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DESIGN AND IN-VITRO CHARACTERIZATION OF ONDANSETRON ETHOSOMES

Amreen Begum, D. Anjali, Y. Ankitha, J. Anusha, T. Anusha Reddy, Sailaja Rao*

Department of pharmaceutics, Teegala Ram Reddy College of Pharmacy, Telangana, India

Corresponding author: Dr. Sailaja Rao
Email: Teegalaramreddymailbox@gmail.com

ABSTRACT

To confirm the presence of vesicular structure, formulations were visualized under microscope at different magnified fields, which showed presence of lipid bilayer as well as spherical structure of vesicles. Using the same microscopic method and special software “particle size analysis”, size of vesicle was determined for sonicated ethosomes respectively. Vesicular size was found to be in the range of 0–5.79 µm. The values of drug release EF1 (20% alcohol) 76.89%, EF2 (20%) 82.31%, EF3 (20% alcohol) 73.62, EF4 (30% alcohol) 86.42%, EF5 (40%) 72.09%, EF6 (50% alcohol) 63.21%, EF7.The order of drug release for optimized gel formulation was found to be zero order. Percentage drug accumulation in to skin for development and scaling up a new formulation.

Keywords: Ondansetron, particle size analysis, ethosomes, Lipid bilayer, Size of vesicle

1. INTRODUCTION

Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery[1]. Transdermal delivery is an important delivery route that delivers precise amount of drug through the skin for systemic action. Improved methods of drug delivery for biopharmaceuticals are important for two reasons; these drugs represent rapidly growing portion of new therapeutics, and are most often given by injection. Discovery of new medicinal agents and related innovation in drug delivery system have not been only enabled the successful implementation of novel pharmaceutical, but also permitted the development of new medical treatment with existing drugs.

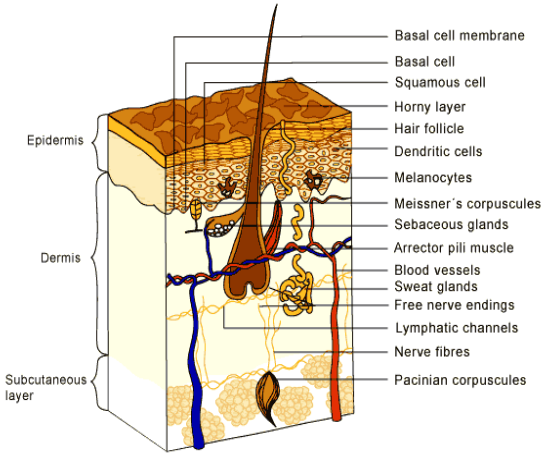


Fig 1: Structure of skin

2. REVIEW OF LITERATURE

Novel Vesicular Carrier – Ethosomes Classic liposomes are of little or no value as carriers for transdermal delivery because they do not deeply penetrate the skin, but rather remain confined to the upper layer of stratum corneum 28. Only specially designed vesicles were shown to be able to allow transdermal delivery.

Horwitz et al.,[2] (1999) evaluated the efficiency of 5 % ACV in a novel liposomal carrier (ethosome) in comparison with that of a commercial 5 % ACVcream (zovirax cream) and that of drug free vehicle in the treatment of recurrent herpes labialis in a armed, double blind, randomized clinical study and found the time to crusting with the ethosomal acyclovir (1.6 days) significantly shorter than the time with the acyclovir cream (4.3 days)

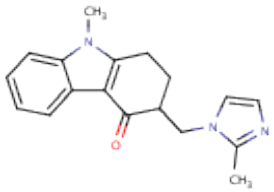
Touitou et al.,[7] (2000) described a novel carrier for enhanced skin delivery, the ethosomal system, that was composed of phospholipid, ethanol and water. The skin permeation of ethosomal components, ethanol and phospholipid, was demonstrated in diffusion cell experiments Ethosomal systems were composed of soya phosphotidyl choline 2%, ethanol 30% and water were shown by electron microscopy to contain multilamellar vesicles.

3. DRUG PROFILE

Ondansetron

A competitive serotonin type 3 receptor antagonist. It is effective in the treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs, including cisplatin, and has reported anxiolytic and neuroleptic properties. [PubChem]

Structure



Weight: Average:293.363

Chemical Formula: $C_{18}H_{19}N_3O$

IUPAC Name: 9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3,4,9-tetrahydro-1H-carbazol-4-one

4. AIM AND OBJECTIVE

The purpose of the present investigation is aimed at: To prepare and evaluate Ondansetron ethosomes containing different concentration of ethanol and phospholipids by sonication for size reduction of vesicles. Designed Ondansetron ethosomes are characterized for Size and shape, Entrapment efficiency, Release study. The effect of sonication also studied on the characteristics of Ondansetron ethosomes.

5. MATERIALS AND METHODS

5.1 Chemicals

Chemicals and Materials

Chemicals	Manufactured by
Ondansetron	--
Soya lecithin	Research lab fine chem. Industries(Mumbai)
Propylene glycol	Research lab fine chem. Industries(Mumbai)
Alcohol	Jiangsu Huaxi International Trade Co.Ltd (CHINA)
Cholesterol	Virat lab(Mumbai).
Carbopol-934	Research lab fine chem. Industries(Mumbai)
Triethanol amine	Research lab fine chem. Industries(Mumbai)
Ultrapure water	Cortex laboratories (Hyderabad)

5.2 Equipment's

Instruments and company

Instruements	Company
Electronic weighing balance	Scimadzu corporation (JAPAN).
Uv.spectrophotometer	Schimadzu 1800(JAPAN).
Magnetic stirrer	REM elektro technik limited.vasai (INDIA)
Refrigerator	Allwyn (INDIA).
Sonicator	SISCO Scientific Instruments sales Corporation, Thana,Mumbai.
pH meter	EI
Scanning electron microscope	Scimadzu corporation (JAPAN).
FTIR	Scimadzu corporation (JAPAN).
Humidity chamber	SISCO Scientific Instruments sales Corporation, Thana,Mumbai

5.3 ANALYTICAL METHODS

Preparation of pH 7.4 phosphate buffer: Dissolve 2.38g disodium hydrogen phosphate, 0.19g potassium dihydrogen and 8g of sodium chloride in distilled water and then make up 1000ml with distilled water.

Preparation of standard calibration curve of Ondansetron[28] .

Preparation of standard solution: Standard stock solution of ondansetron was prepared in methanol. 100 mg of Ondansetron was accurately weighed into 100ml volumetric flask and dissolved in small quantity of methanol.

Preparation of working standard solutions: Further, from (SS-II) aliquots of 0.2ml, 0.4ml,0.6ml,0.8ml and1ml were pipetted into 10ml volumetric flasks. The volume was made up with pH6.8. λ max:212.5nm. Beer's range: 2-10µg/ml.

5.4 Preparation Of Ondansetron Ethosomes (By Cold Method)

Preparation of Ondansetron ethosomes was followed by method suggested by Touitou et al., with little modification.[7]

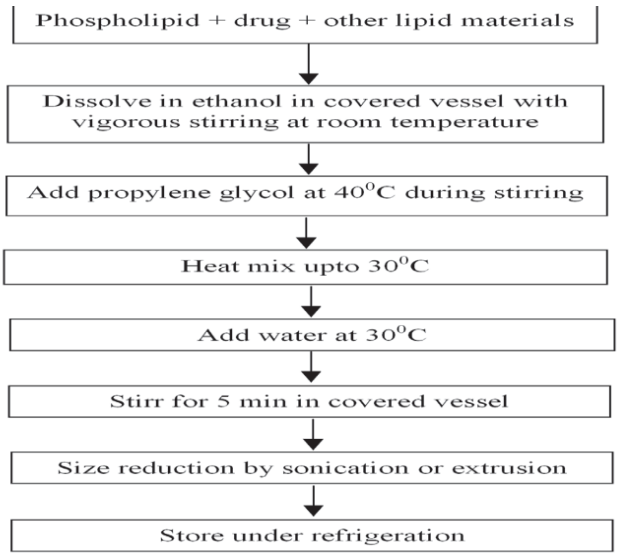


Fig 2: Cold method for the preparation of ethosomes

5.5 Preparation of Ondansetron ethosomal gel

Table 2: Composition of different ethosomal gel formulation

Gel formulation	Ondansetron ethosomal suspension(ml)	Carbopol (%)	Triethanolamine (ml)	Phosphate buffer (pH 7.4)
G-1	20	1	0.5	q.s
G-2	20	1.5	0.5	q.s
G-3	20	2	0.5	q.s
*G-4	0.100g	1.5	0.5	q.s

**G-4 free drug gel.*

5.6 Characterization of Ethosomes

Table 3: Methods for Characterization of Ethosomal Formulation

PARAMETERS	METHODS
Vesicle shape (morphology)	Transmission electron microscopy Scanning electron microscopy
Entrapment efficiency	Mini column centrifugation method Fluorescence spectrophotometry
Vesicle size and size distribution	Dynamic light scattering method
Vesicle Skin interaction study	Confocal laser scanning microscopy Fluorescence microscopy Transmission electron microscopy Eosin-Hematoxylin staining

5.7 In-Vitro Release Studies

The skin permeation of Ondansetron from ethosomal formulation was studied using open ended diffusion cell specially designed in our laboratory according to the literates. The effective permeation area of the diffusion cell and receptor cell volume was 2.4 cm and 200 ml respectively. The temperature was maintained at 37 ± 0.5°C.

5.8 In-vitro release kinetics

To analyze the in vitro release data various kinetic models were use to describe the release kinetics. The zero order rate Eq. (2) describes the systems where the drug release rate is in-dependent of its concentration. The first order Eq.(3) describes the release from system.

5.9 Mechanism of drug release

Table 4: Diffusion exponent and solute release mechanism for cylindrical shape

S.No	Diffusion	Exponent (n) Overall solute
1.	0.45	Fickian diffusion
2.	0.45<n<0.89	Anomalous (non-Fickian) diffusion
3.	0.89	Case-II transport
4.	n>0.89	Super case-II transport

5.10 Stability Studies

Stability study was carried out for Ondansetron ethosomal preparation at two different temperature i.e. refrigeration temperature (4 ± 2° C) at room temperature (27 ± 2° C) for 8 weeks (as per ICH guidelines). The formulation was subjected to stability study and stored in borosilicate container to avoid any sort of interaction between the ethosomal preparation and glass of container,

5.11 In-vitro stability release study

Stability of drug and stability of vesicles are the major determinant for the stability of formulation, studies were carried to evaluate total drug content at room temperature (27±2° C) and refrigeration temperature (4±2° C).samples was collected for every 2 weeks and absorbance was seen at 212.5nm in U.V spectrometer.

6. RESULTS AND DISCUSSION

6.1 ANALYTICAL STUDY

Solubility studies of Ondansetron

Table 5: Solubility parameters

Solvent	Ondansetron
Water	Sparingly Soluble
Methanol	Soluble
Ethanol	soluble
Chloroform	Insoluble
DMSO	Soluble
0.1N Hcl	Soluble
pH 6.8 buffer	Soluble

6.2 STANDARD CALIBRATION CURVE

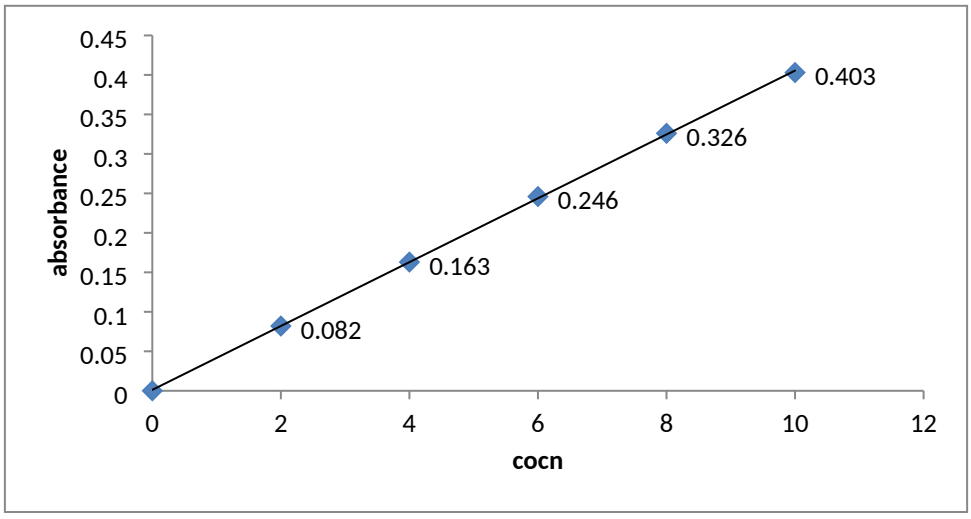


Fig 3: Calibration curve of ondansetron graph

6.3 FTIR STUDIES

IR spectra was compared and checked for any shifting in functional peaks and non-involvement of functional group. From the spectra it is clear that there is no interaction between the selected carriers, drug and mixtures.

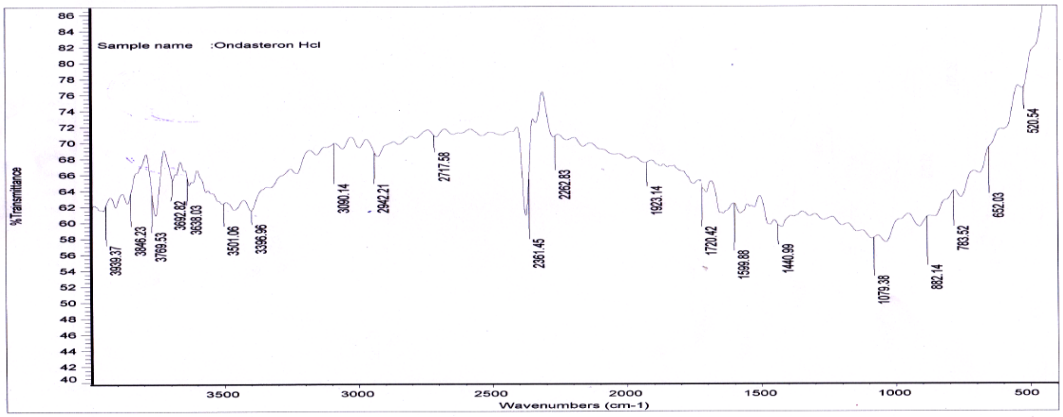


Fig 4: FTIR Spectra of Ondansetron pure drug

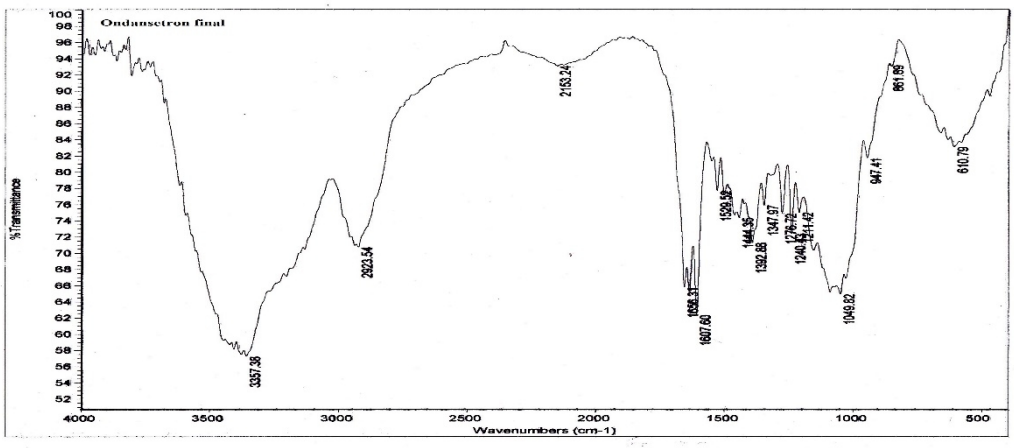


Fig 5: FTIR Spectra of Ondansetron Final formulation

6.4 PREPARTION OF ONDANSETRON ETHOSOMES

Ethosomal formulations composed of phospholipid, drug and ethanol were prepared using the method detailed in last chapter materials and methods and also according to literature with little modification

6.5 SCANNING ELECTRON MICROSCOPE (SEM)

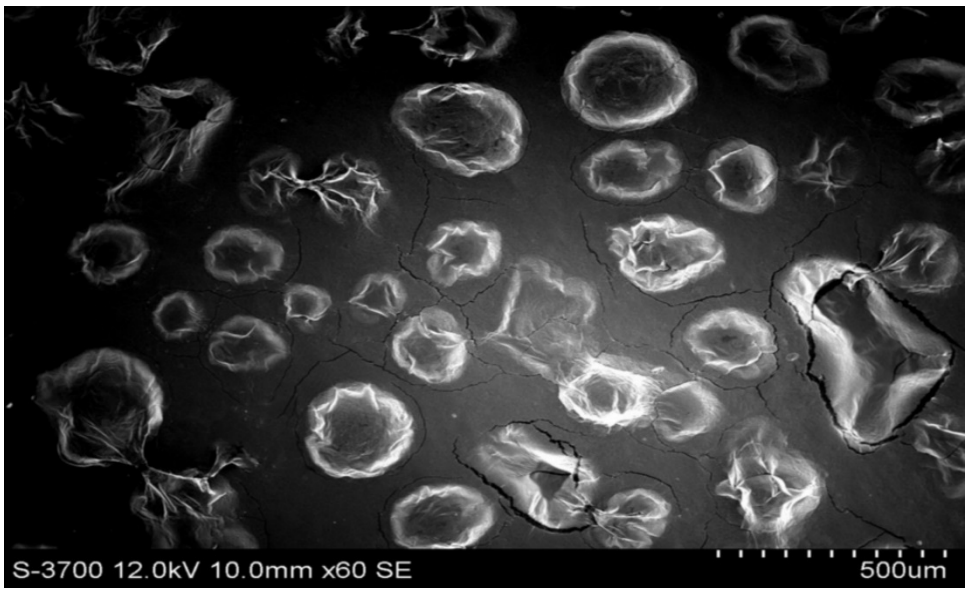


Fig 6: Scanning electron microscope image

6.6 IN-VITRO RELEASE STUDIES

Table 6: In-vitro cumulative % drug release profile Ondansetron Ethosomes

	Cumulative %drug release						
Time(hrs)	**EF1**	**EF2**	**EF3**	**EF4**	**EF5**	**EF6**	**EF7***
0.5	14.56	17.5	12.09	18.09	11.39	10.01	11.21
2	25.62	31.52	23.26	32.51	20.21	18.09	23.62
4	30.10	38.3	28.21	39.42	25.22	22.31	29.72
6	33.08	42.52	32.71	46.42	30.09	27.69	33.32
8	38.62	47.81	37.21	49.31	36.21	30.03	37.29
10	40.07	54.32	39.05	56.51	37.02	33.61	40.25
12	43.62	58.5	43.02	60.41	42.3	37.32	47.91
14	49.30	61.32	48.05	63.21	46.31	40.65	52.41
16	52.41	64.92	51.51	66.72	53.65	43.32	52.56
18	59.32	69.07	58.37	71.46	57.21	48.32	52.56
20	66.02	75.41	66.42	76.32	65.21	52.09	-
22	70.52	78.2	70.31	82.31	68.71	56.31	-
24	76.89	82.32	73.62	86.42	72.09	63.21	-

7. SUMMARY

Transdermal route offers several potential advantages over conventional routes. These advantages includes avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in the blood levels, and most important. It provides patient convenience. But one of the major problem for efficient drug delivery is low penetration rate. While optimizing the topical drug delivery, vesicular system (liposomes and niosomes) appears as upcoming development. Recently advancement in liposomes was done and result obtained “Ehosomal system” which showed topical delivery with higher transdermal flux and higher skin deposition as it is attractive and has desirable advantages.

8. CONCLUSION

It is well known that if drug molecules presenting any difficulties in it’s solubility and bioavailability along the GI tract, are candidates for other routes of administration and if the site of action for drug candidate is subdermal, an effective penetration enhancers are required to provide the drug molecule deeper into skin tissue for optimized therapeutic delivery of drug. It is generally agreed that classic liposomes are of little or no value as carriers for transdermal drug delivery because they do not penetrate the skin. The method described by Touitou et al., (2000) was employed with little modification for the preparation of various ethosomal formulations containing different concentration of ethanol (20 % to 50 %) with sonication . The techniques used were simple and reproducible. The prepared ethosomes were spherical and discrete in shape. The size of vesicles were found to be in the range of 3.26 µm – 5.79 µm sonicated ethosomes.

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