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Formulation and evaluation of doxazosin mesylate loaded niosomes for prostate cancer

Dr. Syed Mohammed kazim[1], Fareeaa Ashar[2], Arifa Banu[3], Mukund Panukanti[4]
[1] Professor and Principal, Nizam institute of pharmacy, Hyderabad, Telangana, India
[2, 3] Assistant, Professor, Department, of Pharmaceutics, Nizam Institute of pharmacy, Hyderabad, Telangana, India
[4] Head of the Department, Department of Pharmaceutics, Nizam Institute of pharmacy, Hyderabad, Telangana, India

Abstract
Cancer is defined as an uncontrolled growth of abnormal (neoplastic) cells. Prostate cancer is the second most commonly occurring cancer in men and the fourth most commonly occurring cancer overall. Use of chemotherapeutic agents is treatment of choice for prostate cancer. Doxazosin Mesylate, an α-1 adrenoreceptor antagonists, have shown anticancer activities against prostate cancer via induced apoptosis. Niosomes are the promising surfactant-based drug carriers, formed mostly by non-ionic surfactant and cholesterol. Formulation of Doxazosin mesylate as niosomes helps in passive targeting of drug delivery.
Doxazosin Mesylate loaded niosomes were prepared using thin film hydration method. Different grades of spans and tweens were selected for the preparation of niosomes. The prepared niosomes were evaluated for size, shape, lamellarity, entrapment efficiency and percentage drug release. Fourier-transform infrared spectroscopy of doxazosin mesylate and the excipients has shown no incompatabilities. Scanning electron microscopy of the niosomal formulations (F1-F4) has shown that all the prepared niosomes are spherical in shape with smooth surface and are multilamellar in nature. Entrapment efficiency of the niosomal formulations (F1-F4) were evaluated and F1 has shown the maximum entrapment efficiency of 94.87%. All the prepared niosomal formulations (F1-F4) were evaluated for percentage drug release and F1 formulation has shown the maximum drug release over a time span of 12h. From the above discussion it can be concluded that doxazosin mesylate loaded niosomes can help in treatment of prostate cancer by passive targeting.

Keywords: doxazosin mesylate, niosomes, cancer, anticancer, prostate cancer, targeted drug delivery system

1. Introduction
Cancer is defined as an uncontrolled growth of abnormal (neoplastic) cells. Current treatment strategies for cancer include combination of radiation, chemotherapy and surgery [1]. The long-term use of conventional drug delivery systems for cancer chemotherapy leads to fatal damage of normal rapidly proliferating cells. These chemotherapeutic agents are particularly used for the management of solid tumors, where utmost tumor cells are not invaded quickly [2].
Doxazosin mesylate, a quinazoline based α-1 adrenoreceptor antagonists, used in past as an antihypertensive, have shown now to induce apoptosis in prostate cancer cells via an α-1 adrenoreceptor independent pathway involving activation of transforming growth factor-β-1 signaling. It is shown that doxazosin mesylate exerts its apoptic effect against benign and malignant prostate cells via a death receptor mediated mechanism [3, 4].
These findings demonstrate the ability of doxazosin to suppress prostate cancer cell growth *in vitro* and *in vivo* by inducing apoptosis without affecting normal cells. This evidence provides the rationale for targeting both drugs, already in clinical use and with established adverse-effect profiles, against prostatic tumors for the treatment of advanced prostate cancer [5, 6].
A targeted drug delivery system is a system, which releases the drug at a preselected biosite in a controlled manner [7]. This can be achieved by passive targeting and active targeting. In passive targeting the drug success is directly related to circulation time whichis achieved by cloaking of the nanoparticle with some sort of coating which renders them hydrophilic. Active targeting of a drug loaded nanoparticles enhances the effects of passive targeting to make the nanoparticle more specific to target site [8].
Niosomes are one of the promising drug carriers that have a bilayer structure and are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase. Niosomes are biodegradable, biocompatible, and nonimmunogenic. They have long shelf life, exhibit high stability, and enable the delivery of drug at target site in a controlled and/or sustained manner. They can entrap both hydrophilic and lipophilic drugs, either in an aqueous layer or in a vesicular membrane made of lipid material [12, 16].
Doxazosin mesylate being a BCS Class II drug with low solubility can be incorporated in niosomes for targeted drug delivery.

2. Methodology
Materials
Doxazosin Mesylate, span 60, Span 40, Tween 60, Tween 40, Cholestrol and chloroform were of analytical grad

3. Preparation of Niosomes
Drug loaded niosomes were prepared using thin film hydration method. The surfactants and drug in 1:1 ratio and cholesterol were dissolved in chloroform in a round bottomed flask. The organic solvent was removed using a rotary vacuum evaporator to obtain thin film on the inside wall of the flask. The dried film was hydrated with phosphate buffer of pH 7.4 for 1 hour while rotating the flask, then it was subjected to sonication for 20 minutes to

obtain niosomaldispersion. The prepared niosomes were evaluated for size and shape analysis, percent entrapment efficiency and percentage drug release.

Table 1: Formulation Table

S. No	Chemical Name	Formulation code			
		F1	F2	F3	F4
1	Doxazosin Mesylate	50mg	50mg	50mg	50mg
2	Span 60	50mg	-	-	-
3	Span 40	-	50mg	-	-
4	Tween 60	-	-	50mg	-
5	Tween 40	-	-	-	50mg
6	Cholestrol	10mg	10mg	10mg	10mg

4. Evaluation Parameters

1. Preparation of Calibration Curve

Standard stock solution was prepared by dissolving Doxazosin Mesylate in phosphate buffer pH 7.4 to make final concentration of 100 µg/ml. Different aliquots were taken from stock solution and diluted with phosphate buffer pH 7.4 separately to prepare series of concentration from 2 – 10 µg/ml. An independent stock solution of 5 µg/ml was also prepared. The λ_{max} was found by UV spectrum of Doxazosin Mesylate in phosphate buffer pH 7.4 in range of 200 – 400 nm. Absorbance was measured at λ_{max} against phosphate buffer pH 7.4 as blank. The calibration curve was prepared by plotting absorbance versus concentration of Doxazosin Mesylate.

2. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of doxazosin mesylate and excipients were determined individually and in combination for compatibility studies using potassium bromide dispersion method.

3. Scanning Electron Microscopy

The scanning electron microscope (SEM) is one of the most limited instruments widely applied to surface microstructure imaging. SEM is a type of electron microscopy that images the sample surface of a solid specimen by using a focused beam of high-energy electrons. Niosomes were characterized by SEM. Niosomes containing doxazosin mesylate was taken in a cover glass and transferred on a specimen stub. Dried samples were coated with a platinum alloy to a thickness of 100° A using a sputter coater. After coating, scanning was done to examine the shape and size.

4. Entrapment Efficiency

The prepared Niosomes were evaluated for the entrapment efficiency. The entrapment efficiency of prepared Niosomes were determined by ultracentrifugation at 30,000- 40,000 rpm and 4°C for 1 hour using ultracentrifuge. Following centrifugation, the supernatant and vesicles were separated. The supernatant was removed and drug quantity in supernatant was analyzed by spectroscopic method.

5. Percentage Drug Release

In vitro release pattern of niosomes suspension was carried out by dialysis bag method. A dialysis sac was washed and soaked in distilled water. The vesicle suspension was pipette into a bag made up of tubing and sealed followed by placing the dialysis bag into a beaker containing 200 mL of phosphate buffer. The vessel was placed over magnetic stirrer (50 rpm) and the temperature was maintained at 37°C ± 0.5°C. Samples were withdrawn at predetermined time intervals and immediately replaced with the fresh medium to maintain the sink condition throughout experiment. Samples were diluted and analyzed for drug content by using UV/visible spectrophotometer.

5. Results and Discussions

1. Calibration Curve of Doxazosin

The λ max of Doxazosin mesylate was found to be 245nm. The calibration curve of Doxazosin Mesylate was prepared by plotting absorbance versus concentration of Doxazosin Mesylate

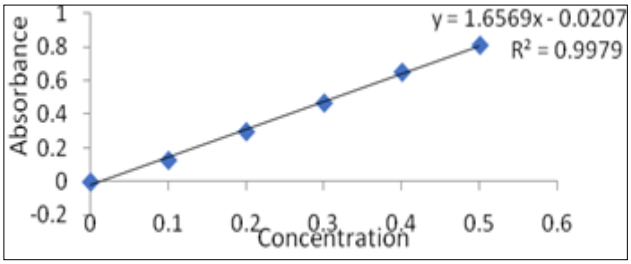

Fig 1: Calibration curve of Doxazosin Mesylate

2. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of doxazosin mesylate and excipients were determined individually and in combination for compatibility studies. The most important band in spectrum of doxazosin occurs in 1691.66 cm^{-1} attributed to the presence of tertiary amide band (C=O).Spectral broad band corresponding to N-H stretching of amine salt is localized at 2917.74 cm^{-1}. The strong band at 1605.48 cm^{-1}can be attributed to N-H bending of aromatic amines. The four C-O bands (stretching) that are presented in doxazosin structure may appear in the region of 1306.20 to 1012.70 cm^{-1}.The above characteristic bands were undisturbed in the presence of excipients hence shows that drug and excipients are compatible.

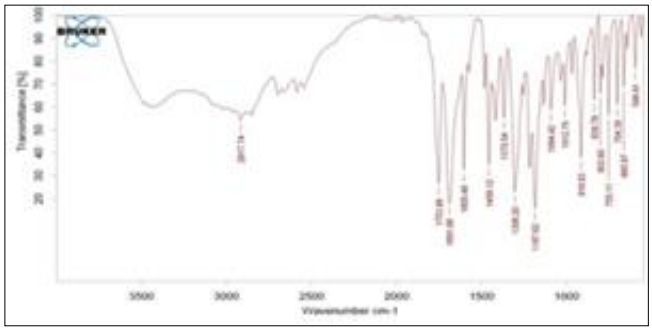

Fig 2: FTIR of Doxazosin mesylate

3. Scanning Electron Microscopy

SEM analysis of the formulations (F1-F4) showed that all the prepared noisome are spherical in shape with smooth surface and are multilamellar in nature. Average particle size of the niosomes are listed in table 1:

Table 2: Average Particle size of the niosomal formulations

S. No	Formulation Code	Average Particle size (µm)
1	F1	5.02±0.08
2	F2	6.08±0.02
3	F3	7.98±0.06
4	F4	9.88±0.01

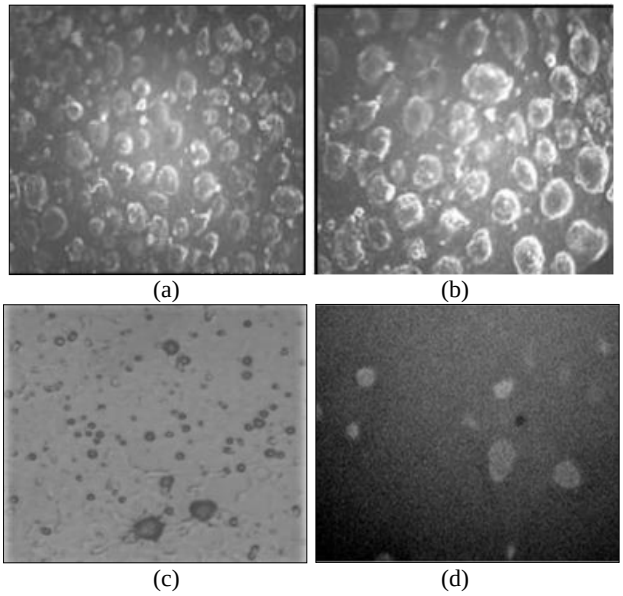

Fig 3: SEM analysis of (a) F1 b) F2 c) F3 d) F4

6. Entrapment Efficiency

Entrapment efficiency of the niosomal formulations (F1-F4) is tabulated below. Maximum entrapment efficiency of 94.87% was shown by F1 formulation code.

Table 3: Entrapment efficiency of the niosomal formulations

S. No	Formulation code	Entrapment efficiency
1	F1	94.87%
2	F2	87.2%
3	F3	85.2%
4	F4	83.7%

7. Percentage Drug Release

The percentage drug release of all four niosomal formulations were determined over a period of 12hrs and the results are tabulated in table 5.F1 formulation showed maximum release of 96.5% over 12hrs.

Table 4: Percentage drug release of the niosomal formulations

S.NO	Time (h)	F1	F2	F3	F4
1.	**0**	0	0	0	0
2.	0.5	3.9	3.5	2	2.9
3.	1	11.0	10.4	4.5	5.8
4.	2	19.6	16.7	7.5	10.8
5.	3	27.8	23.7	12.5	15.7
6.	4	34.1	31.2	18.1	20.9
7.	5	42.5	39.9	23.5	27.8
8.	6	51.9	47.1	29.2	34.7
9.	7	59.4	55.1	35.9	40.9
10.	8	67.3	60.3	42.1	49.1
11.	9	76.0	66.4	50.1	55.2
12.	10	85.7	74.3	58.7	63.8
13.	11	91.8	80.1	67.5	73.1
14.	12	96.5	85.3	76.8	82.8

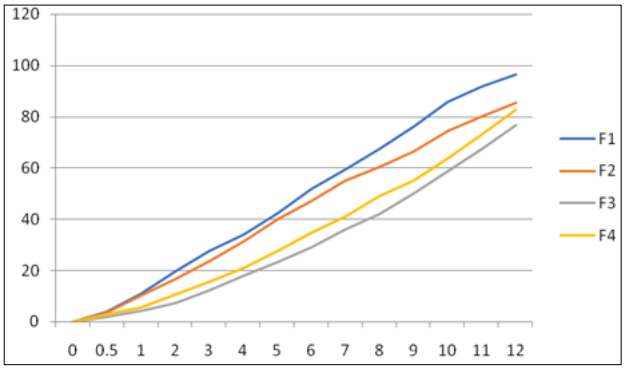

Fig 4: Percentage drug release of niosomal formulations (F1-F4)

8. Conclusion

Doxazosin Mesylate, a quinazoline based α-1 adrenoreceptor antagonists, has shown to be effective against prostate cancer. It acts by inducing apoptosis in cancer cells via an α-1 adrenoreceptor independent pathway involving activation of transforming growth factor- β-1 signaling.

Niosomes are the drug carriers that are formed by self-association of non-ionic surfactants and cholesterol in an aqueous phase. Formulation of Doxazosin Mesylate as niosomes helps in passive targeting of the drug towards cancer cell.

Doxazosin Mesylate niosomes were prepared using thin film hydration method using different grades of spans and tweens. The prepared niosomes were evaluated.

Fourier-transform infrared spectroscopy of Doxazosin Mesylate and excipients were determined individually and in combination for compatibility studies. The resultant studies has shown no incompatibility.

Scanning Electron Microscopy of the prepared niosomal formulations (F1-F4) has shown that all the prepared niosomes are spherical in shape with smooth surface and are multilamellar in nature.

All the prepared niosomes were evaluated for entrapment efficiency of drug. F1 Formulation has shown the maximum entrapment efficiency of 94.87%.

Percentage drug release of the prepared niosomal formulations (F1-F4) were studied and F1 formulation has shown the maximum drug release over a time span of 12h.

From the above discussion it can be concluded that doxazosin mesylate loaded niosomes can help in treatment of prostate cancer by passive targeting.

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