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FORMULATION AND EVALUATION OF TRANSFEROSOMAL GEL AS A POTENTIAL THERAPY FOR TREATMENT OF CELLULITIS

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ABSTRACT

The present study is about formulation and evaluation of transferosomal gel for the treatment of mild cellulitis. Cefazolin is an antibiotic that is used to treat a wide variety of bacterial infections, specifically those caused by streptococci and staphylococci. The transferosome is the first generation of elastic liposomes. Cefazolin-loaded transferosomes were prepared through the thin film hydration technique using soya lecithin as a lipid and span 80 and sodium deoxycholate as an edge activator, and the vesicles were characterized for entrapment efficiency, particle size, zeta potential, shape, and in-vitro drug release. From the above evaluation test, optimized batches were selected for the formulation of gel. Gel was prepared by using carbopol 940 and HPMC and evaluated for spreadability, viscosity, ph, drug release, and stability.TF6 batch is considered as optimized with in-vitro drug release 86.70% for 12 hrs, entrapment efficiency 85.64% and drug content 90.98 %.These findings confirmed that cefazolin transfersomal gel is a promising topical formulation for effective treatment of cellulitis over the conventional formulations of cefazolin.

Keywords: Cefazolin, Transferosomes, Soya lecithin, zeta potential, drug content, In-vitro drug release.

INTRODUCTION

Bacterial infections are still one of the leading causes of morbidity and mortality globally. Ubiquitous Gram-positive microbes, such as staphylococcus aureus (SA), are common causes of bacterial infections which have resulted in global illness and death. The resistant strain of SA, known as MRSA, is responsible for many life-threatening and community acquired bacterial infection that prolongs treatment duration and expands medical costs. New therapeutic strategies are needed to combat multi-drug resistance pathogens.Transdermal delivery offers an alternative route of administration, and it has advantages such as, overcoming first-pass metabolism and gastric enzymatic degradation and it is noninvasive technique. Cefazolin is a hydrophilic drug that is only administered intravenously due to its limited absorption when administered via the oral and transdermal route. Therefore, for successful transdermal delivery of such drugs, innovation strategies are needed.

Transferosomes are increasingly being exploited for the delivery of transdermal drugs. They have an ultra-adaptable bilayer membrane that makes them deformable.Transferosomescan deform and move through narrow constrictions without a measurable loss(from 5 to 10 times less than their diameter, which aids their rapid penetration through the

intercellular lipid pathway of the subcutaneous tissue.Nevertheless,cefazolin transferosomeshave been investigated rarely in literature. So, the objective of this study was to formulate cefazolin transferosomesfollowed by addition in a suitable gel base for further maximum drug loading and higher penetration performance.

MATERIALS& METHOD

Materials

Cefazolin was obtained as a gift sample from Aurobindo Pharma limited Hyderabad,Telangana 502307, Soyalecithin was from Tokoyo Chemical Incorporation Japan, span 80Labochem Mumbai, sodium deoxycholate was from Oxford Lab Fine Chem LLP Phalghar,Carbopol 934 from Labochem, Mumbai,Methanol, Triethanolamine, Methyl partner from Ozone international.

Method

Method of preparation of transferosomes by thin film hydration technique

Transferosomes were prepared by thin film hydration technique. Soya lecithin, edge activator was dissolved in methanol in 100 ml of round bottom flask (RBF). Organic solvent is then evaporated using rotary evaporator at 50ºC and lipid film was deposited on the walls of the flask. The flask was left in vacuum desiccators overnight to ensure complete removal of the residual solvent. The 100 mg drug was dissolved in hydrating media i.e., phosphate buffer (7.4) and it was used as a hydrating media to hydrate the thin-film for 30 min. After rehydration, milky white suspension was formed which was ultra-centrifuged using cooling centrifuge at 12000 rpm and 4ºC for 30 mins. Due to centrifugation final transferosomes were obtained in the form of jelly like substance which was evaluated further.

Table 1: Formulation Table of Transferosomes

SR.NO.	INGREDIENTS	BATCHES									
		TF 1	**TF 2**	**TF 3**	**TF 4**	**TF 5**	**TF 6**	**TF 7**	**TF 8**	**TF 9**	**TF10**
1.	Cefazolin(mg)	100	100	100	100	100	100	100	100	100	100
2.	Soya lecithin(mg)	95	95	90	90	85	85	80	80	75	75
3.	Sodium deoxycholic acid(mg)	5	-	10	-	15	-	-	20	25	-
4.	Span 80(mg)	-	5	-	10	-	15	20	-	-	25
5.	Methanol(ml)	20	20	20	20	20	20	20	20	20	20
6.	Phosphate buffer(ml)	10	10	10	10	10	10	10	10	10	10

Characterization of Transferosomes

1. Drug Entrapment Efficiency

Transferosomal dispersion was subjected to centrifugation on a laboratory refrigerated centrifuge at 14,000 rpm for 90 min. The sediment and supernatant liquid were separated. The amount of drug in the supernatant was estimated using UV-Visible spectrophotometer at 270 nm.

% Entrapment Efficiency= (Total Drug-Free Drug) / (Total Drug) x 100

2. Drug Content

Transferosomes were dissolved in PBS 7.4 by shaking manually for 2min. 1ml of resultant solution was taken and dissolved in PBS 7.4 make upto 10 ml then absorbance was recorded at 270 nm using UV-Visible spectrophotometer.

Drug content (%) = Sample Absorbance/ Standard Absorbance x 100

3. In vitro Drug Release Study

In this method, 5 ml of transferosomes dispersion containing known amount of drug was placed in dialysis membrane (previously soaked overnight). Sample containing dialysis bag was placed in beaker if 100 ml PBS 7.4, maintained at 37ºC and stirred with the help of magnetic stirrer. Samples from receptor compartment were withdrawn at different time intervals and replaced with 5 ml fresh PBS 7.4 to maintain sink condition. After samples were analyzed at 270 nm.

4. Surface morphology by SEM

It is used to study shape and surface morphology of transferosomes**.**

5. Zeta potential, particle size

The zeta potential of optimized formulation was determined by using zetasizer. The samples were diluted in ratio 1:100 with suitable solvent (PBS) and stirred on magnetic stirrer for 1 min.

Method of Preparation of Gel:

Based on the results of transferosomes evaluation, the formulation which showed better entrapment efficiency, drug contentand in vitro drug release was incorporated into gel. Sufficient quantity of water was taken in a beaker and weighed polymer was added gradually on continuous stirring. After complete dispersion, the polymer solution was kept aside for 24 hrs for complete swelling. To this gel mixture add 10 ml of transferosomal dispersion. Finally, the remaining ingredients were added to obtain homogenous dispersion of gel.

Table 2: Formulation Table of Transferosomal Gel

SR. NO.	**INGREDIENTS**	**BATCHES**		
		TG1	**TG2**	**TG3**
1	Transferosomal dispersion (ml)	10	10	10
2	Carbopol 940 (mg)	0.5	1	1.5
3	Propylene glycol (ml)	5	5	5
4	Methyl paraben (gm)	0.020	0.020	0.020
5	Triethanolamine (ml)	q.s	q.s	q.s
6	Water (ml)	Upto 100 ml	Upto 100 ml	Upto 100 ml

RESULTS AND DISCUSSION

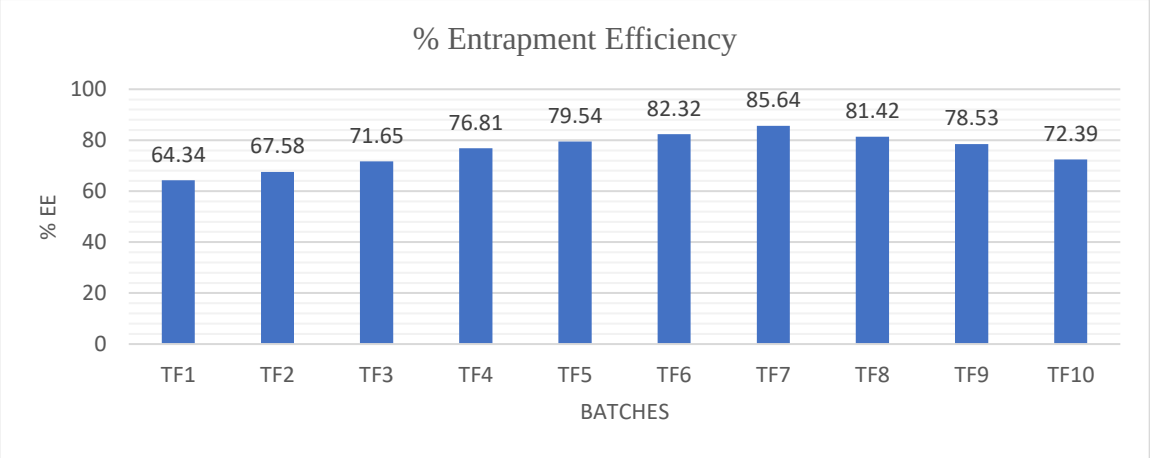
Evaluation of Transferosomes

1. Determination of Drug Entrapment Efficiency, Drug Content, pH:

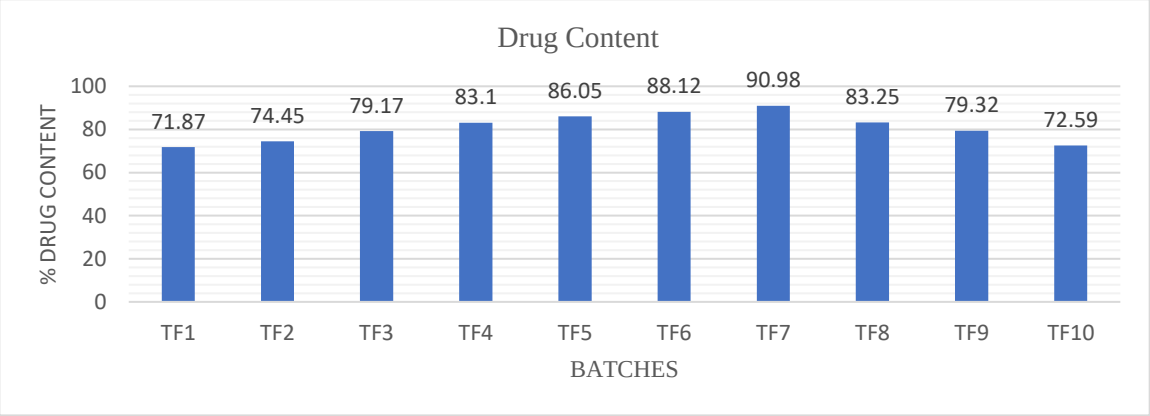
The entrapment efficiency range was found to be in the range of 64.34 – 85.64 %. The F7 batch shows highest Entrapment Efficiency i.e., 85.64%.

Table 3: Evaluation parameter of transferosomes

Batches	**Entrapment efficiency (%)**	**Drug content (%)**	**pH**
TF1	64.34	71.87	7.13
TF2	67.58	74.45	7.24
TF3	71.65	79.17	7.26
TF4	76.81	83.10	7.32
TF5	79.54	86.05	7.30
TF6	82.32	88.12	7.21
TF7	**85.64**	**90.98**	**7.34**
TF8	81.42	83.25	7.21
TF9	78.53	79.32	7.19
TF10	72.39	72.59	7.13



Drug content of all batches was in the range of 71.87 – 90.98 % where highest drug content showed by F7 i.e., 90.98 %, indicating that the medication was distributed uniformly.



2. Zeta potential, Particle size, Polydispersity Index

All the span 80 containing transferosomes exhibited negative zeta potential values. Highest value of zeta potential was observed for the optimized batch (TF7), which was considered favorable for the formulation stability and the enhancement of drug permeation.

The size of transferosomes increased with the increase in HLB value of the non-ionic surfactant, in the following order: Span 80<span 20<tween 20<SD.

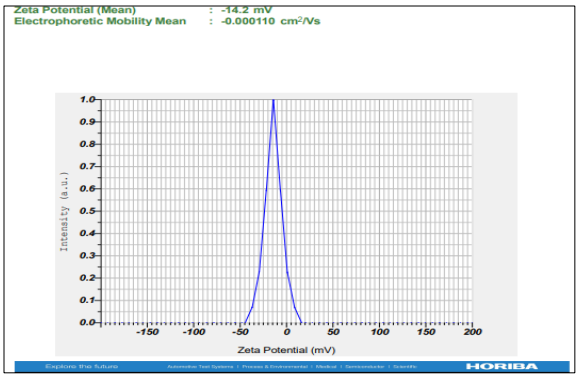


Fig 1: Zeta Potential of TF7 Batch

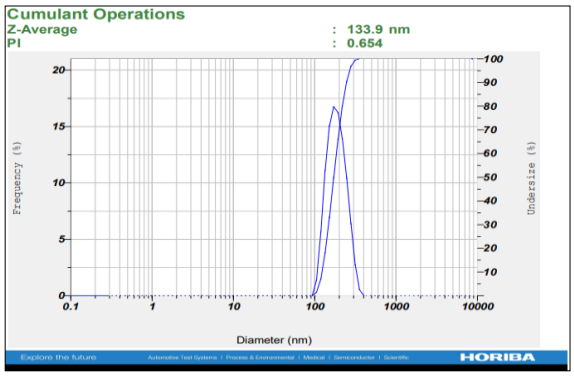


Fig 2: Particle size of TF7 Batch

3. FTIR Spectrum

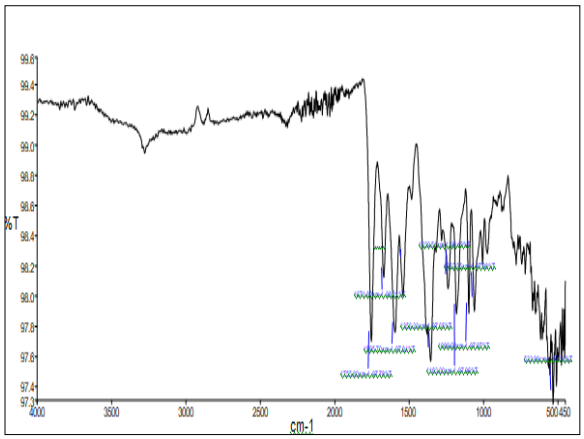


Fig 3. FTIR of Cefazolin API

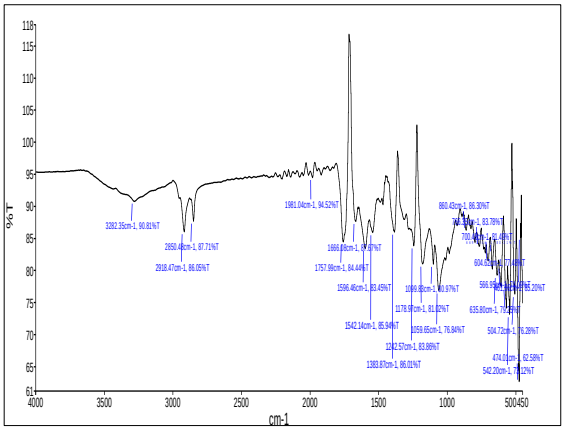


Fig 4. FTIR of physical mixture

4. Scanning Electron Microscopy

The structure of the optimized TF7 formulation was examined by SEM as shown in Fig. 5. It was observed that a SEM image of the optimized formulation contains pores which facilitate the adherence of the drug.

Fig 5. SEM Image of Optimized Batch

5. Optical Microscopy

An optical microscope confirmed the formation of spherical vesicles. Transferosomes were uniformly distributed and found to be somewhat spherical in shape.

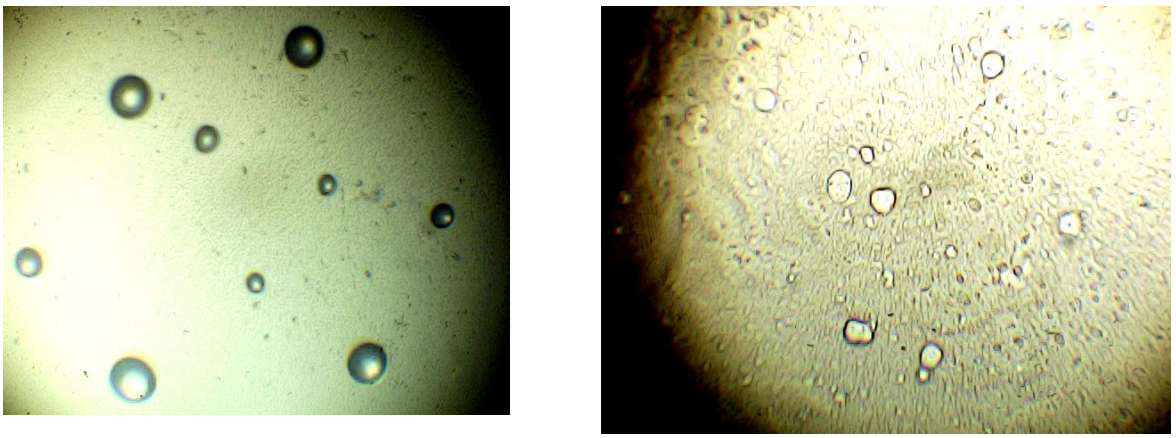


Fig 6. Microscopic Images of Optimized Formulation Batch.

6. in-vitro drug release

The percentage cumulative drug release studied for 12 hrs. highest drug release 86.70 % was for batch formulation TF7. The significant changes in drug release were observed in changing the concentration and type of edge activator used in formation of bilayer.

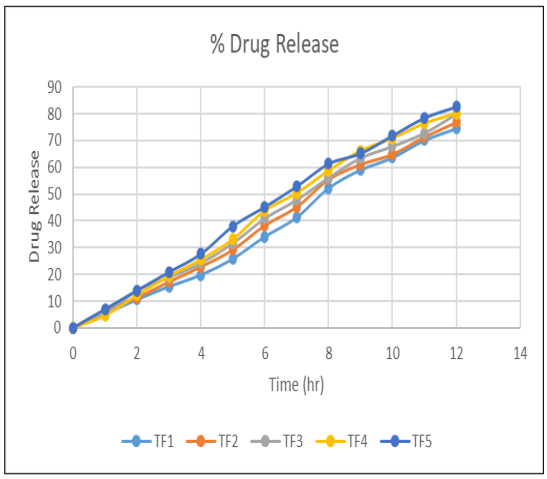


Fig7. % Drug Release [TF1-TF5]

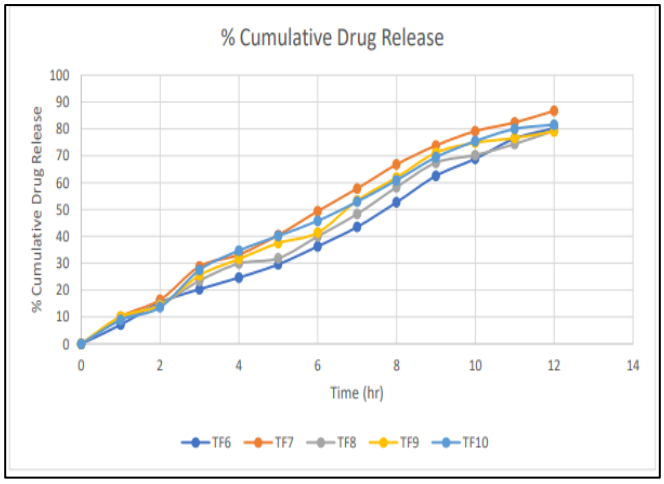


Fig 8. % Drug Release [TF6-TF10]

Evaluation of Transferosomes Gel

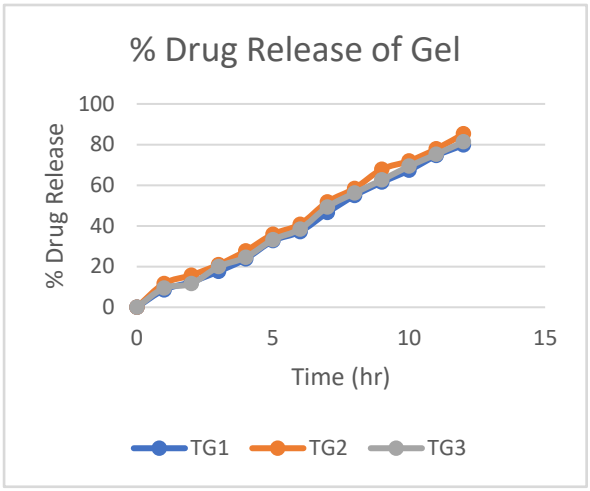
Table 4. Evaluation Parameters of Gel

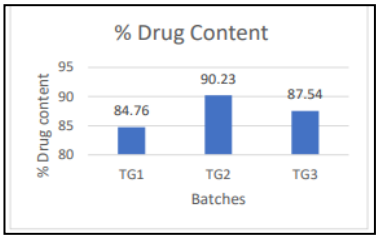
Sr. No.	Formulation Batch	pH	Viscosity (Cps)	Homogeneity	Spreadability (g.cm/sec)	Drug Content (%)
1	TG1	7.32	8200	++	14.34	84.76
2	TG2	7.39	7450	+++	12.87	90.23
3	TG3	7.61	8700	++	13.87	87.12

Table 5. % Cumulative Drug Release

Time (hr)	% Cumulative Drug Release		
	TG1	TG2	TG3
0	0	0	0
1	8.55	11.65	9.43
2	12.43	15.74	11.56
3	17.65	20.94	19.94
4	23.78	27.67	24.56
5	32.71	35.92	33.21
6	37.21	40.83	38.45
7	46.53	51.79	49.32
8	54.9	58.4	56.21
9	61.46	67.86	62.57
10	67.34	71.89	69.34
11	74.54	77.86	75.21
12	79.78	**85.23**	81.34

In-vitro Drug Release





The in-vitro drug release of three gel batches were prepared and measured the release at 1 hr, 2hr, upto 12 hrs. After examining percentage cumulative drug release graph of all formulation, the formulation TG2 shows highest in-vitro drug release i.e., 85.23%.

Stability Study

As per ICH guidelines, accelerated stability studies Transferosomal gel were evaluated for optimized formulation TG2 at 25^0C±2°C/60±5% RH and 40°C±2°C/75±5% RH for 60 days. The optimized formulation TG2 was more stable at room temperature. There was no change in the appearance of formulation.

Sr. No.	**No. of Months**	**Appearance**	**pH**	**% Drug Release**	
				R.T.	**40^0C**
1	Initial	Semi-transparent white	7.39	85.23	85.23
2	One month		7.39	83.24	79.46
3	Two month		7.39	79.01	73.86

Sr. No.	**No. of Months**	**Drug Content**	
		R.T.	**40^0C**
1	Initial	90.23	90.23
2	One month	89.04	87.32
3	Two month	87.54	85.87

CONCLUSION

From the above results, it can be concluded that Soya Lecithin and span 80 can be efficiently form transferosomes containing Cefazolin (BCS III) for improvement of its permeability. Which can be easily develop a topical gel using Carbopol as gelling agent. However, resultsshowed gel with polymer performed better in release. Results also confirmed that transferosomal gelwill improve transdermal delivery, prolongs release and site-specific drug delivery. Still a

thorough experiment will be required based on animal studies and after that we can find the actual mode of action of this king of dosage form. Therefore, a future work will be carried as follows,

- ❖ In vivo Pharmacological work on animals.
- ❖ In vivo Pharmacokinetic studies on animals.

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