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PREPARATION AND EVALUATION OF MICROPARTICLES CONTAINING SOTALOL HYDROCHLORIDE USING NATURAL POLYMERS FOR CONTROLLED RELEASE

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ABSTRACT
The present study aimed at preparation and Evaluation of microparticles for controlled release of Sotalol Hydrochloride using natural polymers 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 ionic cross linking 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 67-98%. 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 Guar gum since the drug is water soluble. This can be adjusted by maintaining the concentration of the natural polymers. The formulation F5 was found to be optimum formulation.

KEYWORDS: Sotalol Hydrochloride, Arrhythmia, guar gum, Xanthan gum Controlled release.

INTRODUCTION
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 natural polymers.

METHODS
Preparation of microparticles
The microspheres were prepared by ionic cross-linking technique. The alginate solution comprising 2.5% sodium alginate, 0.25-0.75% hydrophilic polymer and 100mg of drug were prepared by initially dissolving the polymer in 50% deionized water using gentle heat. On complete dissolution the weighed quantity of drug was add mixed thoroughly and to this solution of sodium alginate were added to afford homogeneous dispersion. The dispersion was added drop wise via 20 gauge hypodermic needle fitted with a 10ml syringe into 50ml 5%w/v of cross linking agent (Calcium chloride) solution, being stirred at 200rpm for 10min. The droplets from the dispersion instantaneously gelled into discrete drug-polymer-alginate matrices upon contact with the solution of cross-linking agent. The formed microspheres were further allowed to stir in the solution of cross-linking agent for an additional of 2hrs. On expiration, cross-linking agent was decanted and microspheres were washed with 3 x 50ml volume of deionized water. The microspheres were there after dried at 80˚C for 2hrs in a hot air oven.

Table 1: Formulation chart of Sotalol Hydrochloride microparticles using natural polymers.

	Ingredients in (mg/ml)				
Formulation No.	**Sotalol hydrochloride**	**Sodium Alginate (% w/v)**	**Guar Gum (% w/v)**	**Xanthan Gum (% w/v)**	**Calcium Chloride (% w/v)**
F1	25	2.5	0.25	-	5
F2	25	2.5	0.50	-	5
F3	25	2.5	0.75	-	5
F4	25	2.5	-	0.25	5
F5	25	2.5	-	0.50	5
F6	25	2.5	-	0.75	5

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 = 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

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 formulateon. 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.

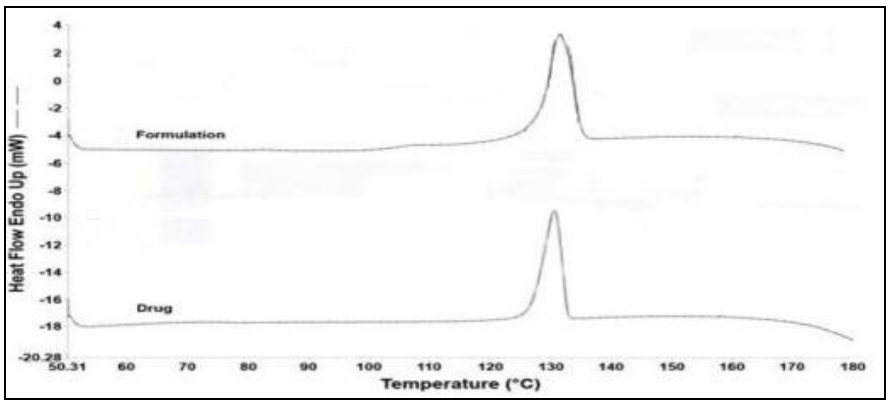

Figure 1: DSC Thermograms of pure drug and the formulation.

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.

Table 2: Drug loading and encapsulation efficiency of prepared microparticles.

Formulation	Drug loading (%) mean ± SD*	Encapsulation efficiency (%) mean ± SD*
F1	51.74±0.28	93.23±0.38
F2	32.23±0,18	70.43±0.28
F3	47.68±0.24	67.80±0.24
F4	33.85±0.21	46.41±0.17
F5	57.38±0.29	98.96±0.21
F6	49.82 ±0.27	76.36 ±0.19

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.

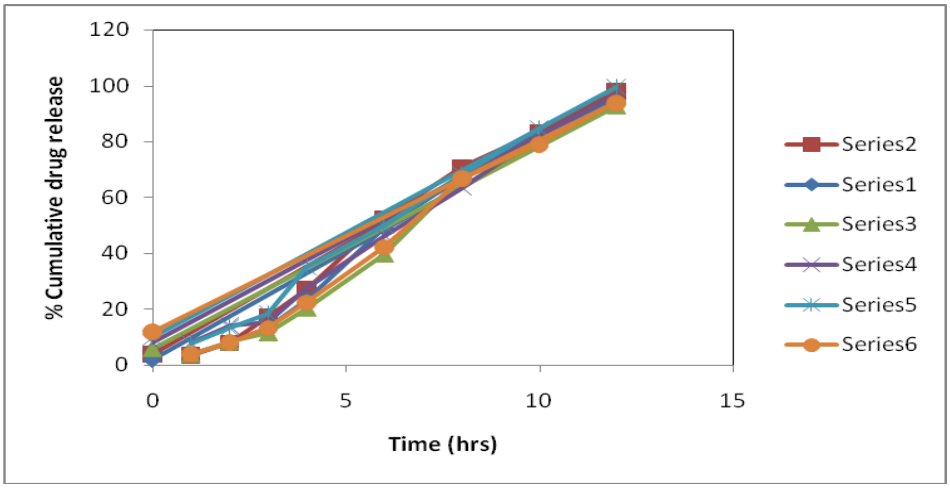

Figure 2: *In-vitro* drug release profile of the formulations.

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 natural polymers 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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