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RESEARCH ARTICLE

PREPARATION AND CHARACTERIZATION OF TOLTERODINE TARTRATE PRONIOSOMES

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Abstract

Objective: Proniosomes are dry free flowing, granular products that are water soluble carrier particles, coated with surfactants and can be hydrated to form niosomal dispersion immediately before use in hot aqueous media. Tolterodine, is medication used to treat frequent urination, urinary incontinence, or urinary urgency. It acts on M2 and M3 subtypes of muscarinic receptors.
Methods: Tolterodine tartrate proniosome formulations were prepared by coacervation phase separation method by using different surfactants in different ratios. The prepared proniosomal formulations were evaluated for vesicle size, rate of spontaneity, encapsulation efficiency, drug content, *In vitro* release study and stability studies.
Results: The size range was found to be 15.28±0.33 to 16.43±0.22 µm. Viscosity of all formulations lies in the range of 7244-9314 cp. Maximum release was shown by formulations of batch PG4 (87.45 %), and minimum for formulations of batch PG4 (50%), after 12 h. Optimized formulations PG4 shows stability at different temperatures.
Conclusion: Tolterodine tartrate proniosome formulations prepared by using coacervation phase separation method are capable of releasing drug for the extended period of time.
Keywords: *In vitro* release, proniosomes, Tolterodine tartrate.

INTRODUCTION

At present scenario vesicular systems have been receiving a lot of interest as a carrier for advanced drug delivery[1]. Encapsulation of the drug in vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation[2]. Proniosomes are water soluble carrier particles that are coated with surfactants and can be hydrated to form niosomal dispersion immediately before use in hot aqueous media. Proniosome is a dry free flowing, granular product that could be hydrated immediately before use and would avoid many of the problems associated with aqueous noisome dispersions and problem of physical stability[3]. Proniosome technology offers novel solution for poorly soluble drugs. Proniosomes avoid many of the problems associated with aqueous niosome dispersions, and problems of physical stability (aggregation, fusion, leaking) could be minimized. The additional convenience of the transportation, distribution, storage, and dosing would make 'dry niosomes' a promising industrial product[4].

Tolterodine acts on M2 and M3 subtypes of muscarinic receptors. Tolterodine tartrate is used for the treatment of overactive bladder with symptoms of urge urinary in continence, urgency and frequency[5]. Use of Tolterodine tartrate is associated with side effects like dry mouth and other side effects like constipation, headache, stomach pain and blurred vision, often leading to discontinuation of therapy[6]. The aim of present study includes development of proniosomes of Tolterodine tartrate to reduce dosing frequency and avoid side effects.

MATERIALS AND METHODS

Tolterodine tartrate was obtained as gift sample from Churchbells Pharma Nigeria Limited. Span 60, Tween 40 and cholesterol were procured from Drugfield Pharmaceuticals Limited, Nigeria. Ethyl alcohol and lecithin was procured from Interpharma Industries Nigeria Limited. All other reagents used were of analytical grades.

Preparation of proniosomal gel

Tolterodine tartrate proniosomal gel formulations were prepared by coacervation phase separation method. Precisely weighed amounts of surfactant, lipid phase and drug were taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol was added to it. All the ingredients were mixed well with a glass rod; the open end of the glass vial was covered with a lid to prevent the loss of solvent from it and warmed over water bath at 50-60°C for about 5 minutes until the drug is dissolved completely in surfactant mixture. Then the aqueous phase 1.6 ml phosphate buffer (pH 7.4) was added and warmed on a water bath until a clear solution was formed. Preliminary the composition of these formulations is reported in Table 1[6].

Evaluation of proniosome formulations

Vesicle size analysis

Hydration of Tolterodine tartrate proniosomal gel (100 mg) was done by adding saline solution (0.9% solution) in a small glass vial with occasional shaking for 10 min. The dispersion was observed under optical microscope at 45x magnification. The sizes of 200-300 vesicles were measured using a calibrated ocular and stage micrometer (Erma, Tokyo) fitted in the optical microscope[8].

Drug content

In a 100 ml volumetric flask, 20 mg of proniosomal gel formulations were taken, and volume was made up to mark with pH 7.4. The flask was shaken for 12 hours using an orbital shaker incubator (Finlab, Nigeria). Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 261 nm[8].

Encapsulation efficiency

To evaluate the loading capacity of proniosomal systems for Tolterodine tartrate gel (100 mg) was dispersed in distilled water and warmed a little for the formation of niosomes. Then the dispersion was centrifuged at 18000 rpm for 40 min the clear fraction was used for the determination of free drug at 281 nm spectrophotometrically[9].

pH and Viscosity

Accurately weighed gel was taken and then diluted with the pH 7.4 phosphate buffer and checked the pH by using pH meter (Finlab, Nigeria) and Brook field viscometer is used to determine the viscosity of the gel[11].

***In vitro* release study**

In vitro release studies on proniosomal gel of Tolterodine tartrate were performed using locally manufactured Franz-diffusion cell. The capacity of receptor compartment was 15 ml. The dialysis cellophane membrane (MMCO 14KDC) was mounted be Tween the donor and receptor compartment[11]. A weighed amount of proniosomal gel was placed on one side of the dialysis membrane. The receptor medium was phosphate saline buffer pH 7.4. The receptor compartment was surrounded by a water jacket to maintain the temperature at 37±1°C. Samples withdrawn and analyzed spectrophotometrically (Finlab, Nigeria) at 281 nm.

Stability Studies

The ability of vesicles to retain the drug was assessed by keeping the proniosomal gel at three different temperature conditions, i.e., refrigeration temperature (4-8°C), room temperature (25±2^{0}C) and oven (45±2°C) for 12 weeks (60% relative humidity). Throughout the study, proniosomal formulations of Tolterodine tartrate were stored in aluminium foil-sealed glass vials. The samples were withdrawn at different time intervals and drug leakage from the formulations was analyzed for drug content spectrophotometrically at 281 nm[8].

RESULTS AND DISCUSSION

Results of vesicle size of Tolterodine tartrate proniosome formulations are presented in Table 2, which indicated that vesicle formed with Span 60 is smaller in size than vesicle formed with Tween 40. The reason for this may be higher hydrophobicity of Spans as compared to Tweens. As hydrophobicity increases, surface energy of surfactants decreases, resulting in smaller vesicle size[8]. The size range was found to be 15.28±0.33 to 16.43±0.22 µm. Viscosity of all formulations lies in the range of 7244-9314 cp. Drug content is important parameter to maintain the minimum effective concentration and it is also used to estimate the drug release profile. The percent drug content was higher for PG4 that is 99±0.47% and lower for PG2 (88±0.12%).

Table 1: Composition of Tolterodine tartrate pronisomal gel formulations.

Code	Drug (mg)	Span 60 (mg)	Tween 40 (mg)	Ethyl alcohol (ml)	Lecithin (mg)	Cholesterol (mg)	Observations
PG1	100	-	1500	10	900	200	Yellowish gel
PG2	100	1500	-	10	1800	400	Creamish semisolid
PG3	100	1500	-	10	900	200	White semisolid
PG4	100	-	1500	10	1800	400	Yellowish gel

Table 2: Characterization of the proniosomal formulations of Tolterodine tartrate.

Batch Code	Mean particle size (µm)	Encapsulation efficiency (%)	% Drug content	pH	Viscosity (cp)
PG1	15.28±0.33	77.2±0.45	95±0.32	7.12	7244
PG2	8.34±0.45	79.4±0.39	88±0.12	7.34	8247
PG3	7.27±0.67	81.2±0.48	90±0.77	7.42	9314
PG4	16.43±0.22	88.3±0.55	99±0.47	7.11	7642

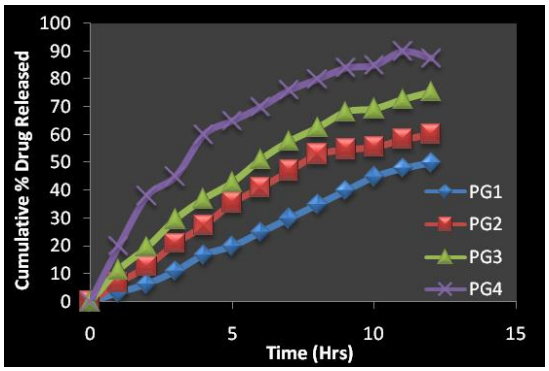

Figure 1: Comparative *in-vitro* release study of different proniosome formulations of Tolterodine tartrate.

In vitro release studies (Figure 1) are often performed to predict how a delivery system might work in an ideal situation. The amount of drug released from different proniosomal formulations was found in the order of PG4 > PG3 > PG2> PG1. *In vitro* release study were performed on different proniosomal gel formulations shows maximum release for formulations of batch PG4 (87.45 %), and minimum for formulations of batch PG4 (50%), after 12 h.

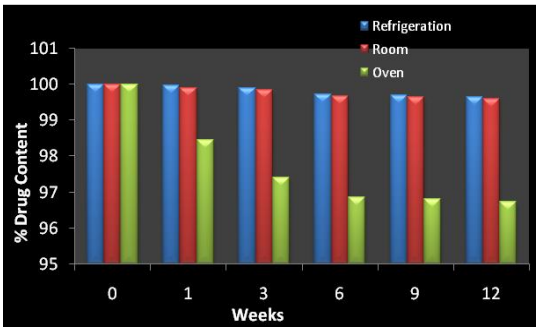

Figure 2: Stability study of formulation (PG4) at different temperature conditions.

Stability studies performed on optimized formulations PG4 shows 96.74% drug content at refrigeration condition, 94.74% drug content at oven condition and 99.59% drug content at room temperature during the studies performed for 12 weeks on the formulations (Figure 2).

CONCLUSIONS

The results obtained from the present study clearly revealed that Tolterodine tartrate proniosome formulations prepared by using coacervation phase separation method are capable of releasing drug for the extended period of time. Results of the present work have shown that surfactant type affect the encapsulation efficiency and drug release rate from proniosomes. Based on different parameters formulation of batch PG4 was considered as an optimum formulation.

AUTHOR'S CONTRIBUTION

Ugochukwu AE: writing original draft, conceptualization. **Nnedimkpa OJ:** Writing, review, and editing. **Rita NO:** writing, review, and editing. Final manuscript was read and approved by all authors.

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DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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