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Development and Evaluation of Dosage Form for Dental Drug Delivery System

Mayuri Bhandari[1], Yogesh Chaudhari [1]
1 Assistant professor, Department of pharmaceutics, Dr L. H. Hiranandani College of Pharmacy, Ulhasnagar
1 Assistant professor, Department of pharmaceutics, Dr L. H. Hiranandani College of Pharmacy, Ulhasnagar 421003

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ABSTRACT: Controlled drug delivery system has more important in dental drug delivery system so as to overcome the problems related to certain periodontal diseases condition like Gingivitis and Periodontitis. This research paper will overcome the problems related to the pain and loosening of the teeth by loading the transferosomes into the film by using the drug levofloxacin hemihydrate. Instead conventional dosage forms like tablet and capsules the transferosomes loaded drug film will be more patient compliance and will be sustained release of the drug by not getting the drug waste.
KEYWORDS: Transferosomes, Controlled drug delivery, periodontal diseases, loaded drug film

I. INTRODUCTION

Periodontal disease is commonly cause in the teeth and gum and often it has major concern in oral health. Dental disease is commonly among the widely spread in the chronic disorder affecting the mankind.

The word periodontal means round the teeth. The harmful microorganism that are affecting round the teeth that causes the pain. There are basically group of conditions of periodontal diseases Gingivitis and Periodontitis. These two types of condition mainly affect the outer layer of the teeth such as gums, periodontal ligaments, alveolar bone and dental cementum.

Periodontal diseases is the localized type of inflammatory response. Gingivitis is the mildest of periodontal diseases is highly prevalent and reversible by simple, effective oral hygiene. These condition mainly affect 50%-90% of adults worldwide. Inflammation which causes the extend deep into the tissue and causes the loss of supportive connective tissue and alveolar bone is known as periodontitis. Periodontitis results in the formation of soft tissue pockets between the gingiva and tooth root.

If it causes severe periodontitis can results in loosening of teeth occasional pain and discomfort impaired mastication and eventual tooth loss. If the periodontal diseases is not treated results in the destruction of the bone and soft tissue supporting the tooth leading to tooth loss. Different treatment has be used such as used of antibiotic medication and conventional surgery such as scaling has been proposed.

In the early stage of the diseases it was observed the swelling, bleeding upon probing and bad breathe. Periodontitis diseases are classified as gingivitis and periodontitis.

The mouth budget numerous cracks and crevices where the pathological bacteria harbor. This bacteria excrete toxins add a waste products in the pocket and broken immune response which leads to inflammation. Gingivitis does not cause loss of attachment fibers or bone supporting structures.

II. MATERIALS AND METHODS

Thin Film Hydration Technique:
It is employed for the preparation of transferosomes which comprised of three steps:
1. A thin film is prepared from the mixture of vesicles forming ingredients that is phospholipids and surfactant by dissolving in volatile organic solvent. Organic solvent is then evaporated above the lipid transition temperature using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.
2. A prepared thin film is hydrated with buffer by rotation at 60 rpm for 1 hour at the corresponding temperature. The resulting vesicles were swollen for 2 hour at room temperature.
3. To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50°C for 30 min. using a bath sonicator or probe sonicated at 4°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.

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I. EXPERIMENTATION

PREFFORMULATION STUDY OF LEVOFLOXCIN HEMIHYDRATE

- **Solubility Study of Drug in Different Solvents**

The solubility study of Levofloxacin hemihydrate was determined in distilled water, methanol, ethanol, chloroform and phosphate buffer pH 6.6 Solubility of levofloxacin hemihydrate in different solvents is given below.

Sr. No.	Solvent	Solubility
1	Chloroform	Freely Soluble
2	Methanol	Freely Soluble
3	Ethanol	Sparingly soluble
4	Phosphate buffer	Freely soluble
5	Water	Insoluble

Table 3: Solubility of Levofloxacin hemihydrate in various solvents

- **Melting Point Determination**

Melting point of levofloxacin hemihydrate was found to be **235°c** as reported in literature, thus indication purity of drug sampl

wavelength	Comment
2939.56 cm-1	**C-H Stretch(aliphatic) alkyl group**
3254.56 cm-1	**O-H stretch of hydroxyl group**
1721.53 cm-1	**C=O stretch**
1289.73 cm-1	**C-N stretch group**
1087.36 cm-1	**C-F stretch group**

Spectral Characterization by UV Spectroscop

UV Spectrum of drug in Methanol: Chloroform and in Phosphate buffer

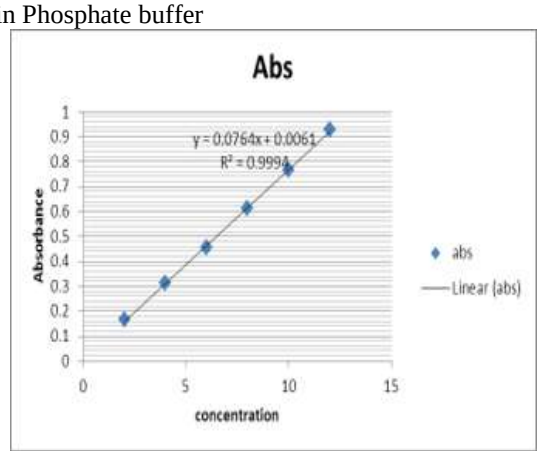

Fig. 5: Calibration curve of the drug

Lipid	Absorbance
Soya Lecithin (Oil)	1.791
S 100	3.422
E 80 S	1.021
Soya Lecithin (Powder)	2.733
Phospholipon 90H	**0.053**

FORMULATION AND OPTIMIZATION OF TRANSFEROSOMES

Selection of Lipid

Surfactant	Cone of drug(mg)	Cone of lipid(mg)	Cone of EA(mg)	Quantity of Solvent(ml)	Entrapment efficiency (%)
Span 80	30	300	0.075	15	89.09%

Table 4: Selection of lipid on basis of absorbance

Phospholipid 90 H batch gave lowest absorbance in comparison to that of other lipids, so phospholipid 90 H was used in further formulation trials to avoid interference with drug

Selection of Surfactant

Surfactant	Absorbance
Span 20	0.067
Span 40	0.050
Span 80	0.287
Deoxycholate	0.048
Tween 20	0.043
Tween 60	0.049
Tween 80	0.072
Cholate	Not dissolved
Span 80	**0.042**

Table 5: Selection of surfactant on basis of absorbance

Span 80 batch gave lowest absorbance in comparison to that of other surfactant, so Span 80 and Deoxycholate was used in further selection.

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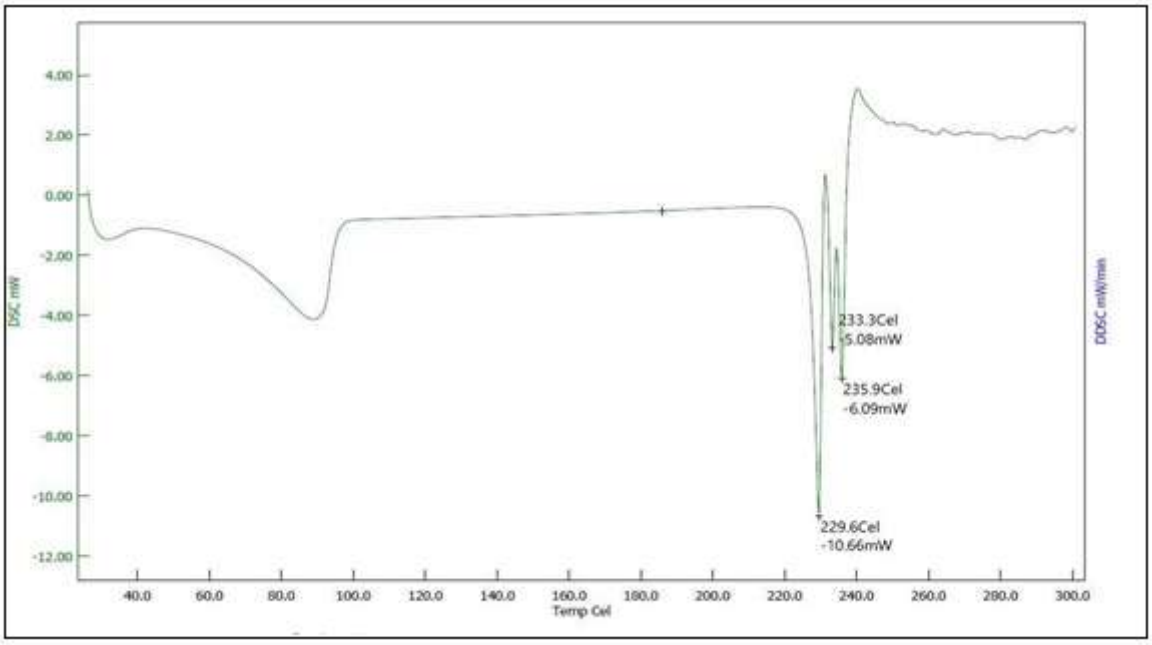

Table 6: Selection of surfactant on basis of entrapment efficiency

Two surfactants were screened for their effect on entrapment efficiency. Based on results of percent entrapment efficiency, **Span 80** was used in further formulation trials to avoid interference with drug

DETERMINATION OF DRUG-EXCIPIENT COMPATIBILITY

Fig.6: DSC thermogram of levofloxacin hemihydrate

DSC thermogram of levofloxacin hemihydrate showed the melting point at 229.6°c as shown in fig 11 and the levofloxacin hemihydrate loaded transferosomes showed peak at 129.1°c. Thus, from the thermogram it is shown as there is no interaction between the drug and excipient as the peak of the drug is shifted to 129.1°c along with decrease in entrapment of drug

variable	Experiment variable	High level	Low level
1	RPM	60	80
2	Temperature	45	60
3	Surfactant	0.075	0.150
4	Hydration time	30	60
5	Solvent ratio	1.1	1.2
6	Drug	25	50

The screening of factors or experimental variables involved in the formulation of transferosomes was carried out using Placket-Burman design.

SCREENING OF FACTORS INVOLVED IN FORMULATION OF TRANSFEROSOMES.

variable	Experiment variable	High level	Low level
1	RPM	60	80
2	Temperature	45	60
3	Surfactant	0.075	0.150
4	Hydration time	30	60
5	Solvent ratio	1.1	1.2
6	Drug	25	50

Table 7: The Experimental variables and levels of PB design

From the results of Placket – Burman design following inferences could be drawn

- As the surfactant decreases % E.E increases.
- As the hydration time decreases % E.E increases.

As the concentration of drug increases % E.E increases

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APPLICATION OF EXPERIMENTAL DESIGN FOR OPTIMIZATION OF TRANSFEROSOMES USING 2^3 FACTORIAL DESIGN.

Based on the results obtained from PB design, a 2 full factorial design was employed to study the effect of independent variables i.e. the lipid concentration, surfactant concentration and hydration time on dependent variable i.e. percentage entrapment efficiency. Total eight batches were formulated and entrapment efficiency was calculated and optimization method was evaluated by Yates's method of analysis. The data was analyzed by ANOVA and was reported to be significant. Further the challenge batches were taken and compared with the predicted results. From the results obtained from challenged batches it was noted that the difference between the predicted and observed results is within the experimental variability. Hence, it was found that the selected independent variables significantly influenced the percentage entrapment efficiency.

Batches	X1	X2	X3	Entrapment efficiency (%)
F1	**-**	**-**	**+**	**89.09%**
F2	+	+	+	75.25%
F3	-	+	-	65.21%
F4	+	+	-	74.01%
F5	-	+	+	80.45%
F6	+	-	+	77.12%
F7	-	-	-	54.45%
F8	+	-	-	73.58%

Table 10: Optimization batches for levofloxacin hemihydrate

EVALUATION OF OPTIMIZED TRANSFEROSOME FORMULATION

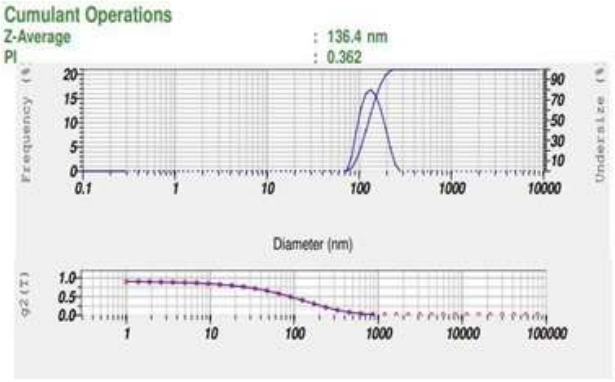
Scanning Electron Microscopy (SEM) Analysis of Transferosomes

Fig 8: SEM analysis of Transferosomes

Particle Size, Zeta potential and Polydispersity index

Batch	Particle size	Polydispersity index	Zeta potential
Transferosome	136.4	0.362	-10.4

Table 11 : Vesicle size, size distribution and zeta potential of optimized bat



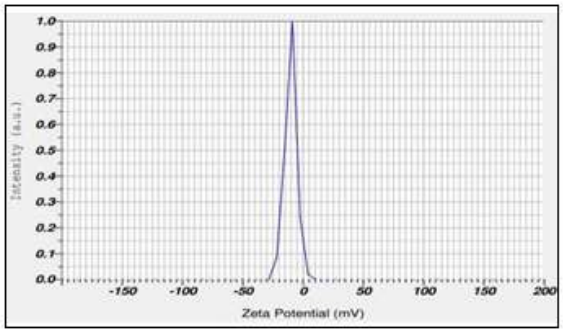


Fig 9: Graph of Particle size **Fig10 Graph of Zeta Potential**

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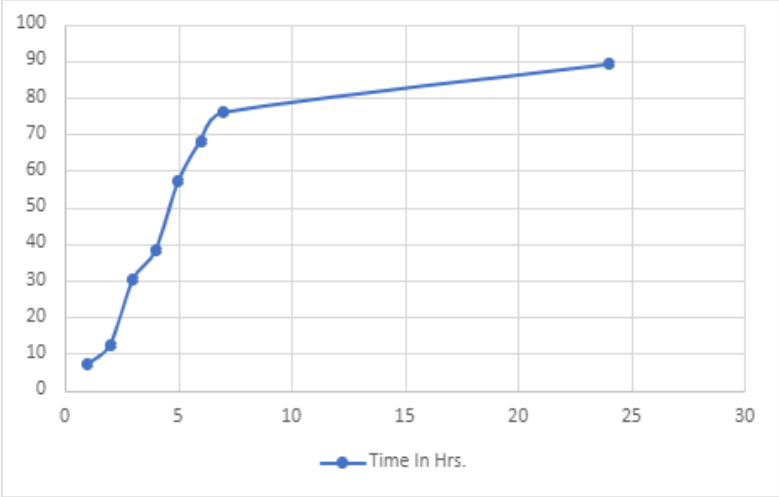
Entrapment Efficiency

The % Entrapment efficiency of optimized batch of transferosome was found to be 89.09 %

- **In-Vitro Diffusion Study**



Time hours	% cumulative release
1	7.15
2	12.45
3	30.12
4	38.15
5	57.01
6	68.21
7	75.89
24	89.09

III. SUMMARY AND CONCLUSION:

The term 'periodontal diseases' encompasses a wide variety of chronic inflammatory conditions of the gingiva (or gums, the soft tissue surrounding the teeth), bone and ligament (the connective tissue collagen fibers that anchor a tooth to alveolar bone) supporting the teeth.

The problem of administering drugs systematically such as adverse effects have focused to treat plaque associated periodontal diseases in a attractive prospect, since conventional treatment can be demanding for patients and the operator. Periodontal pockets being easily accessibly are therefore a convenient site for localized drug delivery system containing antimicrobial agent, which could be inserted into the pockets.

Levofloxacin hemihydrate is active against most aerobic, gram positive and negative bacterial the controlled drug delivery of antimicrobial agent eliminates the unnecessary systemic side effects and therefore have received great interest in the periodontal therapy.

The films were formulated by solvent casting method and the drug was incorporated into it . Polyethylene gycol-400, polyvinyl alcohol was used as the plasticizer and various batches was optimized using different polymer and plasticizer.

All the formulations were subjected to various evaluation parameters like weight determination, drug contents, tensile strength, film thickness, folding endurance, in vitro release studies, in vitro antibacterial activity and stability study.

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Transferosomes were found to be spherical, multilamellar and from invitro studies of transferosomes showed that controlled release of drug occurs from the transferosomes.

Formulation of transferosomes includes lipid Phospholipon 90H, surfactant Span 80 and solvent Methanol: Chloroform (2:1). Selection of lipid was based on avoiding interference with the drug and selection of surfactant was based on entrapment efficiency. Transferosomes was prepared by thin film hydration method. Drug excipient compatibility study showed no interaction between drug and excipient

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