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PREPARATION AND EVALUATION OF MICROPARTICLES CONTAINING SOTALOL HYDROCHLORIDE FOR CONTROLLED RELEASE

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ABSTRACT
The present study aimed at preparation and Evaluation of microparticles for controlled release of Sotalol Hydrochloride in the treatment of Arrhythmia. Sotalol has both beta-adrenoreceptor blocking and cardiac action potential duration prolongation and antiarrhythmic properties. The microparticles of Sotalol Hydrochloride were prepared by solvent evaporation method .The prepared microparticles were evaluated for drug polymer compatibility, the results shown that there were no significant interactions. The encapsulation efficacy was ranging from 66-85%. The *in-vitro* drug release studies indicate the release of drug in a controlled manner over a period of 12 hrs. It was found that the Sotalol Hydrochloride release rate increased with a decreased amount of Ethyl Cellulose since the drug is water soluble. This can be adjusted by maintaining the concentration of the polymers. The formulation F4 was found to be optimum formulation.

KEYWORDS: Sotalol Hydrochloride, Arrhythmia, Ethyl Cellulose, Controlled release.

INTRODUCTION
The design of controlled-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drugs are very important for designing a sustained release dosage form mainly physicochemical and biological properties of the drug are most important.

Controlled drug delivery systems containing polymeric carriers has gained increased interest in last two decades, because they can be fabricated into films, rods capsules and microparticles[1] they mask the unacceptable taste or odor of drugs, they stabilize drugs sensitive to oxygen, moisture or light, they eliminate incompatibilities among drugs.

Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class I) and cardiac action potential duration prolongation (Vaughan Williams Class I) antiarrhythmic properties. Sotalol inhibits response to adrenergic stimuli by competitively blocking β1-adrenergic receptors within the myocardium and β2-adrenergic receptors within bronchial and vascular smooth muscle. The electrophysiologic effects of sotalol may be due to its selective inhibition of the rapidly activating component of the potassium channel involved in the repolarization of cardiac cells. The class II electrophysiologic effects are caused by an increase in sinus cycle length (slowed heart rate), decreased AV nodal conduction, and increased AV nodal refractoriness, while the class III electrophysiological effects include prolongation of the atrial and ventricular monophasic action potentials, and effective refractory period prolongation of atrial muscle, ventricular muscle, and atrio-ventricular accessory pathways (where present) in both the anterograde and retrograde directions.[2] Here an attempt was made to reduce the dosing frequency and to maintain the drug level at therapeutic concentration range, by formulating a Controlled drug delivery system in the form of microparticles using blend of hydrophilic and lipophilic polymers.

METHODS
Determination of λ max of Sotalol Hydrochloride in pH 7.4 buffer
Stock solution of Sotalol Hydrochloride in pH 7.4 buffer (100 mg in 100 ml) was prepared. From the stock solution 30 µg /ml solution of was prepared in pH 7.4 buffer and scanned between the wavelength of 200-400 nm.[3]

Preparation of microparticles

Sotalol Hydrochloride microparticles were prepared by solvent evaporation method. Different ratios of HPMC and Ethyl cellulose combination were dissolved in 8.5 ml acetone separately and dispersed by using a magnetic stirrer. The core material, Sotalol Hydrochloride was added to the polymer solution and mixed for 15 minutes, followed by magnesium stearate (100mg) and then mixed thoroughly. The resulting dispersion was added in a thin stream to a mixture of 90 ml light liquid paraffin and 10 ml n-hexane contained in a 250 ml beaker, while stirring at 700 rpm using a mechanical stirrer. Stirring was continued for 3 hrs until the acetone evaporated completely. The microspheres formed were filtered using Whatman no.1 filter paper. The residue was washed 4-5 times with 50 ml portions of n-hexane. The product was then dried at room temperature for 24 hours.

Ingredients in (mg/ml)			
Formulation No.	**Sotalol Hydrochloride**	**Ethyl Cellulose**	**HPMC**
F1	25	20	15
F2	25	20	20
F3	25	30	15
F4	25	30	20
F5	25	10	15
F6	25	15	15

Differential Scanning Calorimetry (DSC)

DSC is a technique in which the difference in heat flow between the sample and a reference is recorded versus temperature. All dynamic DSC studies were carried out on Du Pont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with empty cell as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10º C/Min. The runs were made in triplicate. The scanning temperature for reference pure drug and formulation are the same when dynamic measurements are performed, and hence the required heat energy for chemical transformation is directly recorded on a heat flow versus temperature graph. The energy is measured as Joules per kilocalorie.[5,6]

Drug loading and encapsulation efficiency

100 mg of microparticles were weighed and transferred to 100 ml volumetric flask containing pH 7.4 phosphate buffer. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution was diluted to 10 ml and absorbance was measured. The drug content was calculated by using the formula.[7,8]

Amount of drug =

$$\frac{\text{Conc. from standard graph X dilution factor}}{1000}$$

Percentage encapsulation efficiency is found out by calculating the amount of drug present in 100 mg of microparticles. It is further calculated by using formula.

% Encapsulation Efficiency = b/a X100.

Where, '**a**' is the theoretical drug content and 'b' is the drug entrapped.

In vitro drug release studies

Release of Sotalol Hydrochloride was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 900 ml of 0.1 N HCl, phosphate buffer 5.5, phosphate buffer pH 7.2. The temperature was maintained at 37±0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time intervals and replaced with fresh media immediately after sampling. Samples were analyzed for drug content by UV Visible spectroscopy.[9,10]

RESULTS AND DISCUSSION

Ultraviolet spectroscopy

Accurately weighed 10 mg of Sotalol Hydrochloride was transferred to a 100 ml volumetric flask and 1% tween80 was added to increase the solubility of Sotalol Hydrochloride (stock solution). 3ml of stock solution was added to the 50ml volumetric flask and volume adjusted up to the mark with phosphate buffer. The scanning was done from 200-400 nm. The sharp peak was observed at 247.0 nm, which was taken as λ max.

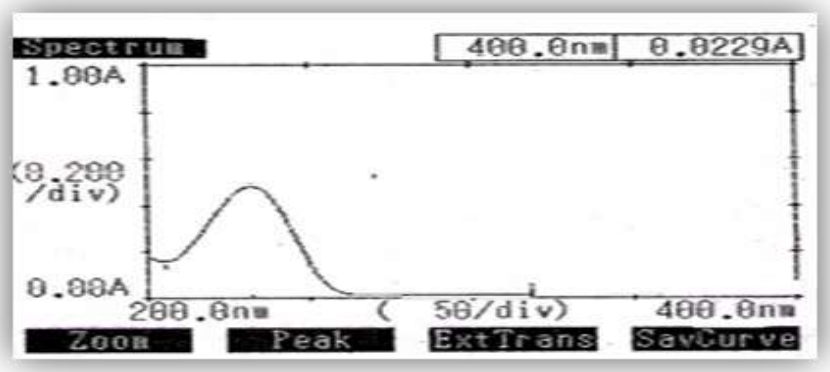

Fig 1: UV absorption spectra of Soalol hydrochloride chloride

Drug-excipient Compatibility Studies

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. The DSC thermograms of the pure drug and formulation were taken, the obtained results indicates that there were no significant interactions between drug and polymer.

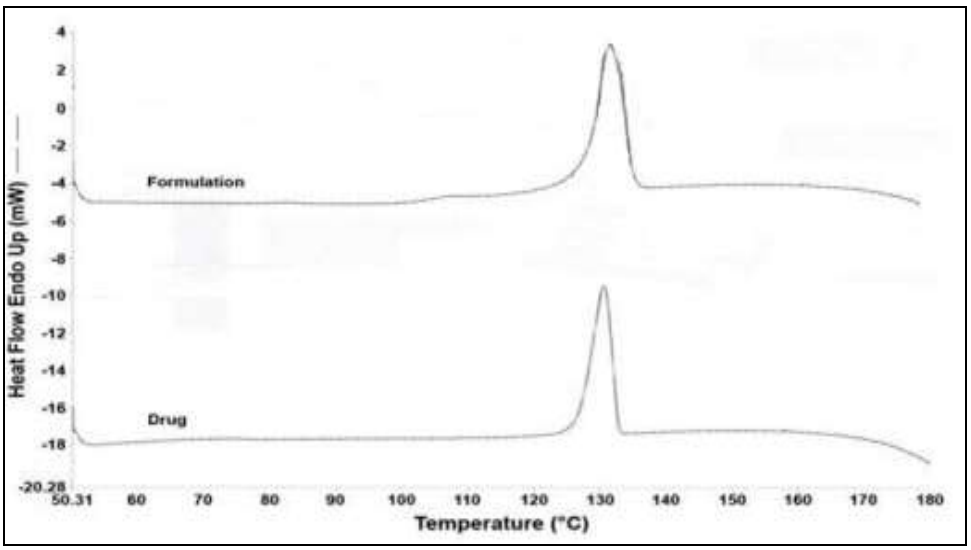

Fig 2: DSC Thermograms of pure drug and the formulation.

Drug loading and encapsulation efficiency

The test for drug content was carried out to ascertain uniform distribution of the drug in the formulation. Drug loading and entrapment efficiency increase with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Sotalol Hydrochloride in the microparticles and the deviation is within the acceptable limits. The decrease in the drug content in the product probably can be due to the loss of drug with the evaporation of the solvent.

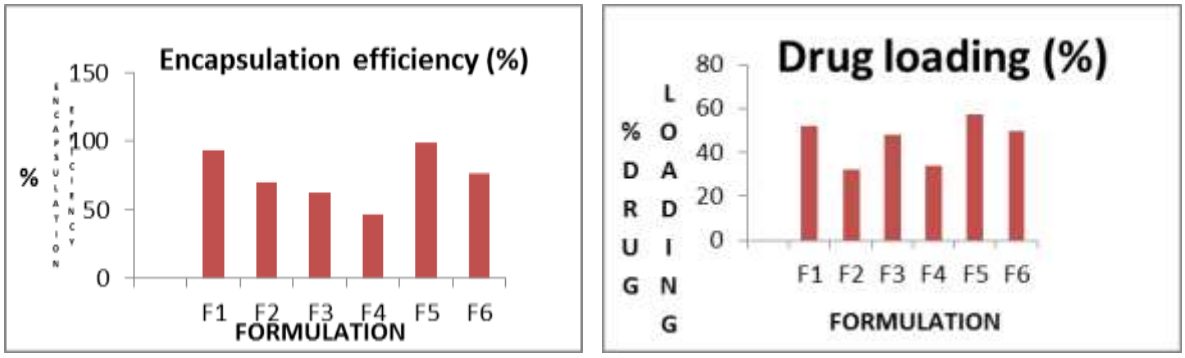

Fig 3: Drug loading and encapsulation efficiency of prepared microparticles.

In- vitro drug dissolution

Release of Sotalol Hydrochloride was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 900 ml of 0.1 N HCl, phosphate buffer 5.5, phosphate buffer pH 7.2. The temperature was maintained at 37±0.5°C. The sample were withdrawn at different time intervals 1,2,3,4,6,8,10 and 12 hrs filtered through whatman filter paper and replaced equal volume of dissolution medium. Sample was suitably diluted and analyzed for Sotalol Hydrochloride using UV-visible spectrophotometer. The percentage of Sotalol Hydrochloride release was calculated.

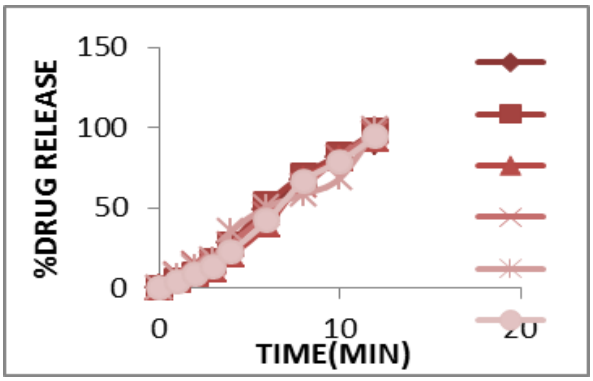

Fig 4: *In-vitro* drug release profile of the formulations.

CONCLUSION

The objective of this study was to prepare and evaluate microparticles loaded with Sotalol Hydrochloride for controlled release using different ratios of drug to polymer and prepared microparticles were characterized. The method is simple, rapid, and economical and does not imply the use of toxic organic solvents. The method used was suitable for both water-soluble and insoluble drugs. The formulation (F5) produced discrete spherical microparticles. The DSC thermogram obtained for the pure drug and formulation shows no significant shift in the endothermic peaks confirming the stability of the drug in the formulation. From the results of drug loading and encapsulation efficiency, it can be inferred that there was a proper and uniform distribution of drug in the micro particles. The *in vitro* drug release data showed the release of a drug in a controlled manner

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