Research Article

MICROPARTICULATE DRUG DELIVERY SYSTEM OF ORLISTAT FOR SUSTAINED RELEASE

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ABSTRACT

Orlistat is an anti- obesity drug, that preventing the digestion and absorption of fat in food. Aqueous solubility of this drug is very less, but freely soluble in ethanol and methanol. It is available as hard gelatin capsules administered in the dose of 60 - 120 mg with the dosing frequency as 3 times a day. It shows half life of 1 to 2 hours with poor bioavailability of less than 1 %. The present work is involved in the formulation of microspheres of Orlistat with the suitable doses for sustaining the release, which aims to reduce the dosing frequency dose frequency, side effects and enhance the bioavailability. The Orlistat microspheres were prepared by solvent evaporation method with hydrophobic ethyl cellulose polymer for retarding the drug release at various concentrations of drug - polymer ratio (1:1, 1:3, 1:5 and 1:7) in the presence of different surfactants such as tween 80 (0.3%) and pluronic F68 (0.2%). The formulated microspheres were evaluated for its particle size distribution (2.322 µm to 5.663 µm), drug content (95-99%) and drug entrapment efficiency (98.89%). The infrared spectroscopy analysis supported to the above data and confirms that there were no interactions between the drug and polymer. The *in-vitro* drug release (58.25% - 62.32%) was carried out using 200ml of phosphate buffer pH 7.4 as the dissolution media by using USP type I(basket) dissolution test apparatus at 75 rpm. The mechanism of the drug release was identified using release kinetic models like Higuchi, Peppas, Hixon, zero order and first order kinetics. The Orlistat microspheres are found to have sustained release of drug for more than 12 hours.

Keywords: Anti- obesity, microspheres, ethyl cellulose.

INTRODUCTION

Orlistat is an anti-obesity drug and aqueous solubility is very less, but freely soluble in ethanol and methanol.[1] It works by inhibiting gastric and pancreatic lipases and it blocks the action of lipase and thereby prevents the breakup and absorption of 25% of the fat in a meal.

Microencapsulation is one of the processes used for controlled drug release that leads to prolongs therapeutic activity.[1-4] In pharmaceutical sustained release preparations, the microspheres will be distributed throughout the gastrointestinal tract.[6] Microspheres are small spherical particles, size ranging from 1-1000 µm.[5] It is important part of such novel drug delivery system and it is prepared for prolonged or controlled drug delivery and to improve the bioavailability of the drug and also to target the specific sites in the body. Microspheres also have some advantages like limiting fluctuation[7, 8] within therapeutic range, reducing side effects, reducing dosing frequency and improving patient compliance.

Ethyl cellulose for emulsion solvent evaporation method is adopted based on literature survey.[9,10] It is a hydrophobic and pH independent polymer and capable of releasing drug in sustained manner.[11,12] In present paper the study was carried out with a view to sustain the release of Orlistat for prolonged action in the GIT and microspheres were prepared by emulsion solvent evaporation method, using a dichloromethane and Ethanol as solvents. After evaporation of solvents ethyl cellulose encapsulates the drug to form microspheres of various size ranges.

MATERIALS AND METHODS

Materials

Orlistat was obtained as a gift sample from (Glue Chem. Pharma, Hyderabad, India), ethyl cellulose (Loba chemie Pvt.Ltd, Mumbai, India) dichloromethane (Fischer Chemie Ltd., Chennai, India), pluronic F68 (Himedia laboratories Pvt.Ltd, Mumbai, India), tween 80 (Loba chemie Pvt.Ltd. Mumbai, India) and the chemical reagents used were of analytical grade.

Methods

Preparation of microspheres

All the microsphere formulations were prepared by emulsion solvent evaporation technique. The effect of various formulation and processing factors on microspheres characteristics were investigated by changing polymer: drug ratio.[13-14] Weighed amount of orlistat and ethyl cellulose (1:1, 1:3, 1:5, 1:7) were dissolved in 10ml of a mixture of dichloromethane and methanol (1:1). The organic solution was then slowly added to water containing tween 80 (0.3% w/v) or pluronic F68 (0.2% w/v) as surfactant with constant stirring for 1h. The resulting microspheres were separated by filtration and finally air dried over a period of 12 hrs.

Characterization of microspheres

Estimation of drug content

An accurately weighed (20mg) portion of microspheres are taken in a 100ml volumetric flask and dissolved in about 5ml of methanol and the volume is made up to the

mark with phosphate buffer pH7.4.[16,17] After filtration the samples were analyzed spectrophotometrically (Perkin Elmer, USA) and the amount of drug encapsulated in the microspheres were calculated.

Percentage yield

The total amount of microspheres is weighted and the percentage yield was calculated depending upon the drug and the polymer using the following formula.[18, 19]

% Yield = (Practical Yield / Theoretical Yield) × 100.

Drug entrapment efficiency

A weighed quantity (20mg) of microspheres were crushed into powder and added to 10ml of phosphate buffer pH 7.4. The resultant mixture was then sonicated for 30 minutes.[20,21] Then the solution was filtered through whatmann filter paper. The resultant solution was analyzed spectrophotometrically (Perkin Elmer, USA) at 280nm. The entrapment efficiency was determined by,

Drug entrapment efficiency = (Experimental drug content / Theoretical drug content) × 100

Particle Size

The Particle size analysis was carried by optical microscopy method, using compound light microscope (Khera instruments, Pvt Ltd, New Delhi) with calibrated eye piece micrometer.[1,22-24] 100 particles were measured and the results were determined and tabulated.

FT-IR spectroscopy analysis

A quantity of the microspheres was ground with a specially purified salt (dried potassium bromide to remove scattering effects from large crystals). [25,26] This powder mixture was then crushed in a mechanical die press to form a translucent pellet through which the beam of the spectrometer can be passed. This makes the observations of chemical reactions and processes quicker and more accurate. The interaction of drug of excipient determined from the IR group of formulation compared with the pure drug.

In-vitro release studies

An accurately weighed Orlistat microspheres (20mg) was dropped in 200ml of phosphate buffer pH 7.4, maintained at a temperature of 37°C ± 0.2°C[27] and stirred at a speed of 75 rpm using USP XXVII dissolution apparatus type I (basket). At different time intervals, aliquot of the sample were withdrawn and the same volume was replaced with an equal amount of plain heat dissolution medium. The collected samples are filtered and analyzed at 280nm, using UV-visible spectrophotometer against the phosphate buffer pH 7.4 as a blank.

RESULTS AND DISCUSSION

Percentage yield

The percentage yield of all the formulation was ranging from 16.28 to 98% respectively (table 1). Orlistat with pluronic F68 shows higher percentage yield compared to the Orlistat with tween 80. This higher percentage yields indicates that this method is very useful for adoption in the formulation of Orlistat microspheres.

Drug loading and Drug entrapment efficiency

The results of the variation in drug loading and encapsulation efficiency with polymer: Orlistat ratio shown in table 1. Higher percentage of loading is obtained by increasing the amount of ethyl cellulose. The percentages of encapsulation of all the formulation are in the range of 16.75 – 102.62%. This improved encapsulation efficiency simply by due to the greater proportion of polymer with respect to amount of drug.

Particle size

The optical microscope images show that the formulated beads are spherical in shape. The average particle size of all the formulations are in the range of 80 - 120µm and particle size was slightly increased with increase in concentration of the polymer.

FT-IR spectral analysis

The FT-IR spectra of pure drug (figure 1) and microspheres of Orlistat revealed its principle peaks of C=O stretch at 1746.52cm-1, N-H stretch at 2976.52cm-1, C-O stretch at 1506.3 shown in figure 2. The FT-IR spectrum of microspheres formulations presented all the peaks characteristics of pure drug indicating no interaction between the drug and polymer.

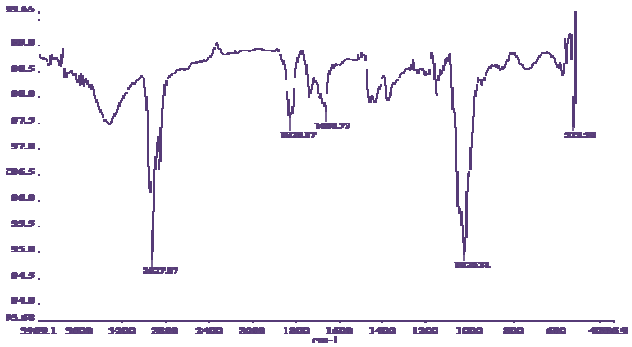


Figure 1: Orlistat (pure)

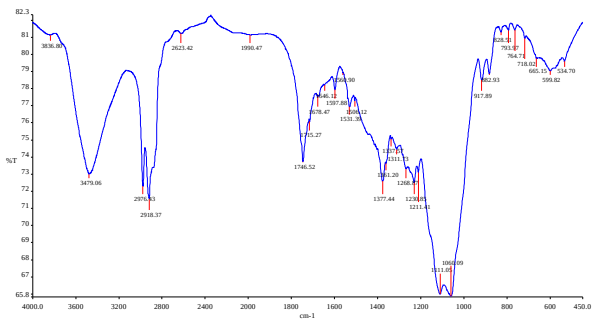


Figure 2: ORT4 (1:7)

Table 1: Comparative study of various physical parameters for microspheres containing orlistat

Formulation code	Drug: polymer ratio	Particle size (μm)	% yield	Drug entrapment efficiency (%)
ORT1	1:1	123.9±0.05	16.26	16.75
ORT2	1:3	104.3±0.04	49.50	48.51
ORT3	1:5	90.3±0.08	68.03	70.07
ORT4	1:7	82.4±0.05	70.63	69.92
ORP1	1:1	113.2±0.07	46.60	47.53
ORP2	1:3	113.7±0.07	62.22	64.08
ORP3	1:5	91.9±0.07	101.66	102.67
ORP4	1:7	120.2±0.05	59.35	61.13

Table 2: Release kinetics of drug release from Orlistat microspheres

Ratio	ORT1	ORT2	ORT3	ORT4	ORP1	ORP2	ORP3	ORP4
Zero order	0.9525	0.9628	0.9849	0.9956	0.9842	0.9939	0.8576	0.8676
First order	0.8513	0.8513	0.8513	0.8513	0.8513	0.8513	0.8513	0.8513
Higuchi	0.9966	0.9886	0.9941	0.9968	0.9923	0.9961	0.9856	0.9886
Korsmeyer	0.9651	0.9735	0.998	0.9808	0.9778	0.978	0.8637	0.9735
Hixon	0.955	0.9718	0.9877	0.9959	0.9881	0.9947	0.8928	0.9718

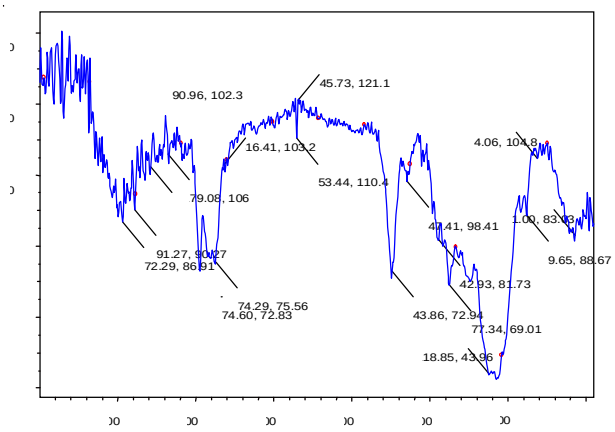


Figure 3: Ethyl cellulose (pure)

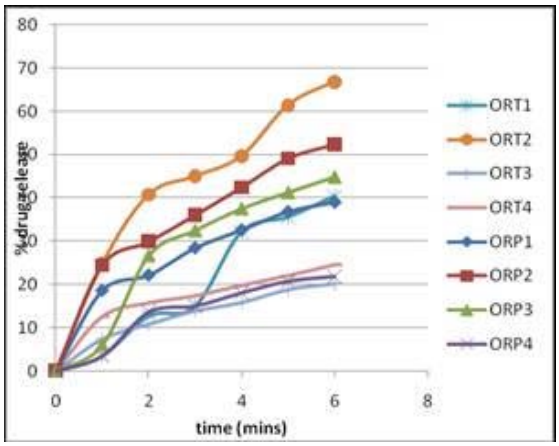
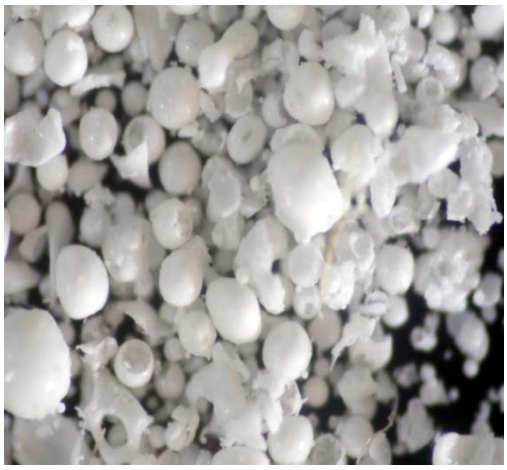


Figure 4: *In-vitro* release of Orlistat

In-vitro release studies

The drug to polymer ratio on drug release was studied (figure 4) on Orlistat microspheres in a dissolution medium of phosphate buffer pH 7.4. Different drug to polymer ratio were taken 1:1, 1:3, 1:5 and 1:7 and increase in polymer concentration resulted in a decrease of drugs release rate. The release of Orlistat is found to be sustained release up to 6th hours was achieved when drug: polymer is taken up to 1:3(ORT2) is found to be 52.40% showed better release as compared to other formulations. The data obtained for *in-vitro* release was fitted into various kinetics equations and the r^2 value estimated for the models were found to be zero order (0.9628), first order (0.8513), Higuchi (0.9886), Korsmeyer (0.9735) and Hixon (0.9718) release models (table 2).



A) 1:3 (40 X)

B) 1:3 (100 X)

Figure 5: Optical microscopic images of orlistat ethyl cellulose microspheres

CONCLUSION

The purpose of present work was to develop sustained release microspheres of water insoluble drug, Orlistat, using ethyl cellulose, as a release retardant by emulsion solvent evaporation method. From these result of characterization and drug release studies of microspheres it is concluded that this method could simplify the traditional manufacturing processes for sustained release microspheres. On the basis of release studies it was indicated that tween 80 enhances the solubility and ethyl cellulose sustained the release of Orlistat from microspheres, hence the present method is suitable for preparing the sustained release microspheres for poorly water – soluble drug.

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