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Synthesis and Characterization of Sustained Release Atenolol Microspheres by Solvent Evaporation Technique

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Abstract

Atenolol is a cardio selective b-blocker, widely used in the management of hypertension, etc. The microparticles can be prepared by using any one of the several techniques but choice of the technique mainly depends on the nature of the polymer used, the drug and the duration of the therapy. In the present paper, a sustained release Atenolol microspheres synthesized by solvent evaporation method in which the different concentration ranges of Atenolol and ethyl cellulose polymer was taken. The reaction mechanism to form sustained release Atenolol microspheres were determined by optical microscopic method and evaluated by using FT-IR spectroscopy. The particle size of Atenolol ranged from 80 to 186 µm. The size of particle was observed to increase with increasing concentration. The present study shows a relatively simple method to design and develop sustained release Atenolol microspheres drug delivery system.

Key words: Atenolol, Adrenergic Agent, Microsphere, Solvent Evaporation Method

INTRODUCTION

Water insolubility has always been a key issue in pharmaceutical formulations, affecting formulation stability and drug bioavailability. Low oral bioavailability of poorly water soluble drugs poses a great challenge during drug development [1] Solubility is an essential factor for drug effectiveness, independent of administration route. It also poses a major challenge for pharmaceutical companies developing new pharmaceutical products, since nearly half the active substances being identified through the new paradigm in high throughput screening are either insoluble or poorly soluble in water. The number of drugs coming from synthesis and being poorly soluble is steadily increasing. At present about 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from synthesis are poorly soluble. A lot of research has been going on during the last two decades in developing adequate drug delivery systems for challenging drug candidates which belong to the classes II and IV of the biopharmaceutical classification system (BCS) and it gave birth to techniques used to solve solubility problems associated with poorly soluble drugs. [1, 2] Micronization is one of the ways to enhance solubility of drugs. Micronization results in decreased particle size and increased surface area. Noyes-Whitney equation explains that smaller the particle size, greater the surface area and more be the solubility and dissolution rate. However, it is important to note that it is not the absolute surface area but the effective surface area that is proportional to dissolution rate. Greater the effective surface area, more intimate the contact between the solid surface and aqueous solvent and faster the dissolution. But it is only when Micronization reduces size of particles below 0.1 microns that there is an increase in intrinsic solubility and dissolution rate of the drug. The surface of such small particles has energy higher than the bulk of solid resulting in an increased interaction with the solvent. E.g. Micronization of poorly water soluble drugs like griseofulvin and several salts of tetracycline results in superior dissolution rates in comparison to the simple milled form of the drugs. Based on their morphology, micro particles are classified into microspheres, microcapsules and micro emulsions.

EXPERIMENTAL

Materials and Methods

Atenolol drug (molecular weight is 266.336), Ethyl cellulose, Polyvinyl alcohol, Dichloro methane, Methanol was obtained from Loba chemie, Mumbai, All the chemicals were of analytical reagent grade and were employed without further purification. All experiments were carried out using Millipore Mili Q deionized and double distilled water. Concentration of the drug solutions were estimated using absorbance recorded on UV-VIS spectrophotometer model number Pharma spec 1700 (M/s Shimadzu Corporation, Kyoto, Japan) over the wavelength of 584 nm. A Three blade propeller stirrer (Remi Instrument Ltd, Mumbai) used for stirring purpose. As Optical microscope Model VJ – 2 Bik (Labo microscope) used for measurements of particle size.

Preparation of Sustained Release Atenolol Microspheres

The sustained release Atenolol microspheres synthesized by the method called solvent evaporation process. A typical procedure was as follows: drug Atenolol and polymer ethyl cellulose were dissolved in 10 ml of dichloromethane and methanol mixture which are present in the proportion of 8:2.Then the slurry was slowly introduced into 50ml of 0.5% w/v of polyvinyl alcohol while being stirred at 900 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature.

Table 1 Concentration Used For Preparation of Microspheres

Batch	*Drug (mg)*	*Polymer(mg)*
1	150	1000
2	150	500
3	150	100
4	100	1000
5	100	500
6	100	100
7	50	1000
8	50	500
9	50	100

The solution was stirred for 2 h to allow the solvent to evaporate completely and the microspheres were collected by filtration. The microspheres were filtered by using Whatman filter paper. The collected microspheres were dried for 1 h at room temperature and subsequently stored in desiccators over fused Calcium chloride. As concentration pattern used for preparation of microspheres as shown in table 1

Microspheres Studies

The particle size was determined by optical microscopic method. For each batch of the microspheres 100 particles were counted and recorded in triplicate. Practical yield also calculated. To evaluate the drug entrapment efficiency, a sample of 20 mg of equivalent to Atenolol was dissolved in 20 ml of distilled water. Then sonicated it and filter by Whatman fitter paper. The drug content of microspheres was determined spectrophotometrically at 273.5nm. In these conditions, used polymers do not interfere with Atenolol absorption.

RESULT AND DISCUSSION

Sustained Release Atenolol Microspheres Studies

Particle size analysis

It is clear from Table 2 that the spherical particles were obtained in all the batches. Clumping of the microspheres was observed in some of the batches. The particle size of microspheres prepared in this study was in the range of 80 to 186 µm. It was seen that as the amount of polymer and drug concentration increased in the microspheres the particle size also increased proportionally. The increase in particle size observed with increase in polymer and drug concentration was due to increase in viscosity of the droplets, which may have caused an increase in the interfacial tension. Further it was also observed that increase in the rate of stirring resulted in decreased particle size of microspheres.

Table 2 Particle Size

Batch	*Particle Size(Micrometer)*
1	185.15
2	83.96
3	80.33
4	87.42
5	89.56
6	123.08
7	150.71
8	178.69
9	98.37

Practical Yield

Solvent evaporation technique offers a versatile, easy and practical method for the manufacturing of sustained release Atenolol microspheres. The effect of different variables such as concentration of polymer and concentration of drug on physical characteristics of microspheres was evaluated. The physical characteristics of microspheres are as shown in table 3**.** Production yield expressed as percent yield with respect to initial amount of drug and polymer. The yield of solvent evaporation method is relatively high for Atenolol-ethyl cellulose microspheres, considering the preparation method employed. The loss of material during preparation of microspheres is due to process parameters as well as during filtration of microspheres.

Table 3 Percentage Practical Yield

Batch	*% Practical Yield*
1	66.26
2	57.69
3	30.00
4	70.92
5	60.56
6	21.36
7	73.33
8	65.00
9	43.33

Drug Entrapment Efficiency

The percentage drug entrapment was found to increase as the concentration of Atenolol and polymer increases. Highest drug entrapment was observed in case of batch 7. Increase in concentration of Atenolol in microspheres there is marginally increase in PDE. Increase in the polymer concentration may be attributed to increase in viscosity, which results in the formation of large microspheres, thus increasing the entrapment of drug which is shown in table 4

Table 4 Percentage Drug Entrapment

Batch	*Drug Entrapment (%)*
1	59.71
2	41.02
3	27.07
4	58.77
5	63.89
6	35.01
7	74.13
8	60.42
9	39.80

Characterization of sustained release Atenolol microspheres

FT-IR analysis

Figure 1 illustrates FT-IR spectrum was recorded on I. R. Affinity – 1 Schimazu apparatus using KBr discs in the range of 4000– 400 cm. FT-IR of sustained release Atenolol drug loaded microspheres are recorded. The IR spectra indicate that there is no interaction between Atenolol and polymers.

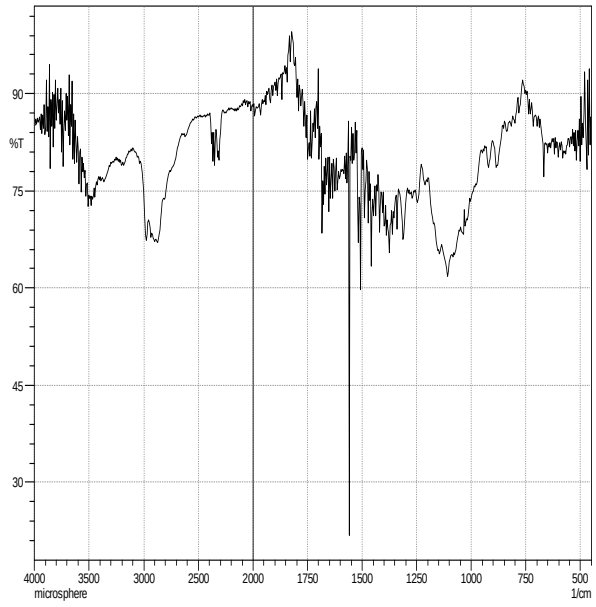

Figure 1. FT-IR of Microspheres

CONCLUSION

The microsphere of Atenolol has been successfully formulated using solvent evaporation technique. This technique offers an easy and practical method for manufacturing of sustained release microspheres. Morphology was studied while particle size of Atenolol microspheres obtained. It was observed that the size of microspheres is significantly affected by concentration of polymer and by stirring speed. Formulation variable such as concentration of Atenolol and concentration of polymer affect rate and extent of release of Atenolol from microspheres. The purpose of preparation of microspheres is achieved.

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