

Development and Characterization of *Cephadrine Proniosomes* for Oral Controlled Drug Delivery

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ABSTRACT

The role of *Proniosomes* in oral controlled drug delivery system is well accepted. Presently, an attempt was made to develop cephadrine (CP) *Proniosomes* to prolong its duration of action with better efficacy. Overall, eighteen formulation trials were developed using variable quantities of sorbitol (FOS-F8S) and maltodextrin (FOM-F8M) carriers along with span60 and cholesterol. Trials were evaluated for powder flowability, drug entrapment efficiency and *in vitro* drug release. Based on the mentioned characteristics, formulations F4M and F4S were optimized. Stability test was performed on optimized *Proniosomes* for three months at temperature (2-8 °C). Comparison for antimicrobial sensitivity against *Staphylococcus aureus* was also made between optimized and marketed conventional CP capsule. More than 80% drug release was observed in 22 hr in the trial formulations. The optimized CP *Proniosomes* were found to be highly stable with % drug entrapment efficiency of 78.60 ± 0.15 and 88.41 ± 0.19 respectively for F4M and F4S. The prepared *Proniosomes* possessed higher bactericidal activity against *S. aureus* than reference products (M1 and M2). In conclusion, CP *Proniosomes* have been successfully prepared using sorbitol/maltodextrin carrier. Sorbitol carrier exhibited marginally better drug entrapment efficiency and bactericidal activity than the maltodextrin trial and marketed brands. This effort offers improved drug delivery with the potential of more effective controlled therapy.

Key words: *Proniosomes*, Cephadrine, Nano-carriers, Niosomes, Bactericidal activity, Controlled drug delivery.

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INTRODUCTION

Conventional pharmaceutical dosage forms are unable to control the drug delivery for longer duration in the body.¹ They are also associated with the problem of dosing interval resulting in large peaks and valleys in the drug plasma profiles.² Moreover, patients' compliance with multiple dosing regimens and drug related adverse effects (especially for potent drugs) are major concerns in clinical setting.³ However, these problems may overcome by designing the controlled and targeted delivery systems⁴ owing to improve overall treatment efficiency along with lower incidence of adverse effect. Unfortunately, very limited drug

delivery system behaves ideally to meet the pharmaceutical and clinical goals. In this regard, many attempts are being made to achieve such targets through novel drug delivery approaches.^{5,6} Vesicular drug delivery is consider to be one among them, improving the bioavailability of medicinal agents, especially poorly soluble moieties. Hydrophilic and lipophilic drugs could be developed into sustained release vesicular systems to overcome the rapid drug elimination of highly metabolizable medicinal components. Consequently, addressing the problems related to drug solubility, stability and degradation.⁶



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Several vesicular drug delivery systems including liposomes, niosomes, transferosomes, pharmacosomes and provesicular systems (proliposomes and *Proniosomes*) have been investigated.⁷ Niosomes and *Proniosomes* are advantageous due to improved solubility, skin adhesion and penetration with drug release sustainability. *Proniosomes* also showed great versatility in lipophilic and hydrophilic drug moieties encapsulation. Unfortunately, physical instability is a critical concern in designing and implementation.⁸ This type of systems not only required an appropriate carrier to protect the drug from rapid degradation and clearance. Rather, selection and preference of non-ionic surfactants over the cationic, anionic and ampholytic surfactants is also quite challenging in formulation development of *Proniosomes*.^{9,10} Various drug deliveries by different route of administration are possible using *Proniosomes* based niosomes such as ophthalmic, topical, parenteral and oral etc.^{11,12}

Presently, no encapsulated cephadrine (CP) *Proniosomes* is available in the local market. The study aimed to fabricate vesicular system of Cephadrine using various combinations of non-ionic surfactant (span 60), membrane stabilizer (cholesterol) and coating carriers (sorbitol, maltodextrin). Influence of these additives on the quality attributes including flowability, drug entrapment efficiency, drug release profile and stability will also be accessed. Moreover, microbiological comparison will be made between optimized CP *Proniosomes* and the conventional marketed capsules. Henceforth, this study is supportive in developing stable and effective sustained release dosage forms for different therapeutic agents/drugs.

MATERIALS AND METHODS

Materials

CP pure with purity 99.7% on dried basis, batch number F1BCO2172W and expiry date 18/ 12/ 2021 was gifted by Opal Laboratory Karachi, Pakistan. Cholesterol, sorbitol and lactose were provided by Venus Pharma, Lahore, Otsuka Hub, Balochistan and Aventis Pharma Karachi, Pakistan, respectively. *Staphylococcus aureus* ATCC® 25923, tryptone soya broth (CM129-OXOID) and span 60 (sorbitan monostearate) were obtained from Sigma Aldrich (St. Louis, MO, USA). Maltodextrin was procured from Grain Processing Corporation (NY, USA). Phosphate buffer saline, hydrochloric acid, potassium chloride, chloroform, ethanol, methanol were procured from Sigma- Aldrich (analytical grade).

Instruments

Rotary evaporator (Lab-scale, REV-1001), water bath (Mettler, WTB), sonicator (Thmos Scientific, USA),

desiccator (Thmos Scientific, USA), centrifuge (Thmos Scientific, USA), optical microscope (LCD Digital Microscope, Thmos Scientific, USA), dissolution apparatus (Erweka DT 700, Husenstamm, Germany), spectrophotometer (Shimadzu UV-1601), electronic balance (AUW220, UNI Blog, Shimadzu Corp.)

Methods

Preparation of CP *Proniosomes*

Proniosomes were developed with some modifications in the previously reported method.^{13,14} The stock solution was prepared using defined quantities (Table 1) of cholesterol, and CP in 10 ml of chloroform and ethanol (1:1, v/v) solvent system. A suitable quantity of prepared stock solution was transferred to 100 ml round bottom flask containing carrier (maltodextrin/sorbitol) (Table 1). Further, span-60 was added to the mixture during the processing to lower the surfactant loading. Excess of solvent was evaporated using a rotary evaporator (60 rpm), temperature of $45 \pm 2^\circ\text{C}$ and at a pressure of 600 mmHg till the dry powder is obtained. This dried powder referred to be "*proniosomes*", was then placed in a desiccator overnight to ensure complete moisture removal from powder *proniosomes*. These powdered samples were stored in the airtight containers (glass vials) at temperature of $2-8^\circ\text{C}$.

Study variables

CP *proniosomes* were prepared with variable quantities of carriers including sorbitol (F0S to F8S) and maltodextrin (F0M to F8M) along with cholesterol and span-60 blend. Effect of formulation variables including surfactant (span-60), carriers (maltodextrin/sorbitol) and membrane stabilizer (cholesterol) were observed on

Table 1: CP proniosome formulation trials containing sorbitol and maltodextrin carriers.

S. No	Code of sorbitol formulations	Amount of sorbitol (mg)	Code of maltodextrin Formulations	Amount of maltodextrin (mg)	Ratio of blend (span-60:cholesterol)	CP (mg)
1	F0S	300	F0M	300	300:0	300
2	F1S	270	F1M	270	270:30	
3	F2S	240	F2M	240	240:60	
4	F3S	210	F3M	210	210:90	
5	F4S	180	F4M	180	180:120	
6	F5S	150	F5M	150	150:150	
7	F6S	120	F6M	120	120:180	
8	F7S	90	F7M	90	90:210	
9	F8S	60	F8M	60	60:240	

the response variables such as morphological appearance, flowability, drug entrapment efficiency and drug release profile. Formulation optimization of proniosomal trials was performed on the basis of above characterization parameters.

Hydration and preparation of niosomes

The *proniosomes* were hydrated at 60-65°C in a water bath for 10 min. Aqueous phase was later added to adjust the volume. The resultant niosomal gel was sonicated for 30sec at room temperature.¹⁴

Microscopic evaluation

Proniosomes and niosomal dispersion were examined by optical microscope to observe the vesicular structures both in dried and hydrated forms. Magnification of 40X was used and images were captured using attached camera device.

Drug entrapment efficiency

The entrapment efficiency of *proniosomes* was estimated by indirect centrifugation method.¹⁵ One milliliter of drug dispersion (niosomes) was centrifuged at 4000 rpm for 40min. The supernatant was taken out, diluted with phosphate buffer and analyzed using UV spectrophotometer at 254nm wavelength.¹⁶ The entrapment efficiency of the vesicles was determined by subtracting the amount of untrapped drug from the total drug¹⁷ using following formula:

$$\text{Entrapment Efficiency (EE\%)} = \frac{\text{Amount of Drug Entrapped}}{\text{Total Amount of Drug}} \times 100 \quad (1)$$

Flowability

The flowability of cephradine *proniosomes* was accessed by angle of repose using fix funnel method. The angle of repose was calculated using below equation:

$$\tan(\theta) = \text{height} / 0.5 \text{ base} \quad (2)$$

Dissolution study

The release of CP from the proniosome powders (F0S-F8S, F0M-F8M) was evaluated as documented previously.¹³ The drug release was conducted using USP dissolution apparatus-I (rotating basket assembly) at $37 \pm 0.5^\circ\text{C}$ and at a motion pace of 50rpm. The drug release was carried out in 500 mL buffer HCl (pH 1.2) for two hours and then switched to phosphate buffer saline (PBS) of pH 7.4 for 24hr. Samples of 2mL was taken at different time intervals (0-24h) with replenishment of equal volume with fresh medium. After

filtration the samples in triplicate were analyzed spectrophotometrically at 254nm wavelength.¹⁶

Stability Testing

CP *proniosomes* exhibiting the best attributes (F4S and F4M) were kept in glass vials at temperature of $5 \pm 3^\circ\text{C}$ in refrigerator for three months.¹⁸ Samples were taken at time interval of 0, 15, 30, 45, 60 and 90 days and assessed spectrophotometrically at 254nm wavelength in triplate for % drug entrapment efficiency and % drug remaining.¹⁶

Filling of optimized CP *proniosomes* in hard gelatin capsules

Optimized *proniosomes* F4S and F4M were filled manually in HGC (12 mm), each containing equivalent amount of CP 250mg. 19.2g of sorbitol *proniosomes* (F4S) with 78.89% entrapment were taken with 0.1% lactose (diluent) for powder mixture filling. Likewise, 16.8g of maltodextrin *proniosomes* (F4M) with 89.31% entrapment were used with 0.1% lactose for powder fill mixture.

Pharmaceutical quality testing of *proniosomes* filled capsules

Weight variation of *proniosomes* HGCs containing sorbitol (F4S) and maltodextrin (F4M) was performed as per BP recommendation. 10 units of each formulation were weighted as intact capsule and its content separately on electronic balance. The capsules are considered to be acceptable, if not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation 10% and none deviate by more than 15%.¹⁹

Microbiological evaluation of marketed CP brands and *proniosomes* filled capsules

Two different brands of CP capsules 250mg were procured from the market and tagged as M1 and M2. Antimicrobial activity of optimized *proniosomes* and marketed CP capsules was performed by well diffusion method using agar nutrition media (Mueller Hinton Agar, MHA) against *staphylococcus aureus* microorganism. Inoculum having density of 10^8 cfu/mL was prepared. McFarland 0.5 standard was obtained by mixing 0.05mL of 1.175% barium chloride dihydrate ($\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$), with 9.95mL of 1% sulfuric acid (H_2SO_4).²⁰ About 40 mL sterile agar along with the 100 μL cultural suspension were poured evenly to each sterile pre-labeled petri-plates. Plates were placed on flat surface for hardening. The cork borer was applied to bore a well of 10 mm diameter. Equal amount from the CP stock solution of test (F4S, F4M) and marketed (M1, M2) having 0.25%,w/v were transferred in each well respectively.

The blank was also set without adding CP to one of the inoculated petri plate. The plates were then incubated at $37 \pm 2^\circ\text{C}$ for 24hr in biochemical oxygen demand incubator (B.O.D). Throughout the study, aseptic environment was maintained and the mean zone of inhibition was recorded and compared.

RESULTS

Formulation trials of CP *proniosomes* with different composition of surfactant and cholesterol blends were effectively obtained using sorbitol and maltodextrin carriers. *Proniosomes* were prepared as an alternative colloidal carrier approach, for controlled drug delivery system, maintaining the drug release for extended time period. These *proniosomes* were aqueously moistened ($60-65^\circ\text{C}$) to obtain niosomal vesicles directly. Upon microscopic evaluation, the vesicular systems were found to be lamellar, comprising of amphiphilic molecules surrounded by an aqueous environment. The prepared *proniosomes* were observed to be identical in dimension and shape. The structures of *proniosomes* and niosomes are shown in Figure 1 and 2, respectively.

Flowability and percent drug entrapment of various trials containing sorbitol (F0S to F8S) and maltodextrin (F0M to F4M) carriers were evaluated and are given in Table 2. *In vitro* drug release of *proniosomes* powder (F0M-F8M and F0S-F8S) was conducted using USP dissolution apparatus-I at 50rpm. *Proniosomes* containing sorbitol (F0S to F8S) and maltodextrin (F0M to F8M) carriers showed linear drug release with respect to time

(Figures 3 and 4). However, drug release was found to be delayed (up to 12 hr) in *proniosomes* containing higher levels of cholesterol (F7S, F8S and F7M, F8M) due to increase lipophilicity. F4M and F4S *proniosomes* were found to be optimized CP proniosomal formulations based on better % drug entrapment efficiency, flowability and the drug release from vesicular system. Stability testing results showed only minor difference in drug remaining and drug entrapment efficiency during stability period between the formulations F4S and F4M (Table 3). Optimized proniosome (F4S and F4M) CP and marketed capsules (M1 and M2) were exposed to pharmaceutical quality control tests. The weight variation for F4S and F4M were found to be $280.9 \text{ (mg)} \pm 1.15$ and $317.3 \text{ (mg)} \pm 1.27$, respectively, whereas for M1 and M2 were $270.9 \text{ (mg)} \pm 5.32$ and $283.0 \text{ (mg)} \pm 2.72$. Weight variation test complied with the pharmacopeial limits as no capsule deviate the filled weight by more than 10%. Comparative microbiological evaluation of CP *proniosomes* with conventional capsules showed that optimized *proniosomes* were found to be more effective against *Staphylococcus aureus* rather conventional capsules. Furthermore, zone of inhibition was found to be small in initial hours with gradual increase up to 24hr (Table 4). This behavior of zone appearing primarily might be attributed to the controlled release of *proniosomes* capsules.

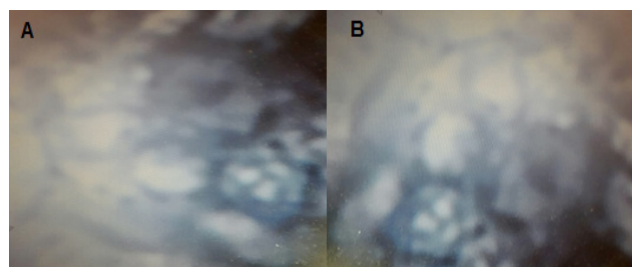


Figure 1: Optical microscopic view of powder proniosome (A) F4M (B) F4S

Table 2: Flowability and percent drug entrapment of powder *proniosomes* containing sorbitol and maltodextrin carriers.

Formulation	Angle of Repose($^\circ$)	Drug Entrapment (%)	Formulation	Angle of Repose($^\circ$)	Drug Entrapment (%)
Sorbitol	41.42	-	Maltodextrin	45.14	-
F0S	36.70	48.45	F0M	39.80	52.12
F1S	34.45	69.33	F1M	37.55	74.44
F2S	32.54	74.05	F2M	36.23	79.92
F3S	30.23	76.87	F3M	33.47	84.22
F4S	20.33	78.89	F4M	23.64	89.31
F5S	27.45	69.44	F5M	30.41	77.35
F6S	26.67	62.75	F6M	29.16	72.87
F7S	24.38	58.12	F7M	27.41	65.19
F8S	21.84	50.28	F8M	24.47	56.55

Table 3: Stability of optimized CP proniosome formulations (F4S and F4M) kept at controlled temperatures ($2-8^\circ\text{C}$) (Mean \pm SD, $n = 3$)

Study Period	CP Entrapment Efficiency %	% CP Remaining	CP Entrapment Efficiency %	%CP Remaining
(Days)	F4S	F4S	F4M	F4M
0	78.89 \pm 0.19	100.00 \pm 0.00	89.31 \pm 0.22	100.00 \pm 0.00
15	78.79 \pm 0.13	99.78 \pm 0.14	89.19 \pm 0.09	99.38 \pm 0.17
30	78.75 \pm 0.10	99.42 \pm 0.09	89.12 \pm 0.12	98.09 \pm 0.10
45	78.72 \pm 0.14	99.13 \pm 0.18	89.03 \pm 0.14	97.89 \pm 0.15
60	78.65 \pm 0.22	98.65 \pm 0.20	88.85 \pm 0.18	97.65 \pm 0.20
90	78.60 \pm 0.15	98.24 \pm 0.19	88.41 \pm 0.19	97.44 \pm 0.12

DISCUSSION

CP, a cephalosporin is the most prescribing antibiotic in health care system due to effectiveness against infections commonly occurring in population.²¹ In the present study, CP *proniosomes* were successfully prepared using cholesterol, span 60 and carriers to provide controlled drug delivery. *Proniosomes* are the vesicular system with improved penetration designed to prolong the drug duration and reduction in dosing frequency. Hence forth, providing drug safety and better patient compliance. Maltodextrin and sorbitol are advantageous carriers in the preparation of *proniosomes* as documented to be

Table 4: Comparative bactericidal activity of optimized CP proniosomal and marketed capsules (Mean \pm SD, $n = 3$)

S. No	Sample	Drug concentration (w/v)	Quantity of sample	Zone of inhibition at 24h (mm)
1	F4S	0.25%	0.1 mL	31.20 \pm 0.19
2	F4M			34.4 \pm 0.23
3	M1			17.2 \pm 0.34
4	M2			19.4 \pm 0.27

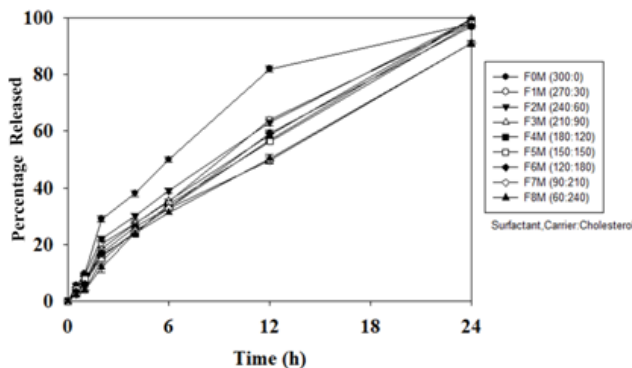


Figure 2: CP release from proniosomes with maltodextrin carrier (F0M to F8M)

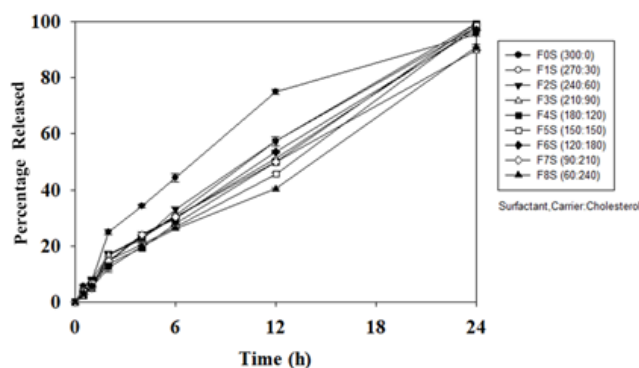


Figure 3: CP release from proniosomes with sorbitol carrier (F0S to F8S)

biocompatible, biodegradable, non-carcinogenic and non-immunogenic. Moreover, nonionic surfactant and cholesterol are beneficial as improving the efficacy and stability of the encapsulated active moieties.^{22,23} Currently, span 60 and cholesterol are used to facilitate stable vesicle formation, enhance the encapsulation of the drug thus improving the oral delivery of CP from *proniosomes*. Not only the selection of surfactant and lipids, rather are their quantities considered to be critical during formulation development of proniosomal system. Alteration in the lipid composition could cause deformation of the vesicle leading to drug leakage prior to diffusion and fusion of vesicle with gastrointestinal epithelium, resulting in less drug entrapment or abrupt drug release.²⁴⁻²⁸ Based on these facts, various ratios of span 60 with cholesterol were tried and the responses against variables were studied to achieve optimized formulation(s).

Not only the formulation ingredients but the employed technique for the preparation plays a significant role in the successful development of a product. Currently, CP *proniosomes* were developed using slurry method owing to benefits as discussed in past studies.^{13,15} The method provides uniform, consistent and thinner coating with higher surface area facilitating the rehydration with better stability of vesicles. Better entrapment of CP was observed in all formulations containing span 60 probably due to longer chain length resulting in larger

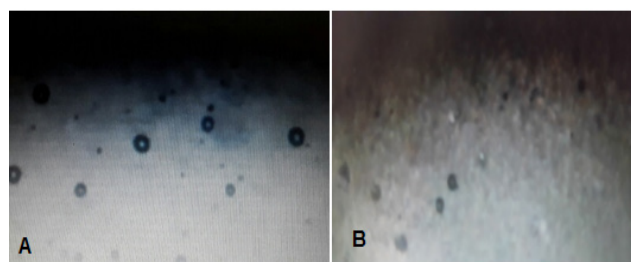


Figure 4: Optical microscopic view of niosomal dispersion (A) F4M (B) F4S

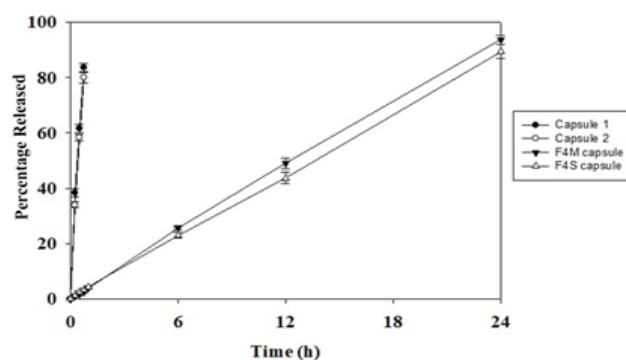


Figure 5: Drug release from the CP capsules marketed brands and proniosomal (optimized formulations of sorbitol and maltodextrin)

core space. Additionally, cholesterol influenced the physical properties and vesicle structures by modulating cohesion and mechanical strength of bi-layers and consequently leading to higher entrapment of the drug. The CP entrapment efficiency was found to be higher in F3S to F5S and F3M to F5M *proniosomes*. Similar findings were reported by Nagalakshmi and coworkers, concluding that the entrapment of the drug was greater in formulation containing approximately equal ratios of surfactant to cholesterol than other experimental runs.²⁹ Low entrapment of CP was noticed in F0S and F0M trials due to the absence of cholesterol therefore, speedy drug release >75 % was obtained in 12hr. While, moderately higher concentration of cholesterol was observed to entrap CP efficiently (F1S to F4S and F1M to F4M). However, decline in drug entrapment was noticed at higher concentration of cholesterol (F5S to F8S and F5M to F8M) leading to decrease CP entrapment in the vesicles (69.44 to 50.28% and 77.35 to 56.55%, respectively). This reflects the fact that cholesterol is prone to make changes in the normal bi-layered structure, resulting in reverse drug entrapment. Excess of cholesterol was unsuitable, as equal molarities of nonionic surfactant and cholesterol might build the membrane dense and ordered.³⁰ Mokhtar Ibrahim *et al.* found that increase in cholesterol after certain level would in turn lower the drug entrapment efficiency.³¹ Actually, cholesterol (above the saturation edge) took the places in the bilayer membrane with its OH moiety (bilayer packing) thus preventing the CP to be entered in the bilayer leading to turn down the CP entrapment.^{32,33}

Proniosomes prepared using sorbitol (F0S to F8S) and maltodextrin (F0M to F8M) carriers showed a comparable drug release profile as presented in Figure 2 and 3, respectively. This indicates that both carriers can be successfully used to prepare CP *proniosomes*. Drug release was found to be mainly governed by the blend ratio of surfactant and membrane stabilizer.

In the present study, niosomes prepared by aqueous hydration of *proniosomes* were found to be discrete vesicles (without aggregation or lumping) with uniform spherical shape and smooth surface. It is also documented in literature that the niosomes prepared from *proniosomes* are superior than conventional niosomes in term of their physical and chemical stability.^{23,34} Song *et al.*³⁵ had also encapsulated Vinpocetine-a synthetic alkaloid in *proniosomes* resulting in higher gastrointestinal absorption ultimately leading to increase in drug bioavailability with improved stability.

Proniosomes being a successful drug delivery system opens a new horizon for the pharmaceutical industries. Such

systems are offering promising benefits due to better flowability and stability of encapsulated drugs. *Proniosomes*, being dry powders are easily fabricated into oral, transdermal and parenteral preparations.^{36,37} Tablets and capsules are among the popular oral dosage forms as providing advantages over other drug administration routes due to self and convenient administration. In this connection, presently the optimized formulations of CP *proniosomes* (F4S and F4M) Figure 5 were filled in hard gelatin capsules. These CP *proniosome* filled capsules were then compared with two conventional marketed brands (M1 and M2) of CP capsules having same strength (250mg). Antimicrobial efficacy of the *proniosomes* was compared with the reference products through well method. Greater zone of inhibition was observed around F4S and F4M *proniosomes* against *Staphylococcus aureus* reflecting their better activity than the marketed CP capsules. Similar findings were reported by Kumar and coworkers presenting higher zone of inhibition with cephalosporin niosomes in contrast to the marketed formulation.³⁸ Thus, the CP *proniosomes* have been successfully obtained by this study is considered to be superior than conventional dosages owing to longer drug stay with controlled drug release and, improved stability and efficacy.

CONCLUSION

Cephadrine *proniosomes* were dry free flowing powders prepared successfully using surfactant, cholesterol and carriers (sorbitol/ maltodextrin). F4M and F4S containing blend of span 60 and cholesterol in ratio of 180:120 were found to be optimized *proniosomal* trials. Optimized formulations were stable showing negligible change in drug content and entrapment efficiency over study period. Being lipid based vesicular system, the designed *proniosomes* prolong the duration of the drug in systemic circulation thus reducing the toxicity by selective up taking. The optimized *proniosomes* enhances the antimicrobial activity of the drug with its sustained effect consequently, improving the patient compliance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CP: Cephadrine.

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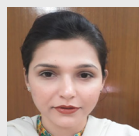
SUMMARY

Proniosomes powders loaded with cephadrine (CP) have been prepared using span60 and cholesterol with malto-dextrin (F0M-F8M) and sorbitol (F0S-F8S) as a carrier. Various formulations prepared were characterized for powder flowability, drug entrapment efficiency, and *in vitro* drug release. It has been found that formulations F4S and F4M possess good flowability, excellent drug entrapment, and sustained drug release. These two formulations were also compared with the marketed conventional capsule brands for microbiological efficacy. It has also been found that the prepared *proniosomes* are highly stable with the drug efficiency (%) of 78.60 ± 0.15 and 88.41 ± 0.19 for F4M and F4S, respectively, and they possess higher bactericidal activities against *S. aureus* than the reference (M1 and M2).

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