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Research Article

FORMULATION AND EVALUATION OF INTRAGASTRIC FLOATING MICROBALLONS CONTAINING DICLOFENAC SODIUM

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ABSTRACT

Floating microballons are prepared to enhance the gastric retention time of incorporated drugs without contact with the mucosa. The objective of the present study was to prepare and evaluate floating microballons containing diclofenac sodium using Eudrajit S 100 as polymer. Diclofenac sodium dissolves slowly in the low gastric pH but allows a rapid release of drug in the higher duodenal pH. Shorter half life of drug causes higher frequency of administration. Slow release from stomach in low pH makes the drug suitable to get sustained delivery from floating microballons. Microballons were prepared by emulsion solvent diffusion technique. The formulations were evaluated for percentage yield, in vitro buoyancy, entrapment efficiency, drug polymer compatibility (IR study), particle size, scanning electron microscopy and in vitro drug release. The scanning electron microscopy confirmed their hollow structure with porous surface. Results showed that increase in stirring rate and drug: polymer ratio affect percentage yield, particle size, in vitro buoyancy and drug release of microspheres. Formulation F4 having drug: polymer ratio (1:2) exhibited excellent percentage yield(61%), in vitro buoyancy (71%), incorporation efficiency and higher percentage drug release 82.63 % for an extended duration of 8 hrs. The drug release data were fitted to various kinetic models and it was observed that the release mechanism was governed by Higuchi model with Fikian diffusion controlled as per n value of Korsmeyer Peppas Model.

Keywords: Diclofenac sodium, Eudrajit S 100, Floating microspheres, Microballons, GRDDS.

INTRODUCTION

Oral drug administration is by far the most preferable route for taking medications. However, gastric emptying rate and different pH in different segment of gastrointestinal tract are the major challenges for developing oral controlled delivery system[1]. The phenomenon of absorption via a limited part of the GIT has been termed the narrow absorption window; once this dosage form passes the absorption window the drug will be neither bioavailable nor be effective. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profile is to retain the drug reserve above its absorption region in git, i.e. in the stomach and to release the drug in controlled manner so as to achieve a zero order release kinetics (i.e. oral infusion) for prolonged period of time[2].

The different approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach are to float the delivery system over the Gastric contents, using bioadhesive delivery systems, which adhere to mucosal surfaces, making delivery systems that rapidly increase in size once they are in the stomach to slow the passage through the pylorus and by controlling density of the delivery system, which either float or sink in gastric fluids[3]. In general, appropriate candidates for controlled release from gastro retentive dosage form (GRDF) are the molecules that have been absorbed at an appropriate rate from the upper parts of git, whereas poorly absorbed from the lower parts such as from colon[4] There are various factors which will influence the GRT of a dosage form, among which density and size of dosage form, type of food intake, sex, age and body postures are important along with the gastrointestinal disorders and concurrent administration of prokinetic agents like cisapride and metoclopramide[4]. Currently more emphasis is given on floating concept of multiparticulate reservoir type delivery system[5]. Floating multiparticulate oral sustained release drug delivery system include hollow microspheres (microballons), low density floating micro pellets, floating micro beads (acrylic resin based) etc.[6,7]

MATERIALS AND METHODS

Materials

Diclofenac Sodium is received as a gift sample from STP Pharmaceuticals**,** Eudrajit S 100 (Rohm Pharma GmbH)**,** Polyvinyl alcohol and Dichloromethane (CDH, New Delhi), Ethanol, Methanol**,** Glyceryl monostearate and were procured from local dealer.

Drug-Excipient Compatibility Studies

Diclofenac Sodium and Eudrajit S100 were subjected to drug-excipients compatibility studies by Fourier Transform Infra Red Spectroscopy (FTIR)[8] . The drug and polymer were mixed physically in 1:1 ratio and the mixtures were placed in sealed vials for 3 months at room temperature. FTIR spectra of pure drug, polymer (Eudrajit S100) and drug-polymer mixtures were obtained on Perkin Elmer FTIR Spectrometer. Samples were prepared by mixing with KBr and placing in the sample holder.

Preparation of Floating Microspheres

Hollow microspheres containing Diclofenac Sodium drug in their outer polymeric shell were prepared by emulsion solvent diffusion method[9]. Weighed amount of diclofenac sodium was mixed with polymer (Eudrajit-S 100) in ratios of 1:1, 1:2 and 1:3 in a mixture of dichloromethane (DCM) and Ethanol (1:1) at room temperature. Glycerol Monostearate was added as the emulsifying agent. The resulting drug-polymer solution was poured gradually into 200 ml of water containing polyvinyl alcohol (1% w/v), maintained at constant temperature of 40^0C and the preparation was stirred at 400-1000 rpm using a mechanical stirrer for two hours to obtain o/w emulsion. The obtained microspheres were filtered, washed with water and dried over night at 60^0C. The representative formulations are given in Table 1.

Table 1: Composition of batches of floating microspheres containing Diclofenac Sodium

Formulation code	Drug (Diclofenac Sodium) mg	Polymer (mg)	Glyceryl monostearate (mg)	Solvent (1:1)	Stirring rate (rpm)
F1	200	400	300	DCM:Ethanol	400
F2	200	400	300	DCM:Ethanol	600
F3	200	400	300	DCM:Ethanol	800
F4	200	400	300	DCM:Ethanol	1000
F5	200	200	300	DCM:Ethanol	1000
F6	200	600	300	DCM:Ethanol	1000
F7	200	400	300	DCM:Methanol	1000

Yield of Microspheres

The prepared microspheres were weighed by using analytical balance and percentage yield was calculated by using the following formula[6].

% Yield = (Actual weight of product / total weight of polymer and drug) x 100

Determination of Drug Entrapment Efficiency

The drug content of diclofenac sodium loaded microspheres was determined by dispersing 50 mg microspheres in 100 ml of phosphate buffer pH-7.4, which was stirred with a magnetic bead for 24 h to extract the drug. The samples were filtered and analyzed spectrophotometrically at 276 nm and the percentage drug entrapment was calculated using the following formula[6].
Drug Entrapment Efficiency (DEE) = (Amount of drug actually present / Theoretical drug load) x 100

In Vitro Buoyancy

All the Prepared formulations F1 to F7 equivalent to 100 mg drug were dispersed in 900ml of simulated gastric fluid, prepared by using 0.1 (N) hydrochloric acid solution having pH 1.2 containing tween 20 (0.02 w/v%) at 37°C. The mixture was then stirred with a paddle at 100 rpm for 12 h. The buoyant microspheres (Wf) were pipette and separated by filtration consecutively sinking microspheres (Ws) were also separated. Both types of microspheres were dried separately at 40°C overnight. Buoyancy was determined by the weight ratio of the floating microspheres to the sum of floating and sinking microspheres[8].

% Buoyancy = [Wf / Wf + Ws)] x 100;

Where Wf and Ws are the weights of the floating and settled microspheres respectively.

Particle Size Analysis

The particle size and size distribution of drug-loaded microspheres was determined by using the Malvern Instruments[9], available at CIF, BIT, Mesra, Ranchi, India.

Shape and Surface Morphology

The shape and surface morphology of Eudrajit microspheres were investigated using scanning electron microscopy (SEM)[8] available at Metallurgy department, Jadavpur University, Kolkata, W. B.

In Vitro Drug Release

Drug release from floating microspheres was carried out using USP dissolution apparatus II at 100 rpm, for the first 2 hrs in pH 1.2 with tween 20 (0.02 W/V%) to simulate gastric fluid and 8 hrs in phosphate buffer pH 7.4. with tween 20 (0.02 W/V%) to simulate intestinal fluid[8]. At specified time interval 1 ml of sample was withdrawn and replaced with fresh phosphate buffer. The amount of drug release was analyzed at 276 nm using UV visible spectrophotometer.

Kinetic Study of Drug Release from Different Formulations

The in vitro drug release data were fitted to various kinetic models to understand the mechanisms of drug release from microspheres prepared using Eudrajit S 100.

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Studies

The FT-IR spectra of pure drug, polymer (Eudrajit S 100) and physical mixture of drug and polymer was depicted in Figure 1. FT-IR spectrum of pure diclofenac sodium exhibited distinctive peaks at 3387 cm -1 (NH stretching of the secondary amine), 1575 cm -1 (-C=O stretching of the carboxyl ion), 1557 cm -1 (C = C ring stretching) and at 747 (C- Cl stretching)[10]. It is indicated from the spectra of drug polymer physical mixture that there was no significant shift in the principal peaks of diclofenac sodium which confirms absence of interaction between the drug and matrix forming polymer Eudrajit S 100.

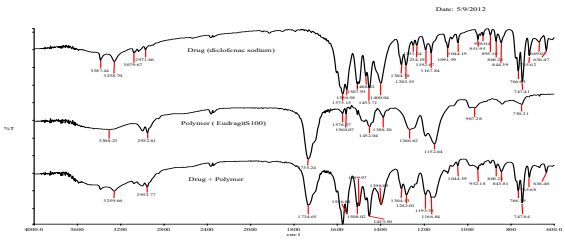

Figure 1: Image showing drug polymer interaction study by FT-IR.

Yield of Microspheres

The percentage yield of formulations F1 to F7 was in range of 20.63 to 64.53 as depicted in table 2. The effect of polymer concentration on the percentage yield was observed by changing drug and polymer ratio. The percentage yield of the microspheres was found very less (20.63) where the polymer concentration is minimum in formulation F5 and is gradually increasing with increase in polymer and found highest in formulation F6.

Drug Entrapment Efficiency

The drug entrapment efficiency is dependent on stirring rate and polymer concentration. As the stirring rate is increased gradually from 400 to 1000 rpm, entrapment efficiency is increasing from 36.53 in formulation F1 to 61.12% in formulation F4 (table2).

In Vitro Buoyancy

The test is carried out to judge the ability of microballons to float and the percentage of formulated product become buoyant. It has been found from the observations that 51.94 to 72.86% of the prepared formulations are able to float (table2) and the duration of floating time becomes longer as the particle size decreases.

Table 2: Percentage yield, in vitro buoyancy and entrapment efficiency of floating microspheres of diclofenac sodium.

Formulation Code	Yield (%)	Entrapment efficiency (%)	In vitro buoyancy (%)
F_1	32.75	36.53	56.42
F_2	44.07	42.20	60.92
F_3	47.95	47.11	60.93
F_4	54.05	61.12	70.76
F_5	20.63	30.66	51.94
F_6	64.53	41.92	64.69
F_7	52.48	58.02	72.86

Particle Size Analysis

Particle size analysis study showed (Fig. 2) that the increase in stirring speed decreases the particle size as found in case of formulation F1 and F2. The average particle size is much lower in F2 (271nm) where stirring speed is increased to 600rpm from 400rpm in F1 for which the average particle size is 452nm. It has also been found to increase with increasing polymer ratio. This is due to the increase in viscosity of the solution and the decrease in stirring efficiency[11].

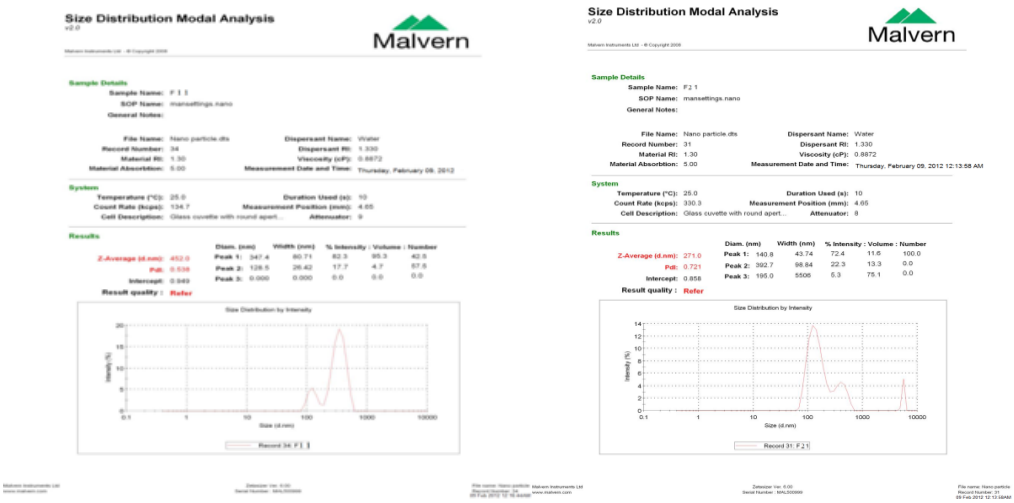

Figure 2: Particle size analysis of microspheres of F1 &F2

Shape and Surface Morphology by Scanning Electron Microscopy (SEM)

Photomicrograph (Figure 3) taken using scanning electron microscope showed that the microspheres were spherical in shape. The porous surface was also clearly seen. The porosity is due to rapid diffusion of solvents at 40^0C from the embryonic microballoons. These images also confirmed that rapid diffusion of dichloromethane causes rapture of microballoons[12].

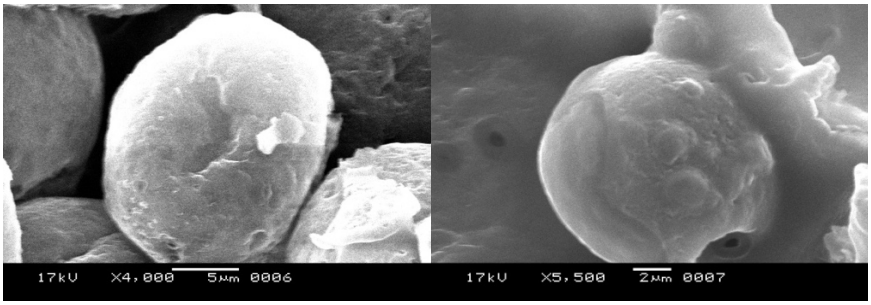

Figure 3: Scanning electron microphotographs of floating microsphere of Diclofenac Sodium.

In Vitro Drug Release

The cumulative % drug released when plotted against time in minute, it had been observed that the drug release is decreasing in formulation F2 (70.47%) and F3 (66.20%) than F1 (73.11) at the end of 8 hours. Here in the formulations F2 and F3 higher stirring rate is used. Although in case of F4 (82.63) the release is higher than F1, where F4 was prepared with highest stirring speed of 1000 rpm. Hence it could be said that the stirring rate has no significant effect on drug release. But when Eudrajit S 100 concentration was increased the rate of release was gradually decreasing as found in comparison of F5 F4 and F6, this could have been due to increase in density of polymer matrix and consequently increase in diffusional path length of the drug. When lower polymer concentration is used in F5, smaller microspheres are formed having larger surface area exposure to dissolution medium and release becomes much faster. The solvent system does not affect the drug release. Formulation F4 (prepared with Dichloromethane:Ethanol) and Formulation F7 (prepared with Dichloromethane:Methanol) were prepared with same amount of polymer (Drug:polymer ratio 1:2) show the drug release 82.63% and 89.21% at 8 hours. The in vitro drug release profile for all the formulations is shown in Figure 4.

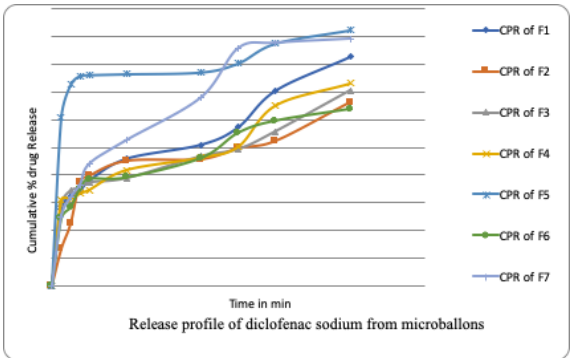

Figure 4: In vitro drug releases from the microspheres of Diclofenac sodium.

Kinetic Study of Drug Release using various In-Vitro Models

The in vitro release data of all the formulations was subjected to various kinetic models of drug release. The R^2 value for zero order, first order and Higuchi's Eq. and the slope (n) for KorsemeyerPeppas Model for all the formulations are shown in table 3. Higuchi's Equation is used as a model for diffusion controlled drug release from insoluble polymeric matrix. Korsemeyer Peppas Model was used to determine the drug release behavior from Eudrajit polymeric system. KorsemeyerPeppas model suggested as the slope (n) is <0.5, the drug release followed Fickian diffusion controlled mechanism[13].

Table 3: Drug release mechanism study by fitting into different kinetic models

Formulation Code	Zero Order Release kinetic	First Order Release Kinetic	Higuchi Model	Korsmeyer-Peppas model
F1	R^2=0.8493	R^2=0.9154	R^2=0.9452	R^2=0.8774 n=0.2423
F2	R^2=0.7159	R^2=0.8322	R^2=0.8346	R^2=0.8297 n=0.3662
F3	R^2=0.7462	R^2=0.9175	R^2=0.9079	R^2=0.8924 n=0.2108
F4	R^2=0.8027	R^2=0.9213	R^2=0.9129	R^2=0.8774 n=0.2423
F5	R^2=0.3503	R^2=0.8315	R^2=0.7852	R^2=0.7995 n=0.0858
F6	R^2=0.7666	R^2=0.9620	R^2=0.9607	R^2=0.9591 n=0.2656
F7	R^2=0.8577	R^2=0.9500	R^2=0.9743	R^2=0.9875 n=0.3855

CONCLUSION

The hollow microspheres (microballons) of diclofenac sodium using Eudrajit S 100 were successfully developed as gastro-retentive drug delivery systems for sustained action. The microspheres were round in shape with porous surface and having hollow cavity; suitable for floating. As the polymer ratio is increased in the formulation drug release is decreased. Drug: polymer ratio of 1:2 gave better entrapment, in vitro buoyancy and drug release among all formulations. The solvent system does not significantly affect the drug release. After application of various kinetic models to the drug release data, it was observed that the drug release is governed by Fickian diffusion controlled mechanism.

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