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Research Article

IRBESARTAN DISSOLUTION RATE ENHANCEMENT THROUGH INCORPORATION INTO EUDRAGIT E -100 POLYMERIC MICROPARTICLES: IN VITRO CHARACTERRIZATION AND INVESTIGATION OF ABSORPTION IN RATS

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ABSTRACT

In this study, irbesartan was incorporated as polymeric microparticles prepared with Eudragit E 100 using the emulsion-solvent evaporation technique, with the aim of improving solubility which in turn leads to enhance dissolution rate of the drug. Scanning electron microscopy indicated the formulation prepared with eudragit showed spherical form with a loading efficiency of 97.5%. X-ray diffraction and differential scanning calorimetry analysis indicated a reduction in the crystallinity of irbesartan after its incorporation into the microparticles, which caused a significant increase in the dissolution rate owing to conversion into amorphous form of drug from highly crystalline nature.FTIR study reveals that the drug was present in the formulation prepared with eudragitmicroparticles and there was no chemical interaction between IBS, other excipients, and solvents used.In- vivo absorption investigation into the rats was carried out using high – performance liquid chromatography analysis of blood samples were collected from eye retro vein at time interval 0 hr, 0.20hr, 0.45hr, 1.5, 2.5, 4 and 12 hrs after the animal were administered Irbesartan suspension (75 mg /kg, orally) or Irbesartanmicroparticles (equivalent to 75 mg /kg of pure drug,p.o.). Animal that were given irbesartan showed Cmax of 2.929µg/ml at 2.5 hrs and AUC of 27.574 µg/ml hour , whereas animal that received polymeric microparticles containing irbesartan showed respective Cmax were of 19.101 µg/ml at 45 mins and AUC was found to be 65.04 µg/ml hour. Our data suggest that the incorporation into eudragit polymeric microparticles significantly enhance the solubility which leads to increased release of irbesartan , improving the absorption inturn bioavailability in rats.

Keywords: Irbesartan, Eudragit E-100, Polymeric microparticles, solubility enhancement.

INTRODUCTION

Irbesartan (IBS) is a non –peptide, blocks binding of angiotensin II to the AT1 receptor, promotes vasodilation and decreases the effect of aldosterone resulting in lowering of blood pressure.For class II-drugs According to the BCS the dissolution rate is the limiting factor for the drug absorption rate. An enhancement in dissolution rate is important to attain suitable blood-levels of these drugs.Irbesartan (IBS), a poorly water soluble BCS class II drug was selected for the study, as the major problem associated with this drug is low solubility in biological fluids, which results into poor oral bioavailability.

About 40-50 % of all compounds in today's pharmaceutical drug delivery pipelines arereported to be poorly soluble in water[1,2,3]. It is estimated that 40% or more of active substances being identified through combinatorial screening programs arepoorly soluble in water[4].Water insolubility can postpone orcompletely halt new drug development, and can prevent the much needed reformulationof currently marketed product[5]. The solid dispersion approach has

been widely and successfully applied to improve solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs[6]. Many hydrophilic excipients like PEG 4000, PEG 6000, Mannitol, PVP, and poloxamers can be used to enhance the dissolution of drug[7].

Several strategies have been employed to improve the solubility of irbesartan& increase in dissolution rate in aqueous media (including solid dispersion with various superdisintegrate such as sodium starch glycolate (SSG), crosspovidone (CP), croscarmellose sodium (CCS) and microcrystalline cellulose (MCC)[8] and solid dispersion of irbesartan (IBS), prepared with small molecules such as tartaric acid and mannitol and polymeric additives like polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) [9]), the Liquisolid technology[10], Particle size reduction by micronization or nanonization[11], Alteration of the solid state at the particle or molecular level[12].

The microencapsulation &nanoencapsulation of drugs have been widely used in pharmaceuticals in recent decades. However use of this technique in order toincrease the dissolution and bioavailability of drugs is still a little explored area and only few studies have focused on this aspect, the preparation of poly(lactide-co-glycolide) nanoparticles to improve the oral bioavailability of cur cumin[13], enteric microparticles to enhance the oral bioavailability of poorly soluble basic drugs[14].

The incorporation of irbesartan into polymeric microparticles have not yet been studied for this purpose and it offers advantage because they can be used to prepare solid pharmaceuticals forms that can be technologically easy to manufacture and can be easily administered to patient.

The aim of this study was to evaluate a new promisingapproach ortechnique to enhance the dissolution rate and the oral bioavailability of IBS on the basis of its encapsulation into polymeric micro particles.

This technique was employed as it is economical from industrial point of view, due to its simplicity and feasibility on large scale as thepolymethacrylate Eudragit E and PVA were widely used in pharmaceutical field, and were used as a polymeric carrier.

MATERIALS AND METHODS

MATERIALS

Irbesartan was supplied by Cadilla health care as a gift samples. Eudragit E-100 was kindly supplied by Evonik Degussa India Pvt.Ltd. Dichloromethane, ethanol, acetonitrile & acetic acid were acquired from Merck . Poly (vinyl alcohol) was acquired from sigma Aldrich ltd.

Experimental methods

A) Construction of calibration curve: The standard curve of IBS was prepared in 0.1N HCl with concentrations in the range of 2-24 µg/ml and the absorbance was recorded on Jasco UV-visible spectrophotometer at 244nm.

B) Drug-Solubilizer spectrophotometric interference study

This study was carried out by recording absorbance of drug in 0.1N HCl alone and then specified amount of solubilizer was subsequently added to the drug solution and suitably diluted and absorbance were recorded at 244nm. Polymer eudragit E-100 was used in the study. The solubilizers did not show interference with the drug and were thus selected for formulation.

C) Ratio optimization and preparation of polymeric microparticles

The Microparticles were prepared by oil-in–water emulsion- solvent evaporation technique. The polymer and 200 mg of drug were dissolved in 15-20 ml of dichloromethane (internal phase) and then emulsified in 100 ml of aqueous phase containing 0.15% of poly (vinyl alcohol) as a stabilizer (external phase). The resulting emulsion was stirred at 700 rpm at room temperature for until the evaporation of the organic solvent. The microparticles were washed with distilled water, centrifuged, dried and stored under vacuum at room temperature.

D) Bioanalytical method development and validation for irbesartan

Bioanalytical method was carried out by using HPLC. Chromatography condition used were detector PDA-MD-2018 Plus PDA, integrator ChromNAVsoftwere, column Princeton , flow length 1ml/min, wavelength used was 200-800.

E) Scanning electron microscopy

The morphology of micro particles was examined in a ZEISS Ultra55 FESEM System.Analysis of the SEM micrographs, by measuring the diameter of approximately 200 randomly selected particles in enlarged SEM images, resulted in the particle size distribution histograms.

F) FTIR ANALYSIS

Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined in the transmission mode in the Shimadzu FTIR spectrometer.

G) DIFERENTIAL SCANNING CALORIMETRY (DSC)

EXSTAR SII 6200 DS Calorimeter was used to confirm the formation of the final selected formulation of hydrotropic solid dispersions of Irbesartan.

H) XRD analysis

Diffracto grams were recorded from $5^0$to 50^0 at a scanning speed of 2^0 min^{-1} on anX-PERT X-ray powder diffractrometer.

I) Loading efficiency[15]

$$LE\% = \frac{\text{Drug found in micro particles (mg)}}{\text{Drug initially added to the formulation (mg)}}$$

J) In-vitro drug release

Hard gelatin capsule were filled with IBS (75mg) or microparticles (equivalent 75mg). Dissolution tests were performed using paddle apparatus, 50rpm and0.1 N HCL dissolution medium.

K) In- vivo study in rats

The in-vivo studies were carried out after obtaining approval from the Institutional Animal Ethics Committee. Male sprauge dawley rats (n=6 for each group) weighing 250-300 g were given IBS(75 mg p.o.) or microparticles (equivalent to 75mg p.o.)[16] at different time intervals blood was collected in previously heparinized tubes. The plasma was analyzed by HPLC in order to quantify the IBS.

RESULTS AND DISCUSSION

Micro particles morphology & LE

The micro particles preparation using emulsion – solvent evaporation technique consisted of the emulsification of an organic solvents solution containing the polymers and the drug in an aqueous phase. The diffusion of the organic phase and its later evaporation at air-water interface lead to the formation of microparticles.

Eudragit E microparticles(Fig. 1) showed the spherical particles, little cluster formation while that of pure IBS showed platy rod shapedcrystal.Micro particles were with improved morphological and flow characteristic compared to IBS.The external surface of the microparticles was rough & porous. (**Fig. 1: Scanning electron micrographs of (a & b) IBS andeudragitmicro particles (c & d))**

Loading efficiencies of IBS was found to be 97.5%, which indicate process condition used to prepare the micro particles was efficient in terms of achieving high drug content.

XRD and DSC

The investigation of solid state characteristic of of pure IBS and after incorporation into eudragitmicroparticles was examined by using XRD and DSC.

X-ray diffraction patterns revealed that pure irbesartan was in crystalline state (Fig 2), As it showed sharp distinct peaks notably at 2θ diffraction angles of 3.70º, 10.38º, 19.19º, 22.97º. Eudragit E-100 was crystalline in nature and gives characteristic peakat 18.05°,other broader one at 31.33º. The reflections (specific peaks) corresponding to the drug and other excipients were found in the formulationdiffractogram with reduced intensity as compared to drug alone. And some characteristic drug peaks 3.70º were disappearing in formulation diffractogram; this suggested destruction of crystalline nature of drug and drug might be converted from crystalline to amorphous form. (**Fig. 2: X-ray diffraction patterns of Eudragit – IBS micro particles, and pure irbesartan)**

The thermogram of pure irbesartan showed a sharp peak at 181.5^0 (Fig.3), which corresponds to the melting temperature of irbesartan, sharpness of the peak indicating crystalline nature of the drug. The thermogramof Eudragit E-100 showed peaks at 141.9º, 167.7º, 205.7º, 272.4º, Which corresponds to the range of melting temperature of the carrier. In the optimized formulation there was no sharp peak observed at melting point of IBS And the area and sharpness of the peaks were decreased, it indicated that the crystallinity of the drug was reduced and might be converted to amorphous form. There was no change in the peak temperature of the optimized formulation when compared to the pure drug, which indicates no interaction between drug and excipients. (**Fig 3. Differential scanning calorimetric (DSC) curves of Eudragit –IBS loaded microparticles, Eudragit E- 100 and Pure IBS).**

The XRD & DSC results suggest that the total amorphization of the IBS did not occur, but a reduction in crystallinity was detected after its incorporation into the micro particles.

FTIR

Characteristic peaks of Irbesartan at 3453 cm-1 (N-H stretching), 3032 cm-1 (Aromatic C-H stretching),1732cm-1(C=O stretching), 1485.7

7 cm-1 (Aromatic C=C bending) and 1614.83 cm-1 (N-H bending) were observ ed. Eudragit micro particles solvent evaporation method showed characteri stic peaks of Irbesartan drug andcarriers.
These results indicated that there is no chemical interaction between drug and carrier when formed as solid dispersion.

In-Vitro release
In order to assess whether the goal of improving the dissolution rate of IBS was reached, invitro dissolution profiles of polymeric microparticlescompared with that of pure drug. (**Fig. 6: Release profile of pure irbesartan and Eudragit E (EU)-IBS microparticles).**

The dissolution rate of pure IBS was very low. As can be seen in figure 4 , only 5.06% was dissolved in first 10 min. , whereas 72.68% was present in the eudragit –polymeric microparticles, dissolved within same time period.
The enhancement of the drug dissolution rate can be ascribed to several factores
i) The improvement of wetting &solubilization by a hydrophilic carrier, ii) the reduction of aggregation of particles iii) the reduction of the drug particles size iv) the transformation of the solid state of the drug particles from a crystalline nature to an amorphous form. From this study , it is considered that the enhancement of the IBS dissolution after its incorporation into microparticles mainly associated with the amorphonization of the drug and with the use of eudragitas polymeric microparticles.

Furthermore, IBS solubility may be increased by the use of the eudragit as a carrier, which has the high solubility in the acid medium (pH>5). The rapid solubilization of this polymer in the dissolution medium may have contributed to thesolubilization of IBS.

In-vivo study
The blood samples were collected from rats showed Cmax of eudragitmicroparticlesas 19.101 µg/ml at 45 minsand that of IBS pure drugCmax was found to be 2.929µg/ml at 2.5 hrs. AUC of eudragitmicroparticlewas found to be 65.04 µg/ml hour compared to IBS showed the AUC of 27.574 µg/ml hour. From AUC data it can be concluded that there is significant increase in the bioavailability of IBS in microparticles.

CONCLUSION
It was conclude from above study that, incorporation of IBS into eudragit polymeric microparticles will be suitable system for enhancement of dissolution rate of poorly water soluble drug inturn aqueous solubility of same. The microparticles promoted a significant increase in the IBS releasebecause of improved solubility in organic fluids. This increase might reduce the time necessary for the effect to begin & the antihypertensive effect could be potentially be enhanced , allowing the use of lower doses & thus minimizing potential side effect.

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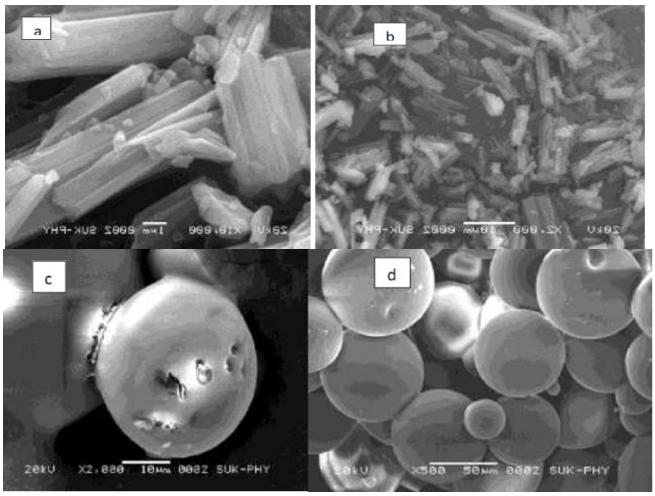

Fig. 1: Scanning electron micrographs of (a & b) IBS and eudragitmicro particles (c & d)

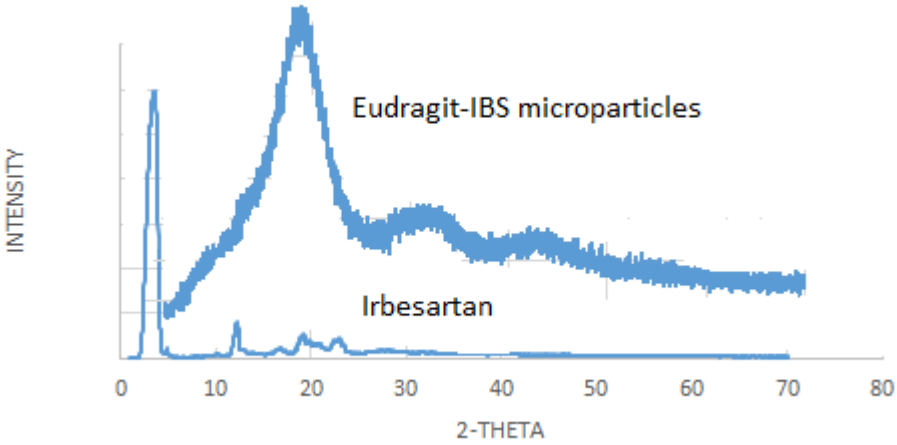

Fig. 2: X-ray diffraction patterns of Eudragit – IBS micro particles, and pure irbesartan)

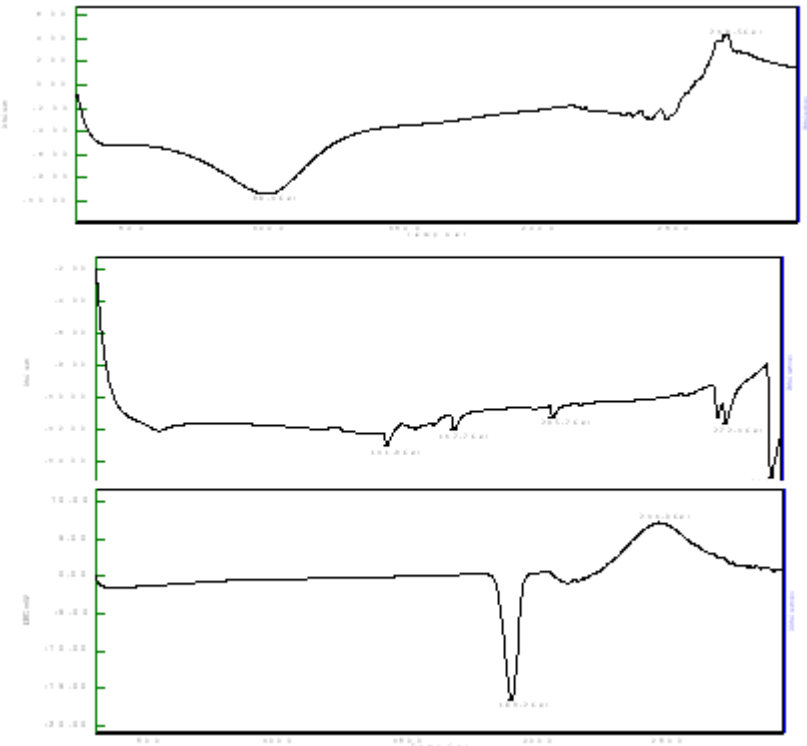

Fig. 3: Differential scanning calorimetric (DSC) curves of Eudragit –IBS loaded microparticles, Eudragit E- 100 and Pure IBS)

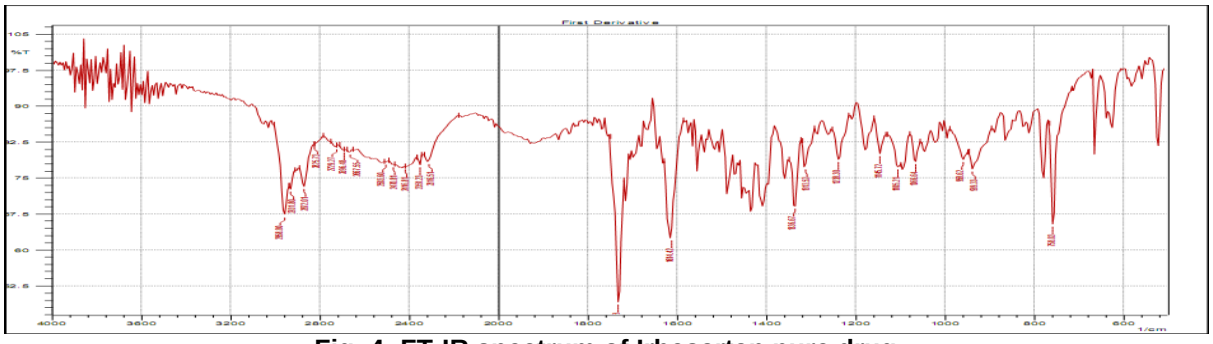

Fig. 4: FT-IR spectrum of Irbesartan pure drug

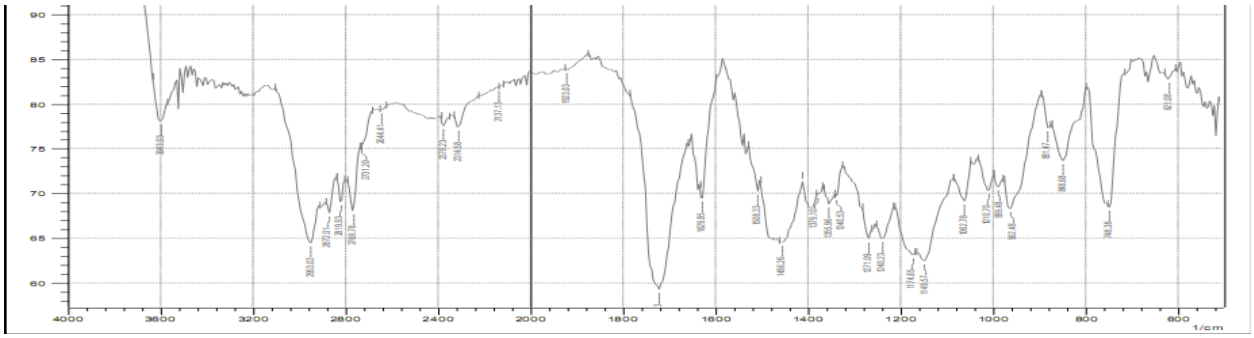

Fig. 5: FT-IR spectrum of Irbesartan –Eudragitmicroparticles formulation

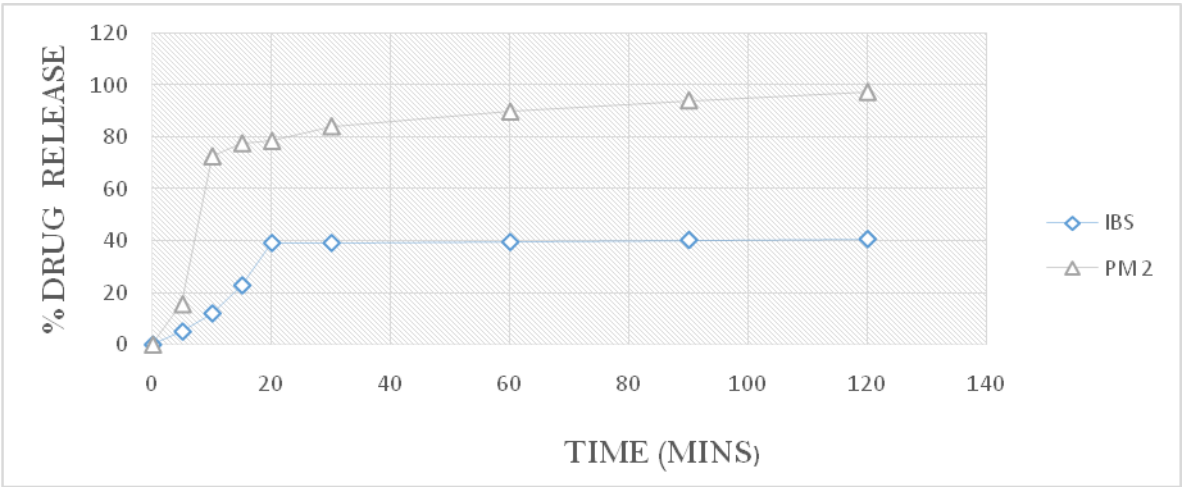

Fig. 6: Release profile of pure irbesartan and Eudragit E (EU)-IBS microparticles

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