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Design and Study of Ritonavir Buoyant Microspheres by Eudragit S100 Polymer

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Multiple unit buoyant delivery systems can be distributed widely throughout the gastrointestinal tract, providing the possibility of achieving longer lasting and reliable release of drug from the formulation. The aim of the present study was to prepare and evaluate buoyant microspheres of ritonavir using eudragit S100 polymer. The formulated microspheres were characterized for their yield, particle size, incorporation efficiency, *in vitro* buoyancy. *in vitro* Release characteristics were studied by 0.1 N HCl and found to be in the range of 63 to 86 %. This investigation concludes that ritonavir loaded buoyant microspheres were successfully formulated.

Keywords: Buoyant, Eudragit S100, Ritonavir, Micorospheres.

INTRODUCTION

The huge investment involved in the development of new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of new drug delivery system[1]. In the past decade extensive research has been made in the development of solid oral modified release formulations. Oral administration offers high patient compliance than invasive modes of drug administration. The gastrointestinal tract remains the most preferred route of administration of drugs. Conventional formulations are required to be administered in multiple doses in long term therapy and therefore have several disadvantages[2,3]. Oral modified release formulations which deliver the drug for a prolonged period of time, it is important to achieve spatial placement of the formulations for efficient therapy.

Multiunit system has relative merits over single unit systems, which distribute the multiunit more uniformly in the gastrointestinal tract. Rapid gastrointestinal transit may result in partial drug release from the formulation leading to diminished efficacy of the administered dose. Multiple unit buoyant delivery systems can be distributed widely throughout the gastrointestinal tract, providing the possibility of achieving longer lasting and reliable release of drug from the formulation. Protease inhibitors are characterized pharmacologically by their ability to inhibit the viral protease enzyme and make an integral part of antiretroviral therapy[4]. Ritonavir is used in the treatment against the acquired immune deficiency syndrome; it is an inhibitor of human immunodeficiency virus protease enzyme[5].

The principal of buoyant formulation offers a simple and practical approach for formulation and to achieve increase gastric residence time for dosage form and drug release in a sustained manner. Thus, the present research work was to develop and evaluate buoyant microspheres of Ritonavir using Eudragit S100 polymer.

EXPERIMENTAL

The active ingredient ritonavir was obtained as gift sample from Hetro drugs, ltd., Hyderabad. Eudragit S100 was supplied by Evonik Degussa India Pvt. Ltd., Mumbai. Polyvinyl alcohol purchased from S.D Fine chemicals, Ltd., Mumbai. All solvents used were of analytical grade.

Formulation of ritonavir microspheres: Ritonavir loaded buoyant microspheres were prepared by previously described emulsion solvent diffusion method[6,7]. Microspheres were formulated by changing the drug to polymer ratio as described in Table-1, From 1:1 to 1:4. Solvent ethanol was used to dissolve the weighed quantity of ritonavir. Eudragit S100 was added to the above followed by the addition of dichloromethane and isopropanol. The above mixture was kept in bath sonicator for few minutes until clear solution is obtained. The above content was introduced into the 0.5 % poly(vinyl alcohol) aqueous solution *via* needle. The mixture was then stirred continuously at 300 rpm for 2 h with a propeller type three blade agitator. The formulated microspheres were separated by filtration, washed with distilled water several times and dried at room temperature.

TABLE-1
FORMULA OF EUDRAGIT S100 LOADED RITONAVIR MICROSPHERES

Formulation	Ritonavir	Eudragit S100
ES1	1	1
ES2	1	2
ES3	1	3
ES4	1	4

Production yield: The yield of microspheres was calculated[8] by dividing the weight of recovered microspheres by the weight of all the solids used for the preparation of microspheres and expressed in terms of percentage.

$$\text{Production yield} = \frac{\text{total mass of microspheres}}{\text{total mass of raw material}} \times 100$$

Particle size analysis: Formulated buoyant microspheres size was measured using an optical microscope under regular polarized light and the mean particle size was calculated by measuring 100 particles in random manner with the help of a calibrated ocular microscope.

Drug loading and incorporation efficiency: Formulated microspheres of all formulations of about 50 mg were weighed and dissolved in methanol. The above solution was suitably diluted and spectrophotometrically measured for the drug content. The drug loading and incorporation efficiency were calculated[9] by using the following equations.

$$\text{Drug loading (\%)} = \frac{M_{actual}}{\text{weighed quantity of powdered microspheres}} \times 100$$

$$\text{Incorporation efficiency (\%)} = \frac{M_{actual}}{M_{theoretical}} \times 100$$

where M_{actual} is the actual drug content in the weighed quantity of powdered microspheres and $M_{theoretical}$ is the theoretical amount of drug in microspheres calculated from the quantity added in the formulation process.

***in vitro* Buoyancy study:** Buoyant microspheres of all formulations were weighed 50 mg and spread over the surface of USP paddle dissolution apparatus. 900 mL if 0.1 N HCl was used for the study, the medium was agitated with a paddle at 100 rpm for 12 h. After the study period the floating and settled portions of microspheres were collected, they were separately dried and weighed individually. Buoyancy percentage was calculated[10] as the ratio of the mass of the microspheres that remain floating and the total mass of the microspheres.

The infrared absorption spectra of the ritonavir, eudragit S100 and formulated microspheres were obtained using a FT-IR spectrophotometer. To find out the state of the ritonavir in the microspheres differential scanning calorimetry were done on microspheres, pure drug and Eudragit S100. The instrument was operated under nitrogen purge at a range of 20 mL/min. Differential scanning calorimetry curves were obtained from 25 to 400 °C at an average heating rate of 10 °C/min. The morphology of the formulated microspheres was examined by scanning electron microscope.

***in vitro* Dissolution study:** *in vitro* Ritonavir drug release from the formulated buoyant microspheres was determined using USP paddle type dissolution test apparatus. 100 mg of microspheres of all batches were carefully spread over the dissolution medium. 0.1 N HCl was used as dissolution medium maintained at 37 ± 0.5 °C. The dissolution apparatus was set to run at 100 rpm for 12 h. A sample of 10 mL was withdrawn from dissolution apparatus periodically and the samples were replaced with the fresh dissolution medium. The samples were suitably diluted with dissolution medium, filtered and analysed spectrophotometrically at 246 nm for the ritonavir content.

RESULTS AND DISCUSSION

Production yield: The production yield obtained for all formulations were high. As shown in Table-2, the percentage yield was found to be in the range of 82.49 to 92.26 %. The percentage yield was found to be increased with increasing concentration of polymer. Formulation ES4 showed the highest yield of 92.26 %.

Particle size analysis: The mean particle size of the formulations were tabulated in Table-2 and found to be in increased with polymer concentration. The size was in the range of 264 to 396 µm. Larger particles were produced due to the rapid polymer precipitation, leading to hardening and avoiding further particle size reduction during the process.

Drug loading and incorporation efficiency: As expected increasing Eudragit S100 amount in the formulation decreased the actual drug loading, but increased the incorporation efficiency. Increasing the amount of polymer in the organic phase increased the viscosity of internal phase. As shown in the Table-2, incorporation efficiency was high in all formulations.

***in vitro* Buoyancy study:** The *in vitro* buoyancy test was carried out to investigate the floating behavior of formulated microspheres with the medium of 0.1 N HCl for 12 h. The study revealed that buoyancy properties of all the formulations were found to be high. Buoyancy percentages were shown in Table-2 and were in the range of 72 to 92 %.

FT-IR spectra of Ritonavir, Eudragit S100 and the microspheres were shown in Fig. 1. There were no significant difference in the IR spectra of pure drug and drug loaded

TABLE-2
In vitro CHARACTERIZATION OF RITONAVIR MICROSPHERES

Formulation	Yield (%) ± SD	Mean particle size (µm) ± SD	Drug loading (%) ± SD	Incorporation efficiency ± (%) SD	Buoyancy (%) ± SD
ES1	82.49 ± 2.64	264 ± 12.62	41.21 ± 2.86	82.43 ± 4.02	72.04 ± 8.04
ES2	88.32 ± 1.96	316 ± 08.46	28.68 ± 1.46	86.04 ± 2.84	78.42 ± 4.62
ES3	91.18 ± 0.86	372 ± 16.62	23.16 ± 2.04	92.64 ± 0.46	88.96 ± 7.06
ES4	92.26 ± 3.68	396 ± 20.84	18.76 ± 2.36	93.84 ± 2.44	92.42 ± 2.48

Data represents the mean ± SD, n = 3

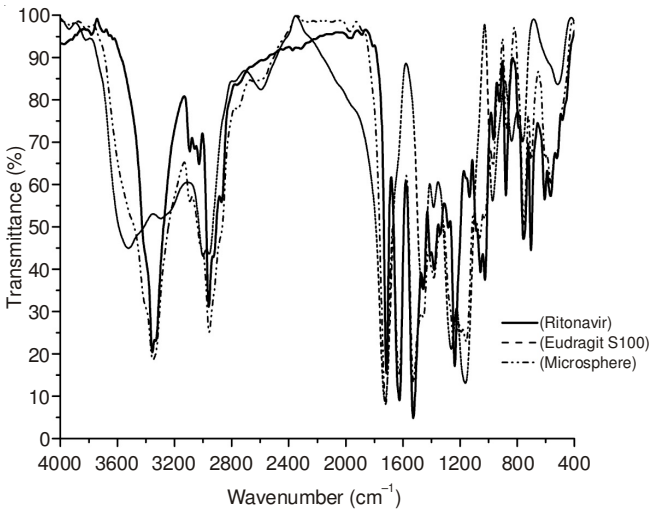

Fig. 1. FT-IR spectra of ritonavir, eudragit S100, microsphere

microspheres. Experimental observations were shown characteristics peak[11] for the drug at 3355, 2960, 1716, 1625 and 1527 cm^{-1}. This result suggested drug stability during the formulation process.

From the differential scanning calorimetry thermograms presented in Fig. 2, which are typical for ritonavir microspheres, it was observed that there is no detectable endotherm in the formulation which stated that drug was molecularly distributed in the microspheres.

Visual images were obtained for the microspheres by SEM to study the surface morphology of the formulation. SEM photographs indicated the presence of minute pores on the surface of the microspheres.

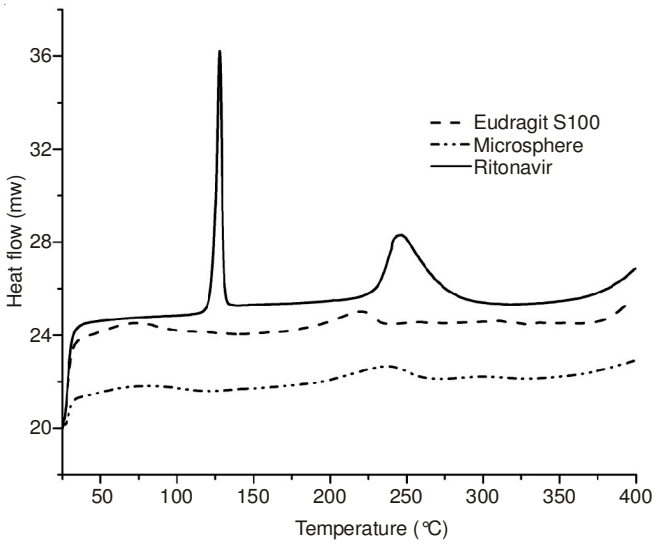

Fig. 2. Differential scanning calorimetry thermograms

***in vitro* Dissolution study:** *in vitro* Drug release studies were carried out for all the formulations using 0.1 N HCl for 12 h. The release profiles of the formulations were shown in Fig. 3. It is evident from the figure eudragit S100 influenced the release rate of the ritonavir from the microspheres. The cumulative percentage of drug release were found to be highest for ES1 as 86 % and lowest was for the formulation ES4 as 63 % which contains the highest amount of Eudragit S100 polymer.

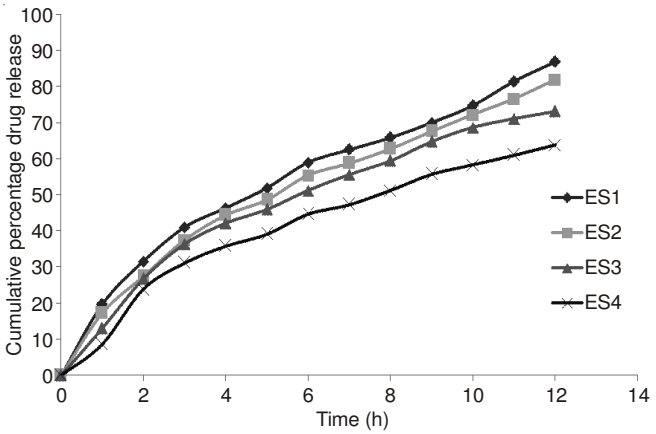

Fig. 3. *in vitro* release studies of Ritonavir Microspheres

Conclusion

The present research describes the development of buoyant ritonavir loaded eudragit S100 microspheres. Thus, Ritonavir loaded buoyant microspheres obtained by this method provide an opportunity and potential for the development of gastroretentive drug delivery system.

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