvt to unit dose	0	0	0.5	50	50	1
TBG8	eqvt to unit dose	0	0	0.75	50	50	1
TBG9	eqvt to unit dose	0	0	1	50	50	1

### **2.5.5 Characterization of transferosomal gels**

Prepared Transferosomal gels were evaluated for various Physico-chemical properties as described below

### **2.5.6 Measurement of pH**

All the prepared formulations pH was measured by calibrated pH meter. Each gel formulation was prepared as 10%w/v solution with water before measurement. Each measurement was done in triplicate.

### **2.5.7 Measurement of viscosity**

All the prepared formulations viscosity was measured by calibrated cone and plate Brookfield rheometer at 50 rpm at 37°C. Each measurement was done in triplicate.

### **2.5.8 Drug content**

Weight equivalent to one unit dose (1g of gel) was taken and added to 50mL of chloroform: methanol (7:3) and mixed well until a homogeneous solution was formed. Then the solution was sonicated for 30 minutes until the entrapped drug is extracted completely into solvent. Sub dilution was made with 7.4 pH buffer by taking 2mL of above solution and diluting to 200mL. Drug content of each formulation was then estimated by measuring the absorbance against blank at 432nm. Drug content of each formulation was measured in triplicate.

### **2.5.9 Spreadability**

Spreadability of each prepared gel was measured by taking one gram of gel and spreading onto glass slide and rated them as poor, average, good and very good.

## **2.6 In vitro diffusion studies of prepared formulations**

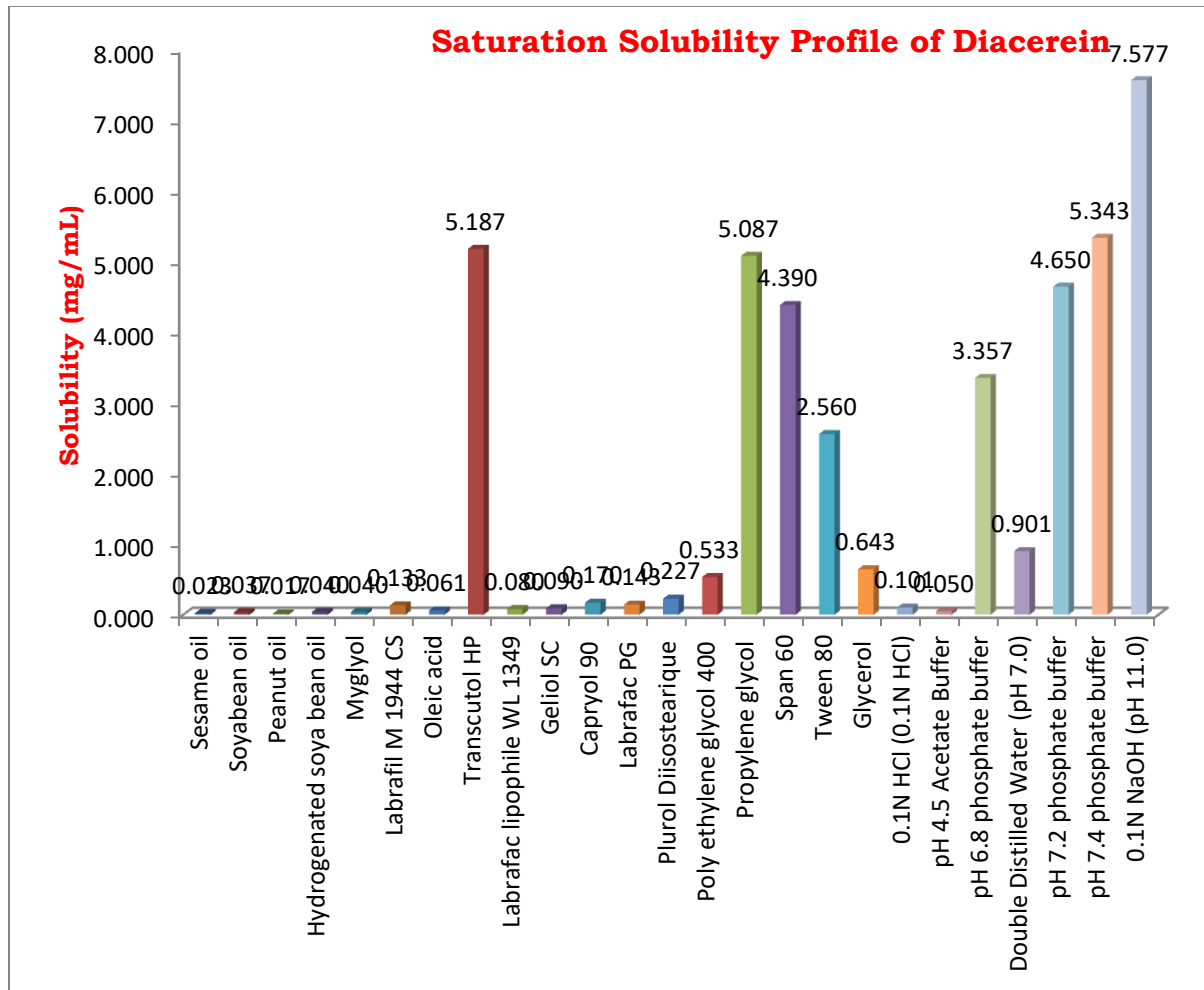
In vitro diffusion study of all the prepared formulations were done using electrolab diffusion cell apparatus. Each formulation diffusion was done with 6 units. Acceptor chamber of diffusion cell was filled with 25mL of 7.4 pH phosphate buffer. Neck of the chamber was covered with 0.45 $\mu$  PES membrane and 100mg of formulation equivalent to 5mg of Diacerein was applied uniformly on the membrane and closed. Diffusion study was done at 100 rpm at 32°C. Diffusion study was continued for 12 hours and samples were collected at predetermined time intervals. % drug diffused was estimated using spectrophotometric method [20-22].

## **3. RESULTS AND DISCUSSION**

### **3.1 Saturation solubility studies**

Results of saturation solubility studies are shown pictorially in figure 2. From the results, it can be understood that the drug is insoluble in water with the solubility of 0.901 mg/ml and solubility is increased in aqueous solvents with increased pH where the highest solubility was observed at pH 11.0 (0.1 N NaOH) with the solubility value of 7.577 mg/ml. In addition, solubility of Diacerein was found higher in Propylene glycol and Transcutol P with the values of 5.987mg/ml and 5.187mg/ml respectively. Hence, these two can be used in formulation of topical gel, Propylene glycol as vehicle (solubilizer) and Transcutol P as penetration enhancer respectively. Drug is also having better solubility in span 60 (4.390mg/ml) and hence has been chosen as surfactant in the formulation trials.

Figure 2: Bar diagram of saturation solubility of Diacerein



### 3.2. Evaluation of transfersomes

#### 3.2.1 Drug content

Estimated drug content values are presented in table 4. From the results it can be understood that assay (drug content) of all the prepared formulations are in the range of  $99.2\% \pm 1.3\%$  to  $101.2\pm 0.5$ . Hence all the formulations are acceptable.

#### 3.2.2 Percentage entrapment efficiency

Entrapment efficiency of each prepared formulation was measured by estimating the free drug concentration by centrifugation method. Results are tabulated in table 4. It was observed that %EE was ranged from  $58.6\% \pm 2.4\%$  to  $85.6\% \pm 3.5\%$ . Formulation (TS10) prepared with 2:1 ratio of drug to total lipid, 2:1 ratio of surfactant to total lipid and 3:1 ratio of phospholipid to cholesterol has shown highest entrapment efficiency. It was observed that as the amount of phospholipid is increased entrapment efficiency was increased and as the ratio of drug to lipid ratio is increased entrapment efficiency was increased.

#### 3.2.3 Vesicle size and zeta potential

Vesicle size and zeta potential of all the prepared formulations were estimated using Malvern Zetasizer Nano ZS. Results obtained are tabulated in table 3.

It was observed from the results that the vesicle size of all the prepared formulations were ranging from 112.4±0.9d. nm to 215.5±1.3 d. nm with the polydispersity index range of 0.217±0.12 to 0.635±0.35. Obtained size range of all formulations indicated that all formulations are nano in size range whereas the poly dispersity index reveals that all formulations are homogeneous in size distribution. It was also observed that zeta potential of all the prepared formulations are in the range of -2.3±0.8 to -9.8±1.4 indicating that all formulations are having negative zeta potential. Based on the overall results of vesicle size and zeta potential formulation TS10 prepared with 2:1 ratio of drug to total lipid, 2:1 ratio of surfactant to total lipid and 3:1 ratio of phospholipid to cholesterol has shown lowest vesicle size with lowest PDI and highest zeta potential indicates high stability. Hence this formulation has been chosen as best formulation for converting into gel form.

**Table 3: Physico-chemical properties of Diacerein loaded transferosomes**

Formulation	Drug content (%) (N=3) (Mean ± SD)	Vesicle Size (d. nm) (N=3) (Mean ± SD)	PDI (N=3) (Mean ± SD)	Zeta Potential (mV) (N=3) (Mean ± SD)	% Entrapment efficiency (N=3) (Mean ± SD)
TS1	100.6 ± 0.3	179.2±1.2	0.525±0.11	-3.4±1.8	66.5±2.3
TS2	100.2 ± 0.3	187.5±1.5	0.575±0.34	-2.6±1.7	62.6±3.2
TS3	99.2 ± 1.3	154.7±2.5	0.423±0.32	-5.7±2.5	72.5±2.6
TS4	99.8 ± 0.6	211.5±1.2	0.612±0.15	-2.5±0.6	59.6±2.8
TS5	100.2 ± 0.4	125.4±0.8	0.312±0.11	-6.8±1.4	78.5±3.4
TS6	99.8 ± 0.6	175.2±1.2	0.512±0.15	-4.5±2.5	68.5±2.4
TS7	100.1 ± 0.3	183.5±1.4	0.534±0.13	-3.8±1.2	63.4±1.2
TS8	99.5 ± 0.4	157.3±2.1	0.409±0.16	-5.8±1.2	71.4±2.5
TS9	100.5 ± 0.5	205.3±1.1	0.601±0.15	-2.6±1.8	57.6±2.5
TS10	100.2±3.5	112.4±0.9	0.217±0.12	-9.8±1.4	85.6±3.5
TS11	99.8±1.5	183.4±1.4	0.545±0.17	-3.2±1.8	63.5±1.5
TS12	101.2±0.5	199.5±1.6	0.595±0.24	-2.4±1.6	59.6±1.5
TS13	100.5±0.3	165.5±2.2	0.455±0.32	-5.5±2.3	68.9±2.3
TS14	99.5±0.6	215.5±1.3	0.635±0.35	-2.3±0.8	58.6±2.4
TS15	100.1±0.8	137.4±0.9	0.355±0.57	-6.2±1.2	75.6±2.3

\*N=Three replicates, SD- Standard deviation, PDI- Poly Dispersity Index

### 3.4 Characterization of transferosomal gels

#### 3.4.1 Measurement of pH

All the prepared formulations pH was measured by calibrated pH meter. Obtained pH values are given in table 5. It was observed that pH of all the prepared formulations are in the range of 6.1±0.5 to 6.5±0.2.

#### 3.4.2 Measurement of viscosity

All the prepared formulations viscosity was measured by calibrated cone and plate Brookfield rheometer at 50 rpm at 37°C. Each measurement was done in triplicate. Obtained viscosity values are tabulated below (Table 5). It was observed that viscosity of all the prepared formulations are in the range of 1755±125cP to 3020±130cP. It can be understood from the result that formulations prepared with carbopol has shown higher viscosity than other polymers whereas formulations prepared with HEC has

shown lower viscosity than all other polymers. It was also observed that viscosity of formulations was increased with increasing the polymer concentration.

### 3.4.3 Drug Content

Drug content of each formulation was then estimated by measuring the absorbance against blank at 432nm. Drug content of each formulation was measured in triplicate. Values obtained are tabulated below (Table 5). And from the results it can be understood that assay (drug content) of all the prepared formulations are in the range of 99.6% ± 0.5% to 101.6% ± 0.2%. Hence all the formulations are acceptable.

### 3.4.4 Spreadability

Spreadability of each prepared gel was measured by taking one gram of gel and spreading onto glass slide and rated them as poor, average, good and very good. All the obtained results are tabulated in Table 4.

**Table 4: Physico-chemical results of Diacereintransferosomal gels**

Formulation	Drug content (%) (N=3) (Mean ± SD)	pH (N=3) (Mean ± SD)	Viscosity (cP) (N=3) (Mean ± SD)	Spreadability/ squeezing ability
TBG 1	100.8 ± 0.5	6.3±0.2	1755±125	Poor
TBG 2	100.5 ± 0.5	6.2±0.2	2050±115	Average
TBG 3	100.2 ± 0.6	6.4±0.4	2340±125	Good
TBG 4	100.5 ± 0.6	6.5±0.2	2150±135	Average
TBG 5	99.8 ± 0.2	6.3±0.2	2475±125	Good
TBG 6	99.6 ± 0.5	6.1±0.5	2750±130	Very Good
TBG 7	100.5±3.5	6.3±0.3	2525±175	Good
TBG 8	99.6±0.7	6.4±0.3	2750±225	Very Good
TBG 9	101.6±0.2	6.4±0.3	3020±130	Poor

**N = Three replicates, SD- Standard deviation**

### 3.5 In vitro diffusion studies of prepared formulations.

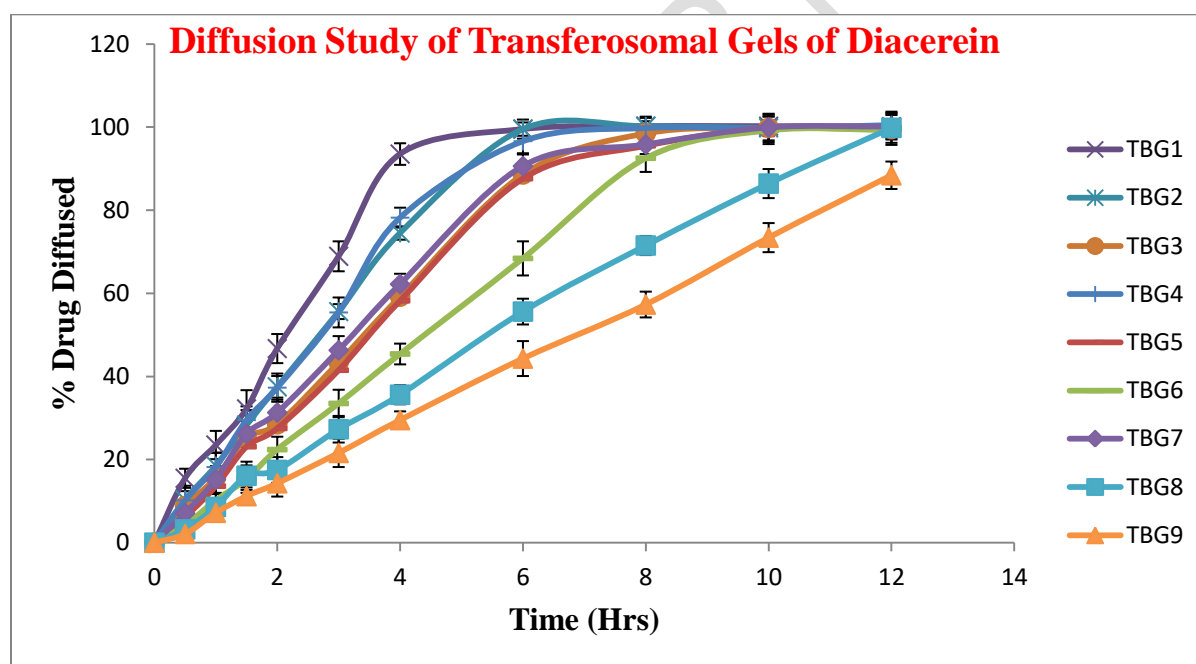
In vitro diffusion study of all the prepared formulations were done using electrolab diffusion cell apparatus. Each formulation diffusion was done with 6 units. Diffusion study was continued for 12 hours and samples were collected at predetermined time intervals. % drug diffused was estimated using spectrophotometric method. % drug diffused was estimated using spectrophotometric method. A graph was plotted by taking time on X-axis and % drug diffused on Y-axis. % Drug diffusion values of all the formulations are tabulated in table 5 and graph is shown in figure 3.

**Table 5: In Vitro drug diffusion results of Diacerein transferosomal gels**

Time (Hrs)	% Drug diffusion (Mean ± SD); N=6								
	TBG1	TBG2	TBG3	TBG4	TBG5	TBG6	TBG7	TBG8	TBG9
0	0	0	0	0	0	0	0	0	0
0.5	15.5±2.3	10.3±3.4	8.8±2.4	10.2±2.2	6.2±2.4	4.2±2.2	7.1±2.1	3.2±1.2	2.1±0.2
1	23.5±3.4	18.5±3.2	15.6±3.4	18.2±3.4	13.6±3.4	10.2±3.2	15.2±3.2	8.6±3.1	7.2±1.3
1.5	32.2±4.5	28.3±3.6	25.3±3.5	29.5±3.3	23.1±3.5	15.3±3.3	26.2±3.1	16.1±3.4	11.2±2.1
2	46.7±3.5	37.5±2.6	28.5±3.2	37.3±3.4	27.5±3.2	22.4±3.1	31.3±3.1	17.5±3.1	14.3±3.2
3	68.9±3.6	55.6±1.8	43.4±3.2	55.4±3.6	41.5±3.3	33.5±3.3	46.3±3.4	27.3±3.2	21.6±3.4
4	93.5±2.6	74.5±1.6	59.2±2.7	78.2±2.4	58.2±2.4	45.4±2.5	62.2±2.5	35.6±2.3	29.5±2.1
6	99.5±2.3	99.5±1.6	88.6±3.3	96.6±3.2	87.6±3.4	68.4±4.1	90.6±3.1	55.6±3.1	44.3±4.2
8	100.2±1.2	100.2±2.3	98.5±2.4	99.8±2.4	95.5±2.2	92.5±3.3	95.8±2.3	71.5±2.3	57.3±3.1
10	100.2±2.4	99.8±1.5	99.8±3.2	99.8±3.4	99.7±3.6	99.2±3.3	99.9±3.1	86.4±3.5	73.4±3.5
12	100.1±1.1	99.9±1.4	99.5±3.2	100.5±3.2	99.8±3.6	99.3±3.6	100.1±3.1	99.8±3.6	88.4±3.3

N= Six Replicates, SD- Standard deviation

**Figure 3: In vitro diffusion study of Diacerein loaded transferosomal gels**



It was observed that the drug diffusion was retarded as the concentration of polymer is increased in the gel. Formulations prepared with HEC have shown faster drug diffusion than formulations prepared with other polymers. About ~90% of drug was diffused within 4-6 hours. Formulations prepared with Carbopol has shown slower drug release pattern than formulations prepared with other polymers. About ~90% drug diffusion was observed within 6-12 hours. Complete drug release within 12 hours was not observed in formulation prepared with 1% w/w of carbopol (TBG 9). Complete drug release was observed (99.8±3.6%) within 12 hours in case of formulation prepared with carbopol 0.75% w/w and hence was chosen as best formulation among all the formulations.

### 3.5.1. Drug Release Kinetics

Drug release kinetics such as zero-order release model, first-order release model, Higuchi model, Hixson-Crowell model, Karsmeyer-Peppas model was done by fitting the obtained data in each kinetic model. Regression value of each formulation in each model was calculated and results obtained are tabulated in Table 6.

**Table 6: Regression Co-efficient values of release kinetics of transferosomal gels**

Release Kinetics	Regression Coefficient (R2)								
	TBG1	TBG2	TBG3	TBG4	TBG5	TBG6	TBG7	TBG8	TBG9
Zero Order	0.54	0.73	0.86	0.72	0.88	0.95	0.84	1.00	1.00
First Order	0.95	0.95	0.95	0.95	0.95	0.93	0.96	0.94	0.95
Higuchi	0.85	0.90	0.90	0.90	0.89	0.86	0.91	0.84	0.82
Karsmeyer - Peppas	0.85	0.90	0.94	0.90	0.94	0.97	0.94	1.00	1.00
Hixson- Crowell	0.97	0.98	0.98	0.98	0.98	0.97	0.98	0.97	0.97

From the above results it can be understood that the optimized formulation TBG 8 is following zero order of release with Karsmeyer-Peppas model.

## 4. CONCLUSION

From the results of in vitro physico chemical properties and diffusion studies of transferosomal gel formulations, it can be concluded that the topical formulation of Diacerein can be successfully formulated with transferosomal gel approach using Phospholipon G and cholesterol as lipid layer, span 60 as edge activator, Transcutol P as permeation enhancer and carbopol as gelling agent and optimized formulation has met the all the predetermined quality attributes. However, evaluation of in vivo pharmacokinetic profile and pharmacodynamics activity is the future scope of the current work.

### COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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