FORMULATION AND EVALUATION OF IVABRADINE HYDROCHLORIDE LOADED EUDRAGIT L-100 MICROSPHERES

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Abstract : The present work is to formulate and evaluate Ivabradine HCl (IBH) microspheres using Eudragit L-100 with the aim to get the best possible drug- polymer ratio giving the sustained drug release. IBH loaded Eudragit L-100 microspheres were prepared by Emulsification – solvent evaporation method. Various evaluation parameters were assessed, with a view to obtain sustained release of drug. 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 Eudragit L-100 polymer was used to maintain a suitable lag period. The FTIR Spectras revealed that, there was no interaction between the polymer and drug. IBH microspheres were spherical in nature, which was confirmed by SEM. Microspheres with normal frequency distribution were obtained. A maximum of 85.80 % drug entrapment efficiency was obtained in the drug loaded microspheres. The *in-vitro* dissolution data maximum of 91.71% 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 DSC pattern shows that there was decrease in the crystallinity of the IBH. The present study conclusively demonstrates the feasibility of effectively encapsulating IBH into Eudragit L-100 microspheres to form potential sustained release drug delivery system. On comparing the dissolution data of all the formulation, the best release was obtained from LF1 formulation, therefore it can be concluded that among all four drug: polymer ratios, LF1 is the best suitable formulation of IBH microspheres as a sustained drug delivery system.

KeyWords: Ivabradine HCl; sustained drug delivery; Eudragit L-100 microspheres; natural polymers; Emulsification – solvent evaporation method.

I. INTRODUCTION

A 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 Eudragit L-100 polymer to reduce dose/dosing frequency in the angina pectoris.

II. MATERIALS AND METHODS

II.a. Materials

IBH was received as a gift sample from Ind. Swift, Jammu, India. Eudragit L-100, paraffin liquid light was obtained from S D fine-chem limited, Mumbai. Tween 80, gluteraldehyde solution 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).

II.b. Preparation of microspheres[10]

Microspheres were prepared by Emulsification – solvent evaporation method. In this method a solution of albumin in 25ml of acetone was prepared and the drug was added to the Eudragit L-100 solution. The formulation was carried out with 1:1, 1:2, 1:3, 1:4 drug: polymer ratios. The contents were slowly added to a beaker containing 100 ml of preheated (35ºC) liquid paraffin containing 0.5ml of span 80 as emulsifying agent and stirred at 1000 rpm for 30minutes to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth walled, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with petroleum ether (40-60ºC), three times and dried at room.

III. EVALUATION OF MICROSPHERES

III.a. 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).

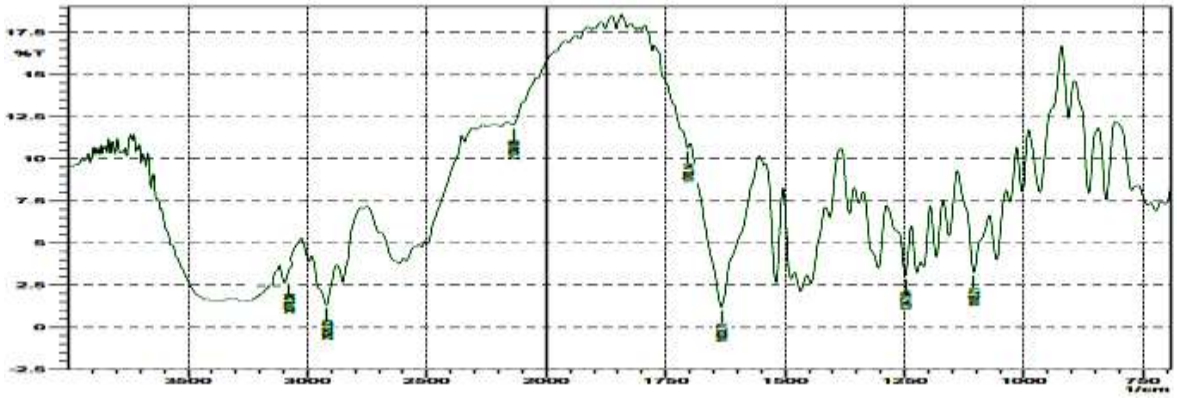

Fig.1 IR Spectrum of Ivabradine Hydrochloride

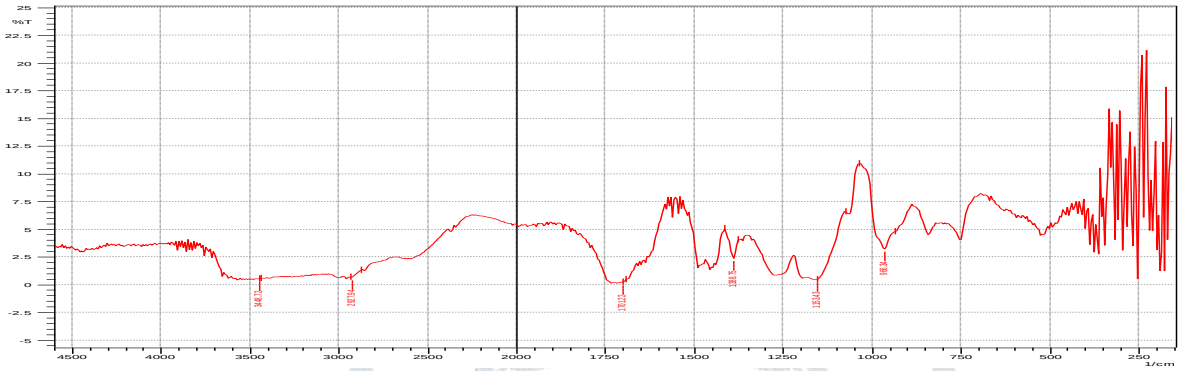

Fig. 2 IR Spectrum of Eudragit L100

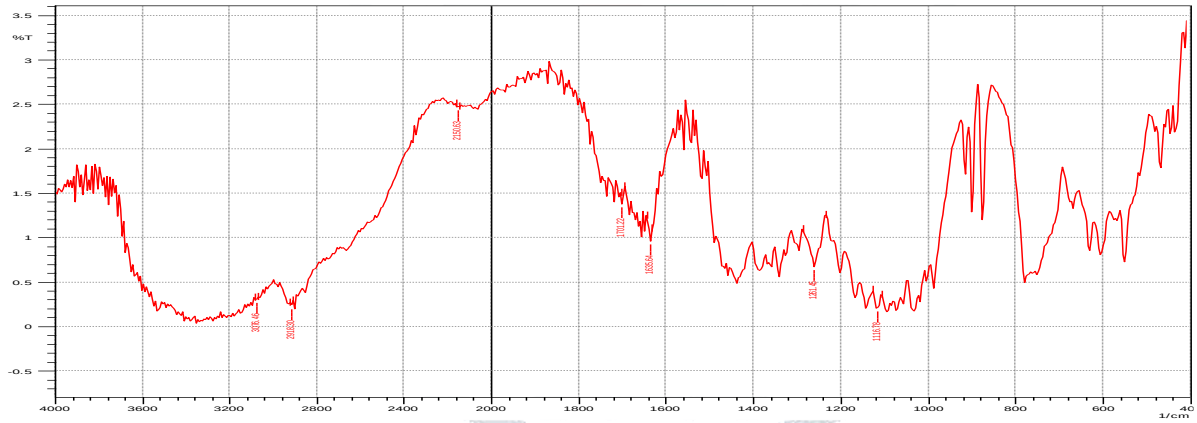

Fig. 3 IR Spectrum of physical mixture of IBH and Eudragit L-100

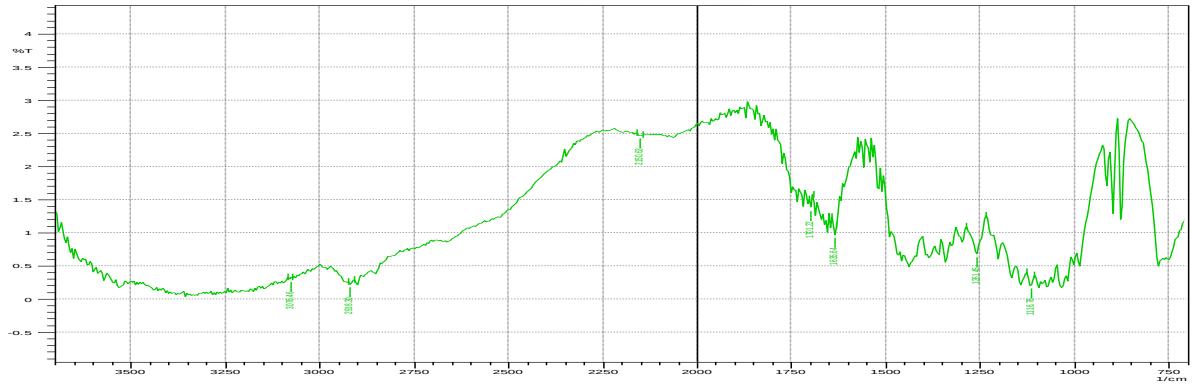

Fig. 4 IR Spectrum of IBH loaded EL-100 microspheres

III.b. 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)

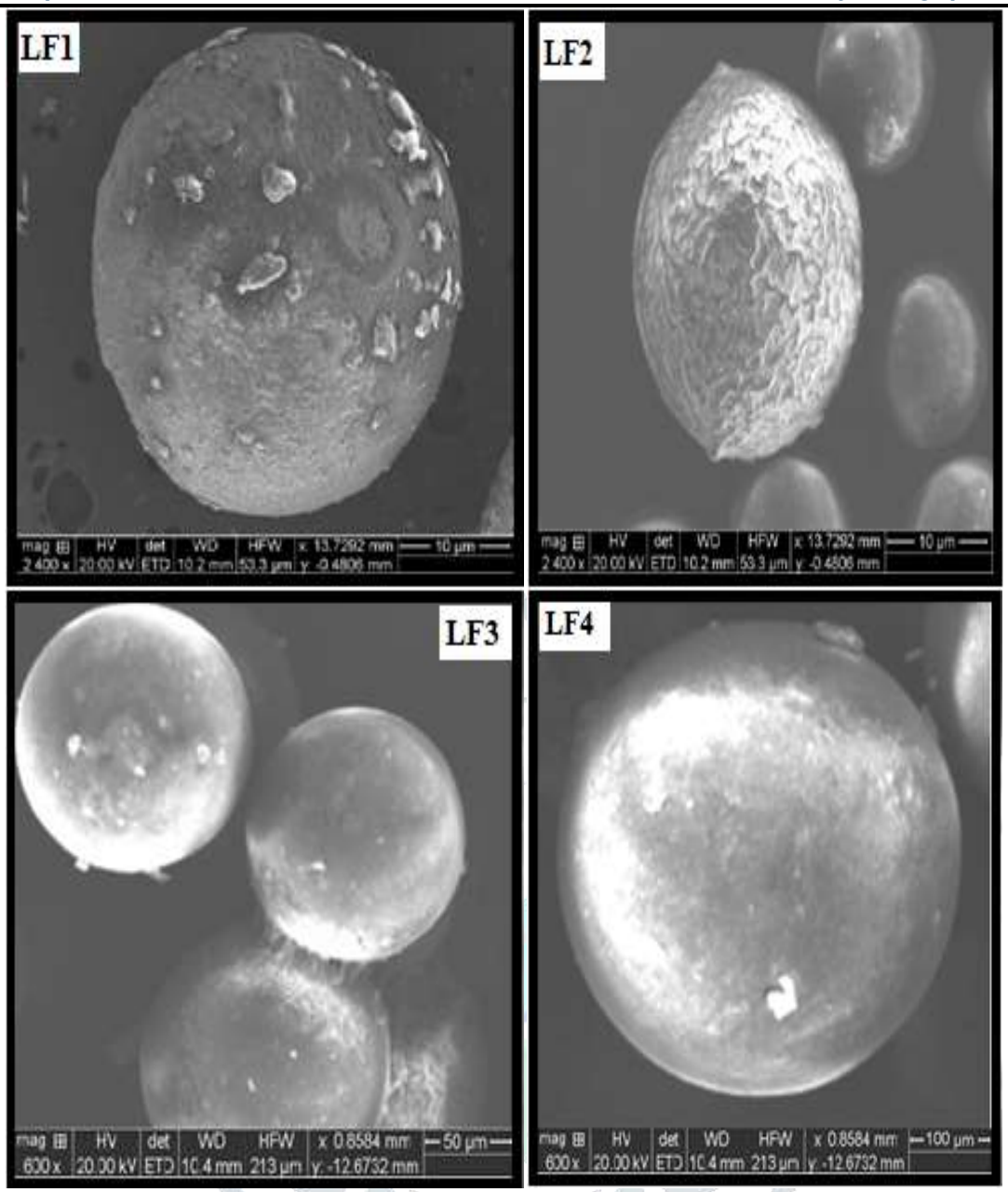

Fig. 5: SEM photographs of IBH loaded Eudragit L-100 microspheres: LF1(1:1 ratio); LF2 (1:2 ratio); LF3 (1:3 ratio); LF4 (1:4 ratio)

III.c. 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(s) 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:

$$\%\ Yield = \frac{wt.of\ microparticles}{wt.of\ drug + wt.of\ Polymers} \times 100$$

III.d. Percentage drug entrapment efficiency (PDE) [12]

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)

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

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

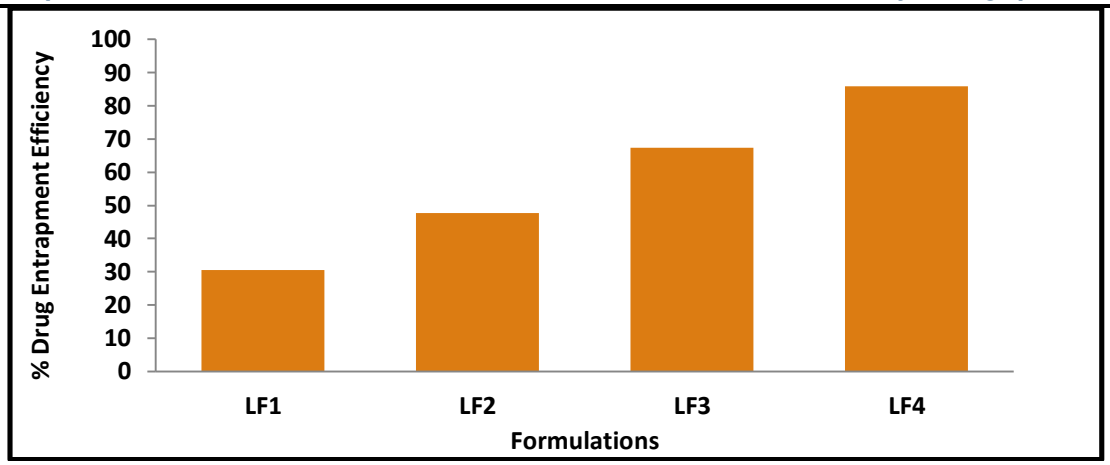

Fig.6: Drug entrapment efficiency of IBH loaded EL-100 microspheres

***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)(Table1)

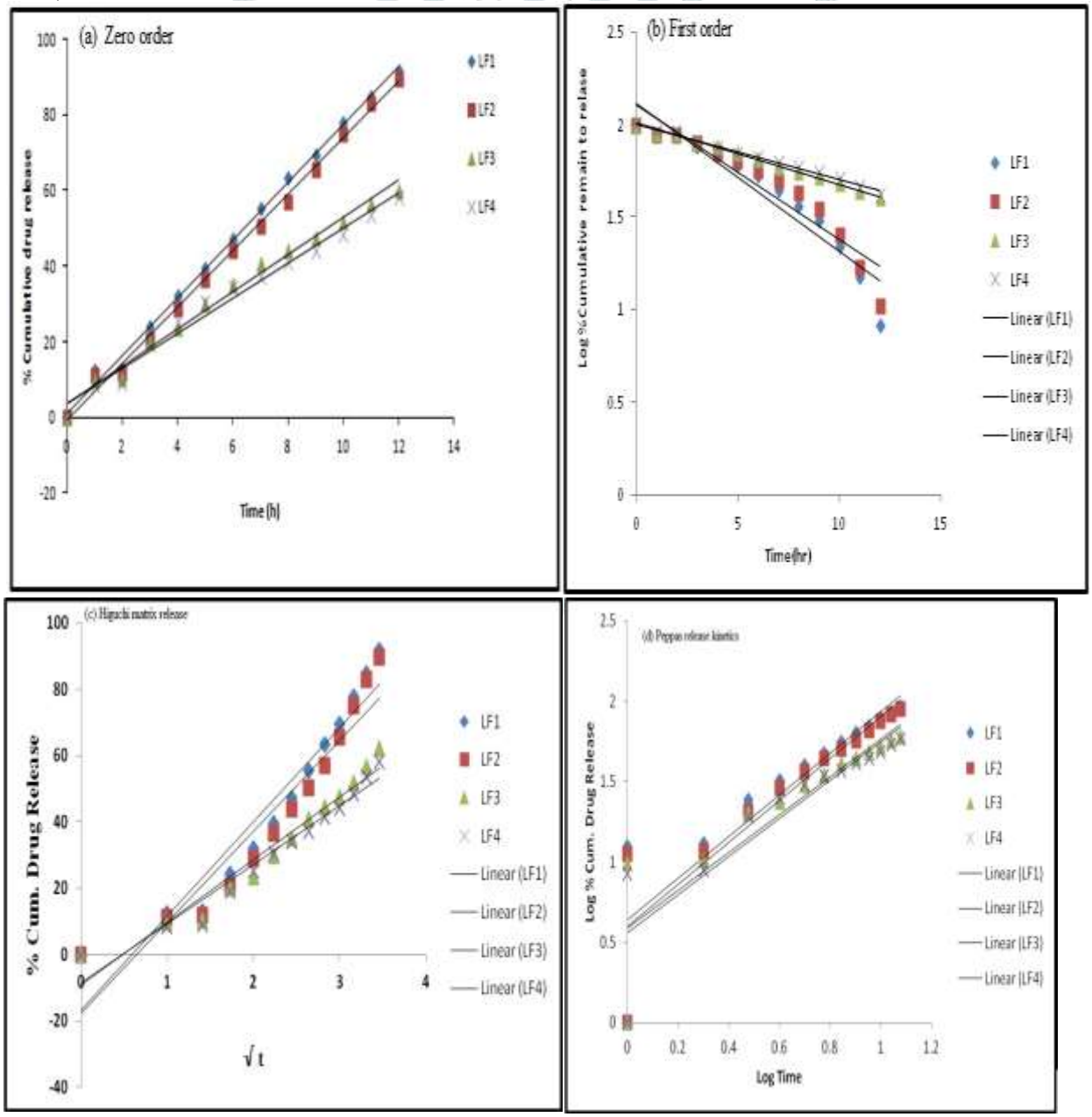

Fig. 7: *In-vitro* release kinetics profile of IBH Microspheres. (a) *In-vitro* drug release was tested for Zero order; (b) First Order; (c) Higuchi; (d) Peppas in pH 1.2 buffer for the first 2 hrs and in 7.4 pH phosphate buffer from 2-12hrs.

Differential Scanning Calorimetry (DSC) [13]

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)

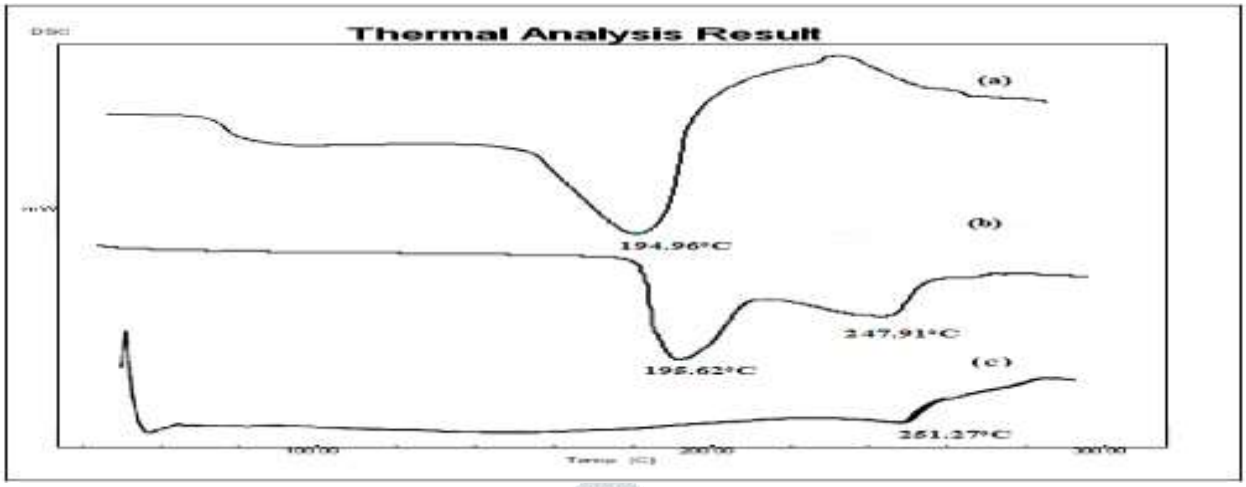

Fig. 8 DSC thermogram of (a) IBH, (b) IBH loaded Eudragit L-100 microspheres, (c) blank Eudragit L-100 microspheres

RESULT AND DISCUSSION

In this present work controlled release microspheres of Ivabradine Hydrochloride were formulated using Eudragit L-100 polymer by Emulsification – solvent evaporation method. 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.(Table 1)

Table 1: Percentage Yield, Drug Content, Entrapment Efficiency and average particles 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 model.

Parameters		LF1	LF2	LF3	LF4
% Yield		86.22	87.70	86.46	91.44
Drug Content %		15.28	15.92	16.84	17.16
Drug Encapsulation Efficiency (%)		30.56	47.77	67.36	85.80
Avg. Particle Size (µm)		79.96	81.74	84.74	129.97
Zero Order		0.9979	0.9972	0.9899	0.9860
First Order		0.9119	0.9026	0.9965	0.9936
Higuchi		0.9286	0.9113	0.9560	0.9575
Peppas Model	**r^2**	0.8442	0.8574	0.8410	0.8522
	n	1.5945	1.5863	1.4536	1.4511

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