International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
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FORMULATION AND EVALUATION OF IVABRADINE HYDROCHLORIDE LOADED ETHYL CELLULOSE MICROSPHERES

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ABSTRACT

The present work was to formulate and evaluate Ivabradine HCl (IBH) microspheres using ethyl cellulose with the aim to get the best possible drug- polymer ratio giving the sustained drug release. Solvent evaporation technique was used for preparation of microspheres. The prepared IBH microspheres were then subjected to FTIR, SEM, particle size and size distribution, % yield, % drug loading, entrapment efficiency, in vitro dissolution studies, release kinetics and DSC. Different concentration of ethyl cellulose polymer was used to maintain a suitable lag period. The FTIR Spectras revealed that, there was no drug-polymer interaction. The spherical nature of IBH microspheres was confirmed by SEM. Microspheres with normal frequency distribution were obtained. A maximum of 86.20% drug entrapment efficiency was obtained in the drug loaded microspheres. The in-vitro dissolution data maximum of 90.40 % cum. drug release was obtained in the IBH loaded microspheres. The in-vitro performance of IBH microspheres showed that sustained release was dependent upon the polymer concentration. The co-efficient of determination indicated that the release data was best fitted with zero order kinetics. The present study conclusively demonstrates the feasibility of effectively encapsulating Ivabradine HCl into ethyl cellulose microspheres to form potential sustained release drug delivery system. On comparing the dissolution data of all the formulation, the best release was obtained from CF1 formulation, therefore it can be concluded that among all four drug:polymer ratios, CF1 is the best suitable formulation.

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KEYWORDS : *Ivabradine HCl; sustained drug delivery; ethyl cellulose microspheres; solvent evaporation method.*

INTRODUCTION

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. Microspheres carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems[1-3]. They have varied applications and are prepared using assorted polymers[4]. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes[5-8]. Ivabradine is a specific heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node. Within the sinoatrial node, IBH is a selective inhibitor of I_f, an important current involved in generating the early phase of spontaneous diastolic depolarisation in pacemaker cells, thereby reducing the frequency of action potential initiation and lowering heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intra-ventricular conduction times, nor on myocardial contractility or ventricular repolarisation or coronary vasomotricity.[9] Hence, there is a need to develop an oral drug delivery system that is convenient for patients. The objective of the present investigation was to develop an extended and controlled release composition and formulation of IBH using ethyl cellulose polymer to reduce dose/dosing frequency in the angina pectoris.

MATERIALS AND METHODS

Materials

IBH was received as a gift sample from Ind. Swift, Jammu, India. Ethyl cellulose, paraffin liquid light, ethanol was obtained from S D fine-chem limited, Mumbai. Tween 80 was obtained from Central drug house (p) Ltd, Mumbai. All other solvents and chemicals used were of analytical grade. FTIR spectroscopy was performed on Fourier transform infrared spectrophotometer (IR Affinity-1, Shimadzu, Japan).

Preparation of Microspheres[10]

Ethyl Cellulose microspheres were prepared by solvent evaporation method. In this method 10ml of dichloromethane and methanol in 1:1 ratio was taken and various drug: polymer ratios (1:1, 1:2, 1:3, and 1:4) were added simultaneously. This above solution was dispersed drop wise in a separate 200ml beaker containing 100ml of liquid paraffin and 0.5ml of span 80. The stirring speed was 1000rpm and stirring was carried out for 30 minutes. Then later obtained microspheres were washed with petroleum ether and dried.

EVALUATION OF MICROSPHERES

Drug polymer interaction (FTIR) study

The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm-1. FTIR study was carried on IBH, physical mixture of IBH and polymer, IBH microspheres (Fig.1 to Fig.4).

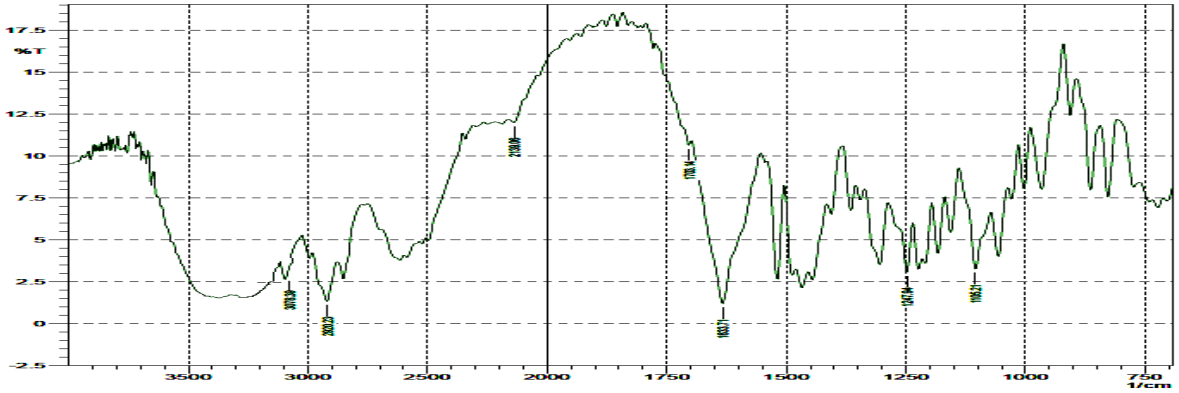

Fig.1: IR Spectrum of Ivabradine Hydrochloride (pure drug)

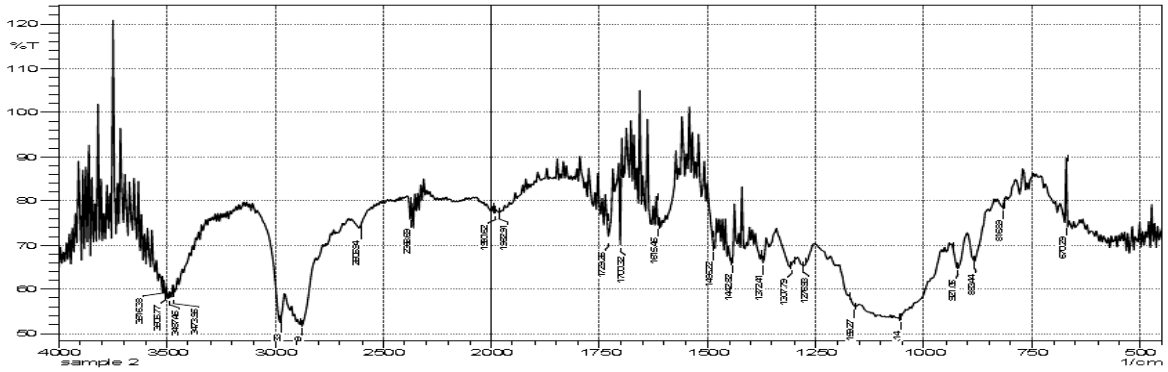

Fig.2: IR Spectrum of ethyl cellulose (polymer)

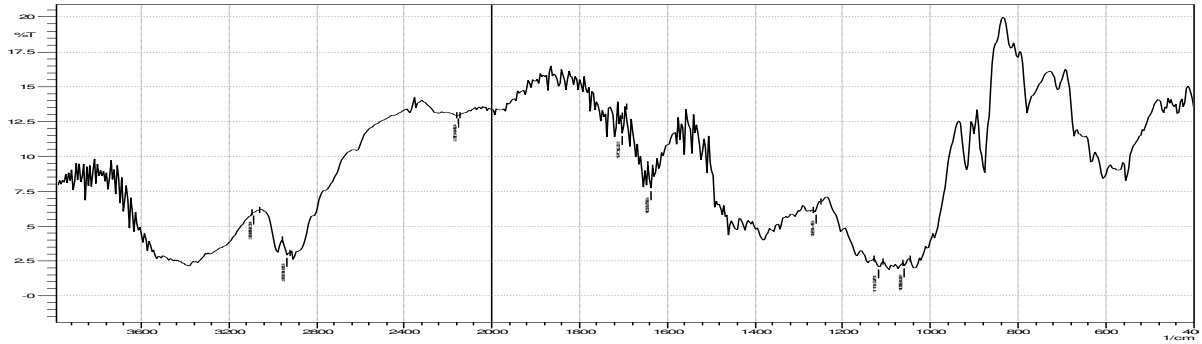

Fig.3: IR Spectrum of physical mixture of IBH and Ethyl cellulose

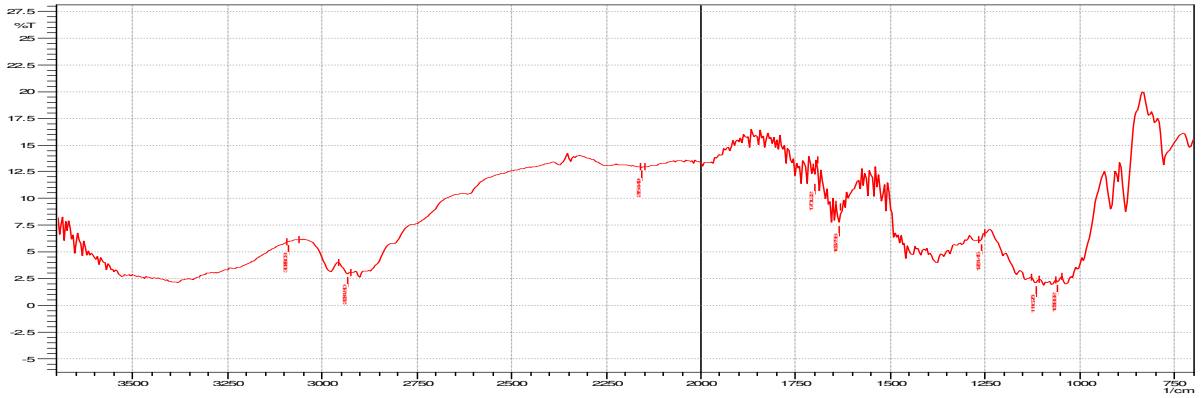

Fig.4: IR Spectrum of IBH loaded ethyl cellulose microspheres

Scanning electron microscopy (SEM) [11]

Scanning electron microscopy has been used to determine particle size distribution, texture and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry IBH microspheres were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of IBH microspheres were taken by random scanning of the stub.(Fig.5)

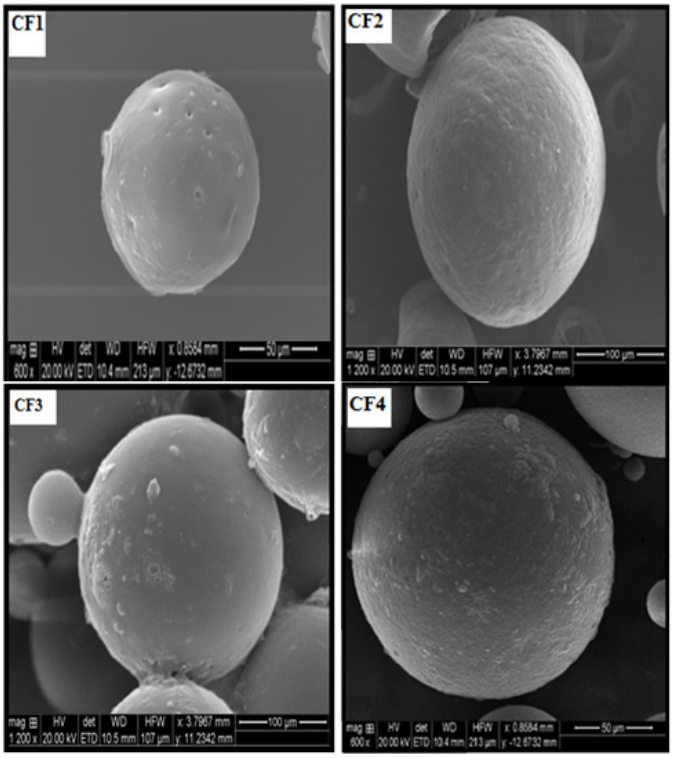

Fig. 5: SEM photographs of IBH loaded Ethyl cellulose microspheres: CF1(1:1 ratio); CF2 (1:2 ratio); CF3 (1:3 ratio); CF4 (1:4 ratio)

Percentage yield

Determining whether the preparation procedure chosen for incorporating a drug into the polymers is efficient and is of prime importance. The raw materials, amount of active compound, polymer and other process parameters are deciding factors for the yield of the product during the preparation of microspheres. The yield was determined by weighing the microspheres and then finding out the percentage yield with respect to the weight of the input materials, i.e., weight of drug and polymers used.

The formula for calculation of % yield is as follows;

The percentage yield of prepared Ivabradine Hydrochloride microspheres was determined by using the formula:

$$\% \text{ yield} = \frac{\text{wt. of microparticles}}{\text{wt. of drug} + \text{wt. of polymers}} \text{ X } 100$$

Percentage drug entrapment efficiency (PDE) [12, 13]

Drug loading is important with regard to release characteristics. Generally, increased drug loading leads to an acceleration of the drug release. Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the microparticles.(Fig.6)

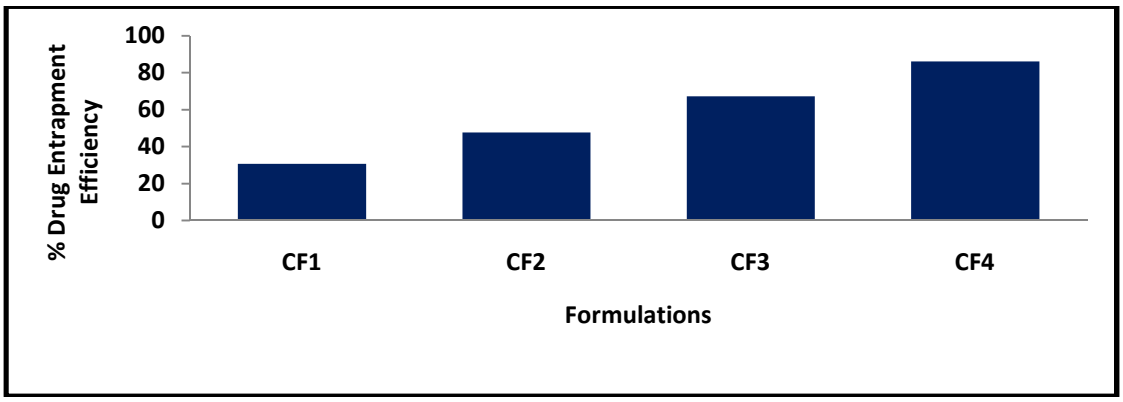

Fig. 6: Percentage drug entrapment efficiency

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula:

$$\text{PDE} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

***In vitro* dissolution studies**

The *in vitro* release of drug from the microparticles was carried out in basket type dissolution tester USP XXIII, TDT-08L, with auto sampler containing 500 ml of pH 1.2 buffer for the first 2 hrs and in 7.4 pH phosphate buffer for the next 10 hrs. The volume of the dissolution media was maintained at 500 ml with constant stirring (50 rpm) and temperature of bath 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 (Shimadzu UV 1601).The release data obtained were fitted into various mathematical models. Dissolution studies were carried out for all the batches of the prepared formulations.(Fig.7)

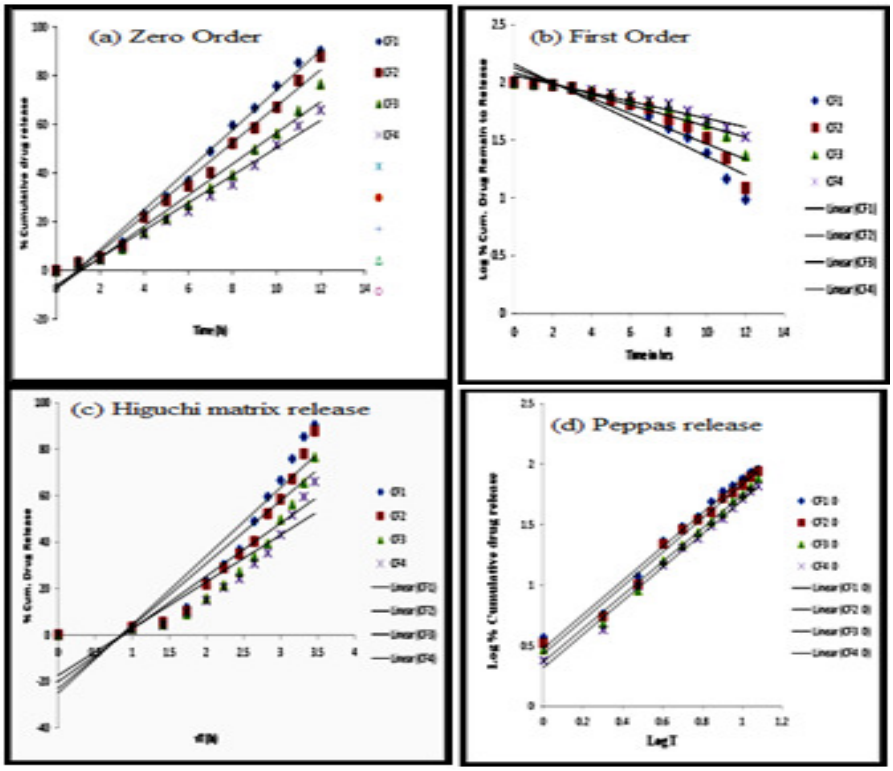

Fig. 7: *In vitro* release kinetics profile of IBH microspheres. (a) In vitro drug release was tested for Zero order; (b) first order; (c) Higuchi; (d) Peppas release in pH 1.2 for 2 hrs and changes to pH 7.4 from 2 to 12 hrs

Differential Scanning Calorimetry (DSC) [14]

The physical state of IBH in the microspheres was analyzed by Differential Scanning Calorimeter (Mettler-Toledo star 822[e] system, Switzerland). The thermograms of the IBH, physical mixture of IBH and polymer, IBH microspheres and blank microspheres were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25–300°C, respectively.(Fig.8)

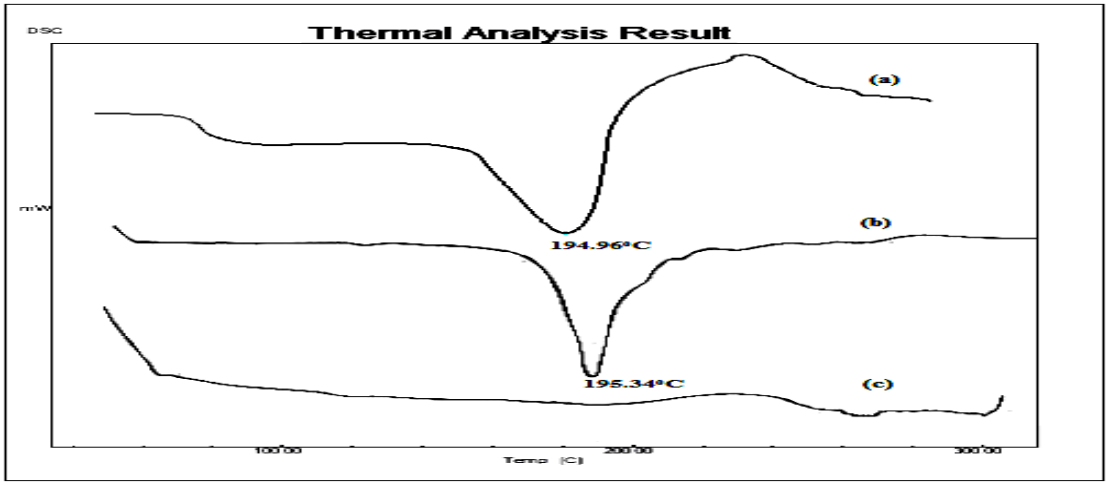

Fig.8: DSC thermogram of (a) IBH, (b) IBH loaded Ethyl cellulose microspheres, (c) blank Ethyl cellulose microspheres

Parameters		CF1	CF2	CF3	CF4
% Yield		81.74	84.21	88.37	90.28
Drug Content %		15.32	15.86	16.80	17.24
Drug Encapsulation Efficiency (%)		30.61	47.62	67.26	86.20
Avg. Particle Size (µm)		72.20	77.28	86.10	128.33
Zero order		0.9805	0.9814	0.9714	0.9769
First order		0.0455	0.0788	0.1410	0.1751
Higuchi		0.8511	0.8412	0.8183	0.8307
Peppas model	r^2	0.9608	0.9651	0.9731	0.9791
	n	1.7402	1.7087	1.6392	1.6108

Table 1: Percentage yield, drug content, encapsulation efficiency and average particle of Ivabradine Hydrochloride microspheres and Diffusion exponent (n) of Peppas model and Regression coefficient (r^2) of Ivabradine Hydrochloride release data from microspheres according to different kinetic models.

RESULT AND DISCUSSION

In the present work controlled release microspheres of Ivabradine hydrochloride were formulated using ethyl cellulose polymer by solvent evaporation technique. 4 batches prepared with different polymer ratios were evaluated for physical properties like FTIR, SEM, particle size, Percentage yield, percentage drug content, encapsulation efficiency, *in vitro* dissolution, release kinetics and DSC of Ivabradine hydrochloride microspheres.

ACKNOWLEDGEMENT

Authors are thankful to Dr. T. Tamizh Mani Principal, Bharathi College of Pharmacy for his support & encouragement in carrying out this work.

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