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Preparation of Bosentan extended release matrix tablets with different viscosity grades of Ethylcellulose polymers

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ABSTRACT

In the present study oral extended release matrix tablets of Bosentan were formulated, characterized and evaluated for in vitro dissolution. The matrix tablets were prepared using different viscosity grades of Ethyl cellulose such as EC N 7, EC N 50, and EC N 100 as the release rate retardant polymers. The tablets were characterized for physical properties, in vitro dissolution, accelerated stability ($40^0C \pm 2^0 C$ and 75 ± 5% RH) testing. In vitro studies revealed that the release rate decreased with increase in polymer concentration, polymer viscosity. The drug release from the matrix tablets followed diffusion mechanism. Comparable correlation of in vitro drug release was observed in the initial and accelerated stability samples of Bosentan matrix tablets prepared with Ethyl cellulose. DSC and FT-IR spectra of initial and stability samples showed good drug-excipient compatibility in the formulations. The developed extended release matrix tablets of Bosentan were stable up to 6 months. The release of the matrix tablets for prolonged periods of time employing Ethyl cellulose as drug rate retarding polymers could be advantageous than conventional Bosentan tablets. The study could be extended for bioavailability studies in clinical subjects.

Keywords: Bosentan, Ethyl Cellulose, Controlled release, Matrix tablets, Stability.

1. INTRODUCTION

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and improve patient's convenience. Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials. The most commonly used method of modulating the drug release is to include it in a matrix system [1,2].

Bosentan is a dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension (PAH) to decrease the rate of clinical worsening in patients with WHO Class III or IV symptoms and to improve exercise ability. Endothelin-1 (ET-1) is a neurohormone and its effects are mediated by binding to ETA and ETB receptors present in the endothelium and vascular smooth muscle. Patients with pulmonary arterial hypertension have elevated levels of ET-1 concentrations in plasma and lung tissue. Bosentan acts as a specific and competitive antagonist of endothelin receptor types ETA and ETB. Bosentan has higher affinity for ETA receptors than for ETB receptors. Route of elimination of Bosentan is by biliary excretion followed by metabolism in the liver. The drug has half life of 5 hours and hence required to administer frequently to maintain the constant plasma concentration. [3-5].

2. MATERIALS METHODS

2.1. Materials

Bosentan was used as active ingredient. Different grades of Ethyl cellulose like EC N 7, EC N 50 and EC N 100 were used as the polymers obtained from DOW chemical company. The other ingredients used were microcrystalline cellulose, magnesium stearate, aerosol were obtained as gift samples from Lupin Laboratories. All reagents used were of analytical grade.

2.2. Methods

The tablets were prepared by direct compression method in which the drug and polymer and diluents were sifted through 40 mesh and mixed thoroughly. The remaining excepients were sifted through 40 mesh and mixed with the above drug mix and finally lubricated with magnesium stearate. The lubricated blend was compressed with the 16 station tablet compression machine using standard punch. The prepared tablets were evaluated for different physic chemical properties, in vitro dissolution, release kinetics study, DSC and FTIR [6].

2.2.1. Analytical method for the Estimation of Drug content and Dissolution

The drug content of the formulated tablets was evaluated by RP-HPLC method using Inspire C-18 column. Mobile phase consisting of phosphate buffer pH 7.4 and Acetonitrile was used in the 40:60 ratio. Standard solution of 100 mcg/ml in mobile phase was prepared. Sample solution of assay and dissolution were filtered through 0.45µ filter and injected into HPLC system. Absorbance was measured at λ max 265 nm.

2.2.3. In- vitro dissolution studies

The release of Bosentan from matrix tablets (n = 3) was determined using USP dissolution testing apparatus type II (paddle method). The dissolution was performed using 900 ml of 0.1 N HCl medium, maintaining 37 ± 0.5°C temperature and 50 rpm. A 5ml sample of the solution was withdrawn from the dissolution apparatus at predetermined time intervals of 1 hr for 24 hours and the samples were replaced with prewarmed fresh dissolution medium. The samples were filtered through 0.45 µ membrane (nylon) filter and diluted to suitable concentration with 0.1 N HCl. The samples were evaluated by RP-HPLC method using Inspire C-18 column at a wavelength of 265 nm.

2.2.4. Kinetic modelling of drug release

The mechanism of drug release from the tablets was analyzed by fitting the in vitro dissolution data of the formulations into the zero order, first order, Higuchi model and Korsmeyer-Peppas model as per the reported method [7-10]

3. RESULTS AND DISCUSSION

The compressed matrix tablets evaluated for physical parameters like weight variation, hardness, thickness, friability and drug content of the prepared matrix tablets. The weight variations of prepared tablets complied within the pharmacopoeia limits. The thickness of the tablets were found between 3.76 mm to 5.51 mm. Hardness of the tablets ranged from 4.5 to 6 kg/cm2 and friability ranged from 0.11% to 0.71% which ensure that the tablets withstand to the shocks of handling during its manufacturing, packaging and shipping. Drug content was found to be in the range of 97 to 101%. The physical properties of the compressed matrix tablets were found to be satisfactory.

The drug release profiles of different formulations of Bosentan matrix tablets prepared with different concentration and grades of ethyl cellulose are shown in Figure 1. The formulation F1, F2, F3 was prepared by increasing the polymer concentrations of EC N 7. The effect of polymer concentration on drug release from the formulations was also evaluated. Drug release of Bosentan from these formulations in these formulation extended the drug relase up to 7- 10 hours this is may be due to low polymer viscosity. The formulations prepared with the EC N 50 extended the drug release up to 11-13 hours where as in EC N 100 the drug release extended up to 16 hours and more. In all the formulation the effect of polymer concentration was observed as the concentration increased the drug release was also increased.

The dissolution data obtained from the matrix tablets for all the formulations were extrapolated to different kinetic models to determine the release mechanism of the drug

Table: Formulation data of prepared Bosentan matrix tablets

	BSN	ECN7	ECN50	ECN100	MCC	Aerosil	Mg Sterate	Wt (mg)
F-1	80	25	--	--	49	5	1	160
F-2	80	35	--	--	39	5	1	160
F-3	80	45	--	--	29	5	1	160
F-4	80	--	25	--	49	5	1	160
F-5	80	--	35	--	39	5	1	160
F-6	80	--	45	--	29	5	1	160
F-7	80	--	--	25	49	5	1	160
F-8	80	--	--	35	39	5	1	160
F-9	80	--	--	45	29	5	1	160

from the formulations. The formulations was found to follow zero order kinetics i.e. drug release is time dependent. It was found that there is no significant change in R^2 values as the concentration and viscosity of the polymers was changed. The release mechanism of drug from the matrix tablets was studied by fitting the dissolution data into Krosmeyer and peppas model. The results showed that the release exponent 'n' values were found between 0.813 to 1.026, indicating that drug release followed non Fickian diffusion mechanism.

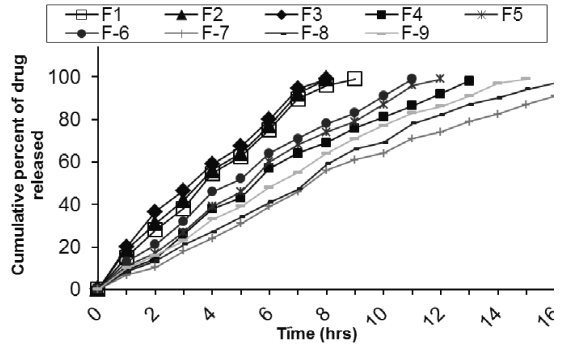

Figure - 1: Dissolution profiles of prepared Bosentan matrix tablets.

3.1. Differential scanning calorimetric stidy

Thermal properties of pure drug and formulations were evaluated by Differential scanning caloriemetry (DSC) using a diamond (DSC) (Mettler star sw 8.10). Accurately weighed 5-6mg samples were hermetically sealed in aluminium pans and heated at a rate 5^0 C/min from 50^0C to 300^0C temperature range under nitrogen flow of 25ml/min.

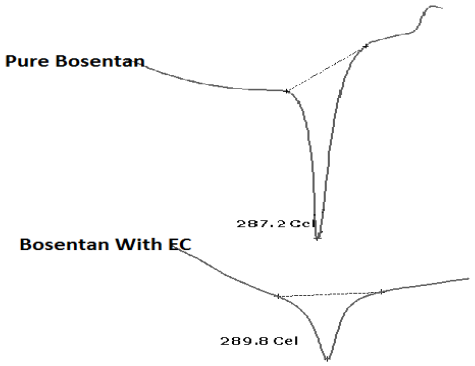

Figure - 1: DSC thermograms of prepared Bosentan matrix tablets.

3.3. Fourier transform infrared spectroscopy

The infrared spectra of Bosentan pure drug and formulation were recorded between 400 – 4000 cm-1 on FTIR. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer. The FTIR spectral peak points were similar indicating the absence of drug – polymer interaction.

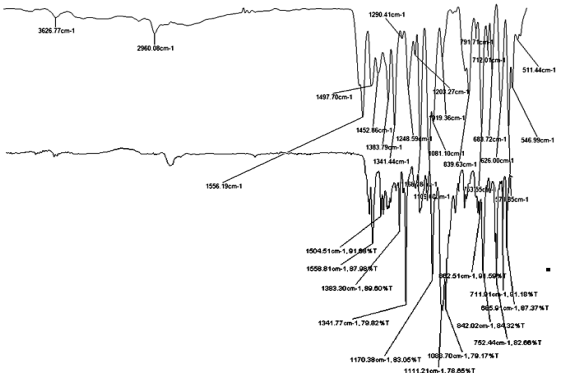

Figure - 1: FTIR spectra of prepared Bosentan matrix tablets.

4. CONCLUSION

Matrix tablets of Bosentan were prepared with different grades of the Ethyl cellulose and the release was extended up to 16 hours and more. The release kinetics followed zero order. DSC and FTIR study showed no drug polymer interaction. Accelerated stability of the prepared matrix tablets showed good stability up to 6 months. The prepared matrix tablets shoed good therapeutic benefit than the conventional tablets formulations.

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