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RESEARCH ARTICLE

FORMULATION & DEVELOPMENT OF ACECLOFENAC AND OMEPRAZOLE SUSTAINED RELEASE MICROSPHERES

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Abstract:

The purpose of this research was to develop and formulate combination of two drug aceclofenac and omeprazole in the form of sustained release microspheres having pH sensitivity property and microspheres were prepared by solvent-evaporation method using different drug polymer ratios (1:1 to1:3), stirring speeds (500-1000rpm), to prevent the side effect of aceclofenac the stomach and small intestine for this proton pump inhibitor omeprazole used. The prepared microspheres were characterized by percentage yield, particle size, entrapment efficiency, micromeritics properties, FTIR, in-vitro release behaviour, etc. The in-vitro release studies was performed by buffer change method to mimic gastro intestine tract (GIT) environment in pH 1.2, carbonate buffer (acidic) and pH 7.2, phosphate buffer (Alkaline). The infrared spectra showed stable character of aceclofenac omeprazole in the drug loaded microspheres and show the absence of drug polymer interactions. The drug loaded microspheres show high entrapment efficiency (74%) and release was extended up to 8 to 12 hrs releasing 86% of the total drug from the microspheres.

Key words: Aceclofenac, Omeprazole, Solvent-evaporation method, Microspheres.

INTRODUCTION:

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they releases the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time.

However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability[1.] Microspheres can be described as small particles (in 1-1000 micrometer size range) for use as carriers of drugs and other therapeutic agents. The term microspheres describe a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particle[2].

Materials and methods

Materials

Aceclofenac and Omeprazole (drug) was provided by Ranbaxy Pvt. Ltd Gurgaon and Biotrans, Chennai . Eudragit S100, HPMC K4M, Span 80, Acetone other chemicals were provided by Sagar Institute of Research Technology & Science-Pharmacy Bhopal.

METHOD OF PREPARATION

The formulation was prepared using solvent evaporation technique, Using Eudragit S100 as polymer. Eudragit was dissolved in required quantity of acetone, the HPMC K4M and drug was dispersed with the polymer solution. The dispersed content was placed drop wise in mineral oil containing span80 maintained at 40^0C while stirring at 800 rpm. The solvent, acetone was then removed by continuous stirring at room temperature for three hours to produce spherical microspheres. Then microspheres were than separated from mineral oil by filtration through whatmann filter paper, the microspheres were collected and washed three times with n-hexane and dried using vacuum filtration. The product was then air-dried to obtain microspheres[3].

Table 1: Formulation of Aceclofenac and Omeprazole Sustained Release Microspheres

S.no	Batch code	Eudragit(mg)	Ethanol(ml)	Hpmc K4M(w/v)	Mineral oil (ml)	Span 80(w/v)
1	AC1	100	35	0.5	35	1%
2	AC2	150	35	0.5	35	2%
3	AC3	200	35	1.0	40	2%
4	AC4	250	35	1.0	40	2%
5	AC5	300	40	1.5	40	2%
6	AC6	350	40	1.5	40	2%
7	AC7	400	40	1.5	40	2%

Optimization

During microsphere formulation, the stirring speed was varied from 400 to 900 rpm for different formulations while keeping the other processing parameters at standard conditions. On increasing the stirring speed decrease in particles size and diameter was observed as shown in table . This occurs because the eternal energy and thus the shear stress causing droplet breakdown is increased with increasing the stirring speed. It was observed that the stirring speed at 800 rpm was found to be optimal as based on particle size and drug entrapment efficiency[4].

Optimization parameter

a) ***Stirring speed*** – Different formulations were prepared at different stirring speed of 400, 500, 600, 700 and 800 rpm and its effect on microspheres properties was studied.

b) ***Stirring time*** – Keeping stirring speed constant at 800 rpm, the stirring time was varied from 45, 60, 90, 120 and 180 minutes for different formulations of eudragit microspheres.

Table 2: Effect of stirring speed on the particle size and drug entrapment of microsphere

S.No.	Stirring speed (rpm)	Average particle size (nm)	Drug entrapment (%)
1	400	627	70.16
2	500	465	82.54
3	600	345	85
4	700	289	87
5	800	205	91.65
6	900	350	78

CHARACTERIZATION OF DOSAGE FORM

Particle size analysis

The microsphere size distribution was determined by the optical microscopy method using a calibrated stage micrometer (μm). The size of microspherewas calculated by using this equation.[5]

$$X = 10 \times [(ni \times \log Xi) / N] \ldots\ldots\ldots (2)$$

Where, X =particle's mean diameter, ni =number of particle in range,

Xi = the midpoint of range and N = total number of particles

Drug entrapment efficiency

The amount of drug entrapped was calculated from the difference between the total amount of drug added and the amount of drug found in the filtered solution. About 100 mg of

microspheres were completely dissolved in 500 ml of phosphate buffer solutions (pH 7.4), and stirred for 1h. Then, 2 ml of solution was filtered and the concentration of drug was determined spectrophotometrically by UV.[6,7]

Efficiency of drug entrapment was calculated in terms of percentage drug entrapment (PDE) as per the following formula:

$$PDE = (Pdl/Tdl) \times 100 \ldots\ldots\ldots\ldots (3)$$

Where,Pdl =Practical drug loading,

Tdl =Theoretical drugloading.

Drug Content

Samples were analyzed spectrophotometrically by SHIMADZU UV 1700 UV-Vis Double beam spectrophotometer at a wavelength of 221nm. Powdered microspheres containing 0.04gm sample was dispersed in 10ml Acetone followed by agitation with magnetic stirrer for 12h to dissolve the polymer and to extract the drug. After filtration, the drug concentration in the acetone phase was determined by proper dilution.[8] Finally, drug encapsulation efficiency was calculated.

In-vitro Drug Release:

Microspheres equivalent to 0.04gm of Isosorbide dinitrate were subjected for dissolution. Dissolution tests were carried out using USPXXI rotating paddle method (Apparatus 2). The stirring rate was 100rpm. The dissolution medium was 900ml of 0.1N HCl (pH 1.2) and the temperature was maintained at 37 ± 0.5^0C. After 2 h, microspheres were removed and transferred to a medium containing phosphate buffer (pH 7.4) for 10 h. Samples of 5ml were withdrawn at predetermined interval with a pipette and filter. The collected samples were analyzed spectrophotometrically at 291nm.[9]

Accelerated Stability Study:

The microspheres from the selected and optimized batch were studied for stability and kept under the accelerated conditions of temperature and moisture (humidity) for the period of six months. This microspheres stability was studied at Temperature 40°C and Humidity 75% RH conditions. Every sample separately weighed and enclosed by aluminum foils and sealed in black PVC bottle and kept in specified conditions at humidity chamber for six months. The formulation was checked for physical changes also analyzed for dissolution study.[10]

Result and Discussion:

The formulation was prepared using solvent evaporation technique, Using Eudragit S100 as polymer. Different formulations were prepared at different stirring speed and the stirring

time was varied. The batch specifications were shown in Table.1. when the optimizing phase increased the steering speed the particle size and entrapment efficiency was dramatically changes. The parameters was shown in Table 2. It was seen that as the ratio of drug to the polymer increased the drug content also increased and was found to be 72 – 84%[11]. All the data was shown in Table 3. It was observed that as the polymer ratio increases, entrapment efficiency also increases. Entrapment efficiency was in the range from 73 to 83%. the entrapment efficiency was shown in table 4. The cumulative percentage of release for all the formulations was found to be 58 to 67%. The effect of polymer on release rate of the formulations was found to be decreasing with increasing the concentration of polymer. The invitro release was shown in table 5.

The stability study was carried out using the batch AC3. The stability of the drug loaded microspheres was evaluated in terms of its drug content. Microspheres formulation was incubated at 4°C, room temperature, 45°C for one month. The amount of drug was detected UV Spectrophotometrically at 285 nm. The stability study results of the best formulation were mentioned in the Table 6.

Table 3- Result of the drug content prepared eudragit microspheres

FORMULATION	DRUG CONTENT
AC1	60.25 ±0.13
AC2	61.34± 0.09
AC3	66.33± 0.11
AC4	65.13 ± 0.12
AC5	61.34 ± 0.13
AC6	59.24 ± 0.09
AC7	57.34± 0.15

Table 4. Effect of stirring time at 800 rpm on the particle size and drug entrapment of microspheres

S.No.	Stirring time (minutes)	Average particle size (nm)	Drug entrapment (%)
1	45	556	77
2	60	340	80.67
3	90	200	88.90
4	120	290	84
5	180	381	80.94

Table 5. *In –vitro* drug release studies of Prepared Eudragit microspheres

FORMULATION	CUMULATIVE % DRUG RELEASE
AC1	66.52
AC2	71.5
AC3	91.36
AC4	86.44
AC5	80.36

Figure 1: In vitro drug release study of different formulation

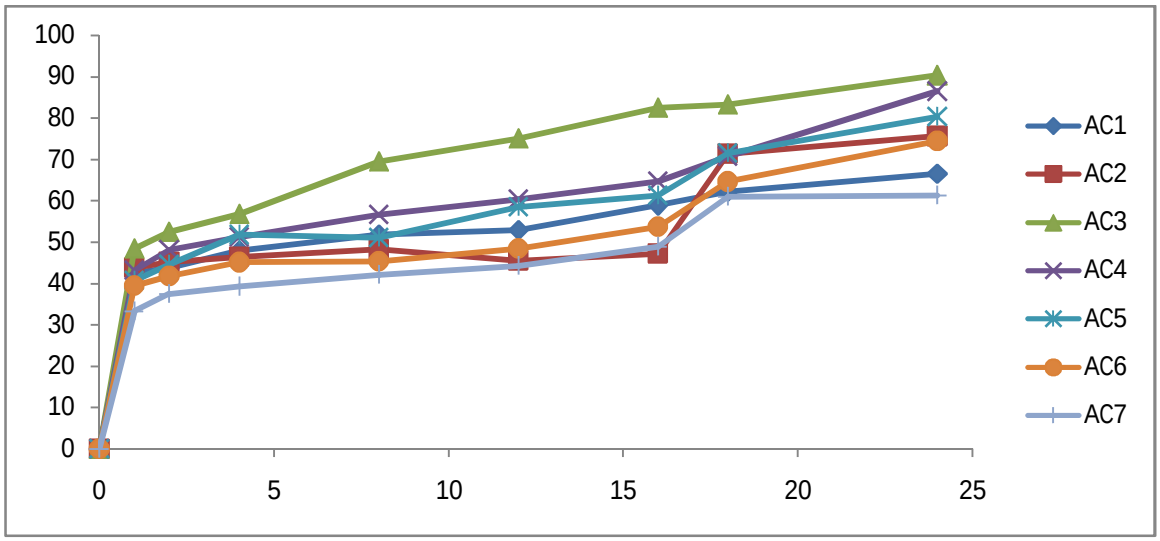

Table 6 - Results for stability studies of prepared best formulation of Eudragit Microspheres containing Aceclofenac and Omeprazole

S.NO.	TIME (IN HOURS)	AC3 FORMULATION		
		4 ±2^{0}C	**25±2**	**45 ±2 ^{0}C**
1	0	100	100	100
2	1	95.56	97.43	94.75
3	2	97.54	95.56	93.54
4	3	93.42	94.32	92.34
5	4	92.65	93.65	88.86

Conclusion:

Microspheres of aceclofenac and omeprazole combination with Eudragit-S 100 polymer in various ratios were formulated by solvent evaporation method. Addition of HPMC K4M to the continuous phase agglomeration of particles were reduced which showed larger in the initial trials.[12]

It was seen that as the ratio of drug to the polymer increased the production yield also increased and was found to be 72 – 84%. Due to increase in polymer concentration which leads to increase in viscosity of the phase the particle size of the formulation also found to be increased and the mean diameter of the microspheres were 91 – 109%.

Entrapment efficiency was in the range from 73 to 83%. It was observed that as the polymer ratio increases, entrapment efficiency also increases. The surface morphology of formulation was evaluated to its texture as well. From the the image obtained it revealed that the morphology of the microspheres were spherical and that the texture was almost smooth.[13]

The in-vitro drug release was carried out using Phosphate buffer pH 6.8 upto 6 hours. The cumulative percentage of release for all the formulations were found to be 58 to 67%. The effect of polymer on release rate of the formulations were found to be decreasing with increasing the concentration of polymer. The burst effect of in-vitro may be due to the adherence of the drug particles at the surface of the microspheres.[14-16]

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