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Novel drug delivery system: Formulation and characterization of exemestane microspheres by chemical cross linking method

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ABSTRACT

This paper present the development and application of *in vitro* release study of exemestane microspheres, the drug is mainly used for the treatment of breast cancer. ethyl cellulose and chitosan are used for the preparation of microsphers through chemical cross linking method by using glutaraldehyde as cross linking agent. the prepared microspheres characterized by particle size 3-7µm, practical yield (53.33% .w/w), drug content (49.19%-65.99%),surface morphology by scanning electron microscopy and *in vitro* release study by using USPXXIII basket apparatus .and the release study shows The increase in concentration of glutaraldehyde also affects the release rate of microspheres. and the kinetic study reveals that with regression coefficient of 0.97, followed Higuchi matrix suggesting diffusion controlled release. it is possible to prepare microspheres containing Exemestane by glutaraldehyde cross linking method, to prolonged activity with increased stability without loosing its therapeutic activity

Key words; Exemesatne, microspheres, cross linking method, glutaradehyde.

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INTRODUCTION

Drug delivery has metamorphosed from the concept of pill to molecular medicine in the past 100 years. Better appreciation and integration of pharmacokinetic and pharmacodynamic principles in design of drug delivery system has lead to improved therapeutic efficacy. Drug research has evolved and matured through several phases beginning with botanical phase of early human civilization, through to the synthetic chemistry age in the middle of 20th century and finally the biotechnology era at the dawn of 21st century

NOVEL DRUG DELIVERY SYSTEM

NDDSS evolved over a period of time to improve patient compliance and optimize the dosage regimen without compromising the therapeutic efficacy The foundation was laid in 1952, with the introduction of first sustained release capsule of Dexedrine. [1] Subsequently several concepts originated, including prolonged release, timed and extended release and finally matured to controlled release systems. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 μm [6]. They are made of polymeric waxy or other protective materials, biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, waxes and fats. Microspheres correspond to polymeric network in which the solid active substance is enclosed and microcapsules are constituted by liquid core with active substance on a polymeric wall [6].

MATERIALS AND METHODS

Exemestane is procured from Ranbaxy laboratories New Delhi. Ethyl cellulose purchased from Kemphasol, Mumbai. chitosan purchased from Nice chemicals, Cochin .and all other chemicals are A.R grade used as received

Preparation of Microspheres

A 4% solution of polymer [2] in 5% acetic acid containing 2% sodium chloride was prepared and 600 mg of this viscous solution was weighed, mixed with exemestane and dispersed in a mixture of 35 ml of liquid paraffin and 25 ml of petroleum ether containing 8ml of span-80 in a beaker at room temperature. The dispersion was stirred using a stainless steel half moon paddle stirrer at 2000 rpm for 5 min ,in addition to of glutaraldehyde saturated toluene,[2] which was introduced initially. The cross linking reaction was allowed to proceed for a total of 1.5 h. The hardened microspheres were then separated by centrifugation, washed four times with petroleum ether, once with acetone, three times with water, centrifuged, dried at room temperature and stored in a desiccator.

CHARACTERIZATION OF MICROSPHERES

Determination of drug content

Practical drug loading was determined by taking a weighed quantity of ethylcellulose microspheres (approximately 2.38 mg equivalent to Exemestane) were crushed in a glass mortar and pestle, and the powdered microspheres were suspended in 10 ml of sodium lauryl sulphate. After 24 hours, the solution was filtered and the filtrate was analyzed for the drug content. The drug entrapment efficiency was calculated using the following formula. [4]

$$\% \text{ yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer}} \times 100$$

Particle size determination

Optical microscope was used to determine the size of the particle that lies within a range from 10 to 40 μm and the particles were measured along an arbitrarily chosen fixed line across the center of the particle. The particle size is a factor to be considered important in formulation of microspheres [5]

Scanning electron microscope study

The microspheres were observed under a scanning electron microscope. The instrument used for this study was Hitachi S-450 scanning electron microscope. The microspheres were mounted directly on to the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

In-vitro release study

The drug release study was performed using USPXXIII basket apparatus (at 37^0C $\pm 0.5^0$C) and at 50 rpm using 900 ml of 0.5 sodium lauryl sulphate as a dissolution medium. Microspheres equivalent to 2 mg of Exemestane was used for the test. 5 ml of the sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µm membrane filter, and analyzed spectrophotometrically. Fresh media was replaced immediately, after each with drawl and % drug released at different time intervals was calculated. [5]

Kinetics of drug release

To study the mechanism of drug release from the matrix tablets, the drug release data were fitted to various kinetic models like zero-order, first order, and higuchi equation and coefficient of correlation (r) values were calculated for linear curves by regression analysis of the above plot. These models used to explain drug releaser mechanism due to swelling (upon hydration) along with gradual erosion of the matrix.

RESULT AND DISCUSSION

CHARACTERIZATION OF MICROSPHERES: % Yield of microspheres

Thoroughly dried microspheres were collected and weighed accurately. The   % yield was then calculated, it was found to be 53.33% w/w

Entrapment efficiency

All batches show percent entrapment more than 45% and it is found that entrapment of drug increases with an increase in the amount of the polymer. Formulation 6 shows maximum entrapment whereas formulation 1 shows minimum entrapment of the exemestane in the polymer as shown in table 1.

Particle size analysis

Results showed that particle size of prepared microspheres was in the range of 3.57 ±7.25 µm to 7.19 ±7.09 µm. It was concluded that with increase in polymer concentration, particle size of prepared microspheres increases as shown in table 2.

Scanning electron microscopy

The scanning electron microscopy of the microspheres was shown in figure 1 and 2. The most of the microspheres were spherical in shape and size ranges from 5-10 µm. Only some spheres were in large size. The size analysis of F5 of microspheres showed that about 75% were in the size range of 10 µm.

***In Vitro* Release Study Fig 7**

The *in vitro* study of microspheres was determined by using USPXXIII basket model containing dissolution medium as Sodium lauryl sulphate.

The increase in concentration of glutaraldehyde also affects the release rate of microspheres. The microsphere prepared with 10 ml of glutaraldehyde was released 98.08 of exemestane after 14 hrs. The microspheres prepared with 15 ml of glutaraldehyde were released 97.08 %. This is may be due to the increasing concentration of glutarldehyde that may cross link more amount of ethylcellulose. The microspheres prepared with 20ml of glutaraldehyde was released 98.34 at 24 hrs this it conclude that increasing concentration of glutaraldehyde above 20 ml may retain release rate of the drug.

From the result 600 mg of chitosan with 300 mg ethyl cellulose and 20 ml of glutaraldehyde shows that better release pattern compared to other formulation.

Kinetics of drug release

➢ The regression coefficient for the formulations. FM-1 of Zero order plots were found to be 0.981.
➢ The regression coefficient for the formulations. FM-1 of First order plots were found to be 0.9469.
➢ These results indicate that formulations FM-1 followed zero order kinetics. Graphical reprasentation of zero order and first order plots are shown in figures 4 and 5
➢ Figure 6 shows the plot of cumulative % drug released Vs.square root of time. It was observed that formulation FM-1, with regression coefficient of 0.97, followed Higuchi matrix suggesting diffusion controlled release.

CONCLUSION

In conclusion, it is possible to prepare microspheres containing Exemestane by glutaraldehyde cross linking method, to prolonged activity with increased stability without loosing its therapeutic activity.
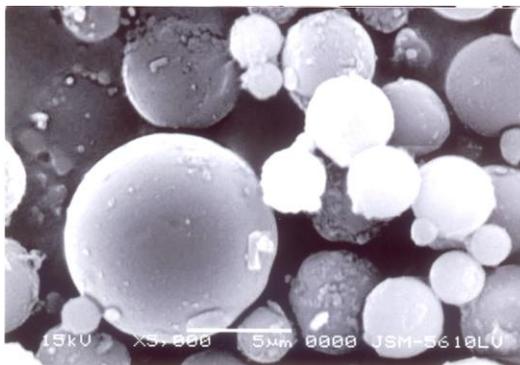
ACKNOWLEDGEMENT

PERCENTAGE OF ENTRAPMENT OF MICROSPHERES [Table no 1]

Sl.No	Formulations	Encapsulation efficiency %
1.	FM 1	49.19
2.	FM 2	51.59
3.	FM 3	60.76
4.	FM 4	61.65
5.	FM 5	63.76
6.	FM 6	65.99

SCANNING ELECTRON MICROSCOPY: Fig1 EXEMESTANE5000x
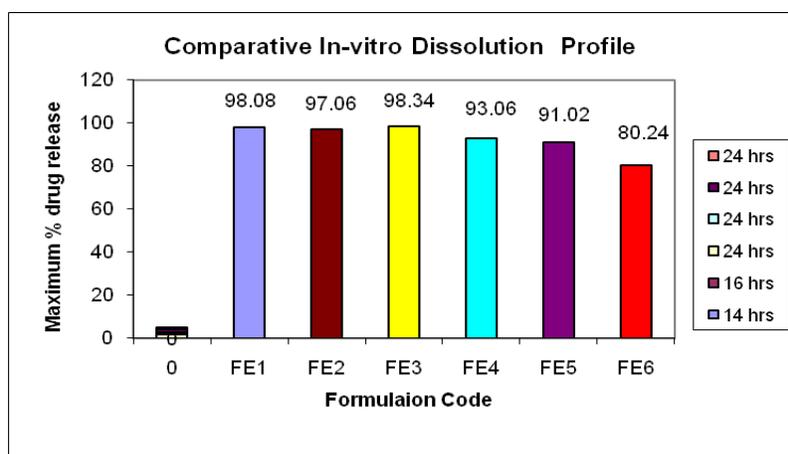
SCANNING ELECTRON MICROSCOPY: Fig 2.EXEMESTANE 2000x

THE ARITHMETIC MEAN SIZES OF MICROSPHERES OF EXEMESTANE Table no 2

Sl.No	Formulations	Particle size ±SEM µm
1	FM −1	3.57 ±7.25
2	FM −2	4.15 ±7.029
3	FM −3	4.47 ±6.99
4	FM −4	5.77 ±7.09
5	FM −5	6.01 ±7.08
6	FM −6	7.19 ±7.09

IN VITRO RELEASE STUDY Fig 3

KINETIC STUDIES OF EXEMESTANE MICROSPHERS
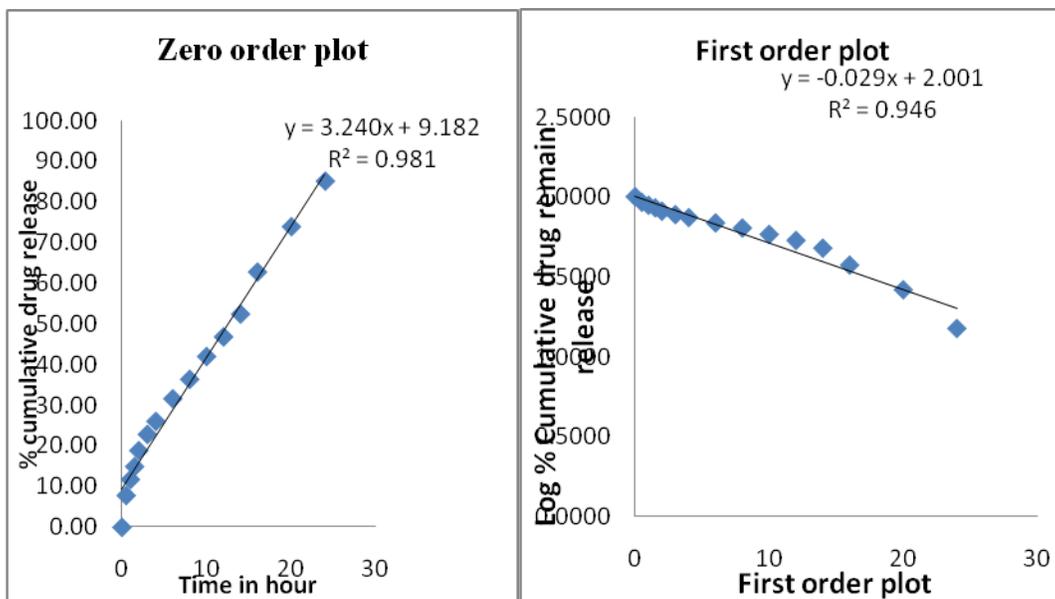
MECHANISM OF DRUG RELEASE EXEMESTANE MICROSPHERS
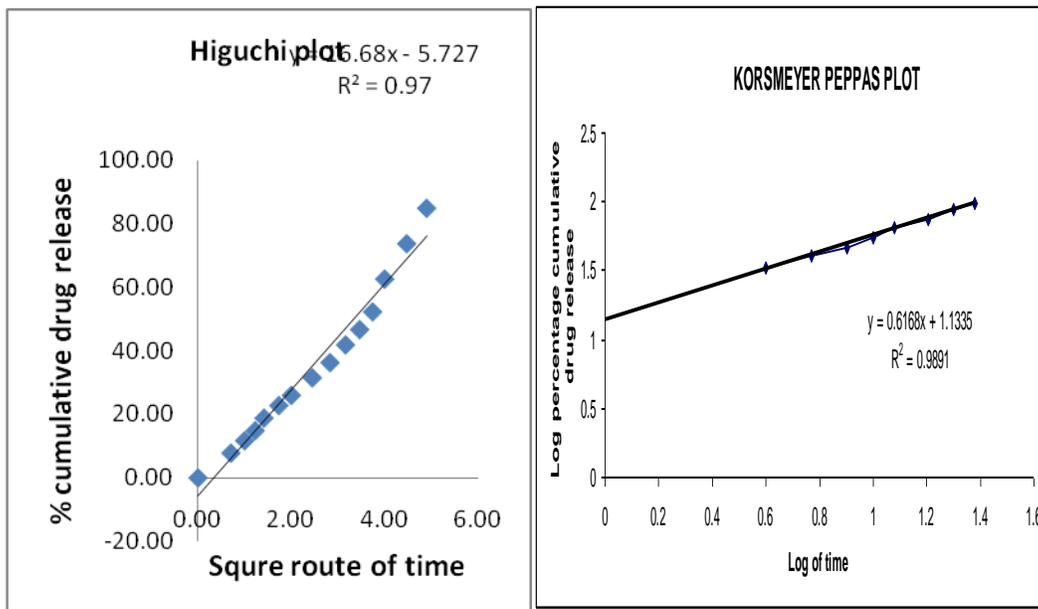

Fig.4

Fig.5

SWELLING CHARACTERISTICS MICROSPHERS

Fig 6

Fig 7

Formulation	Higuchic model		Korsmeyer peppas model	
	Slope	R^2	Slope	R^2
Exemestane microsphers	16.68	0.97	0.616	0.989

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