



FORMULATION AND OPTIMIZATION OF FLOATING PULSATILE ACECLOFENAC MICROSPHERES USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

The purpose of present work is to develop aceclofenac microspheres for floating pulsatile release intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. The floating pulsatile microspheres were prepared by emulsion solvent diffusion technique. A 3² factorial design was employed to study the effect of independent variables, drug to polymer ratio and stirring speed, on dependent variables, particle size and drug entrapment efficiency. The best batch exhibited a high entrapment efficiency of 90.1% and mean particle size 118.66 μm . Polymers used for the preparation were Eudragit L100 and Eudragit S100 which gets solubilized at pH above 6 and 7 respectively. The floating microsphere provides two phase release pattern with initial lag time during floating in acidic medium followed by rapid release in phosphate buffer. This approach suggested the use of floating pulsatile microsphere as promising drug delivery for site and time specific release of aceclofenac for chronotherapy of rheumatoid arthritis.

Keyword: Floating pulsatile drug delivery system, microspheres, Aceclofenac, Rheumatoid Arthritis.

INTRODUCTION

Chronopharmaceutics, the drug delivery based on circadian rhythm is gaining attention worldwide. Various diseases like asthma, hypertension and arthritis show circadian variation that demand time-scheduled drug release for effective drug action, for example, inflammations associated with morning body stiffness, asthma and heart attack in the early hours of the day¹. In this principle, an “ideal” dosage form ought to be taken at a convenient time before sleep, providing maximum drug release in the morning hours.

A pulsatile drug delivery system that can be administered at night before sleep but that release drug early morning would be a promising chronopharmaceutics system. The combinations of floating- pulsatile principle are very suitable for above mentioned diseases. Site and time specific oral drug-delivery have recently been of greater interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site specific drug release in the upper gastrointestinal tract. Pulsatile drug delivery system (PDDS) is characterized by a time period of no release (lag time) followed by a rapid and complete drug release. The combination of floating-pulsatile delivery provides various advantages such as nearly constant drug level at the site of action, avoidance of undesirable side effect, reduce dose, improved patient compliance and increased gastric residence of the dosage form²⁻⁵. Additionally, multiple unit dosage forms provides many relative advantages over single unit dosage forms such as predictable GI transit time, maximum drug absorption with reduced inter and intra subject variability due to difference in gastric emptying rate, thus giving greater product safety. Various approaches like pulsatile release displaying rapid as well as transit release and specific technologies like OROS®, CONTIN®, CEFORM®, TIMERx®, etc. based on various principles and mechanisms have been developed for chronotherapy. The major disadvantage of these systems is that they do not have long residence time which is desired for diseases needing morning medication⁶. To overcome this, novel approach termed as “floating pulsatile drug delivery

system” is to be developed. The main objective of the present work is to develop a multiple unit, floating pulsatile drug delivery system for Aceclofenac to provide relief for rheumatoid arthritis.

Computer-aided optimization technique, using a 3² factorial design, was employed to investigate the effect of 2 independent variables (factors) (i.e., the drug-to-polymer ratio and stirring speed) on particle size and drug entrapment efficiency.

MATERIALS AND METHODS

Aceclofenac was purchased from Amoli Organics Pvt. Ltd. Mumbai India. Eudragit-S100 and Eudragit-L100 were obtained as a gift sample from Evonik Degussa India Pvt. Ltd. Mumbai. All other chemicals/reagents used were of analytical grade.

Preparation of microspheres

Microspheres containing aceclofenac as a core material were prepared by emulsion solvent diffusion technique. Drug, Eudragit S100 and Eudragit L100 were mixed in dichloromethane and ethanol at 1:1 ratio at room temperature. The resulting drug-polymer solutions were poured gradually into 200ml of water containing 0.50%w/v polyvinyl alcohol, maintained between 30-40°C and the preparation was stirred at 500 rpm for one hour using a mechanical stirrer equipped with three bladed propellers. The microspheres obtained were washed repeatedly with water until it was free from polyvinyl alcohol. The collected microspheres were dried overnight at 60°C⁷⁻¹⁰.

Experimental Design

Factorial design was employed during the construction of batches. It was applied for two factors with three levels for each. Thus 3² factorial design was employed to assess the effect of independent variable on the constructed batches and to obtain the desired batch for acceptable particle size and high drug entrapment efficiency in a suitable microspheres formulation. In the formulation of microspheres two factors were varied as shown in Table 1.

Here, a commercially available software program was used (Design Expert, Version 7.0.2). The experimental design

chosen was Response Surface, 2- factor, 3- level factorial; 9 formulations were formulated. As shown in Table 2.

EVALUATION OF MICROSPHERES

Drug entrapment efficiency

About 10 mg of accurately weighed drug loaded microspheres were added into 10ml of methanol and the drug concentrations were determined spectrophotometrically at 275nm in UV-visible double beam spectrophotometer¹¹.

% Drug entrapment efficiency = Actual drug content/ Theoretical drug load expected x 100

Particle size analysis

The particle size of microsphere was determined using optical microscopy method. Approximately 100 microspheres were counted for particle size determination using calibrated optical microscope¹¹.

Floating ability of microspheres

Floating microspheres (100 mg) were placed in 0.1 N HCl (100 ml) containing 0.02% Tween 80. The mixture was stirred at 100 rpm using a magnetic stirrer and the floating times were recorded^{12,13}.

In-vitro release studies

The dissolution studies of the microspheres equivalent to 100 mg of aceclofenac were performed using USP Type 2 dissolution test apparatus. Volume of the dissolution medium was 900ml with a stirring speed of 100 rpm and the temperature was maintained at 37°C ± 0.5°C. These conditions were kept constant for all dissolution studies. The drug release study was carried out in 0.1 N HCl (pH 1.2) for a time period equivalent to floating time which varied for each batches of microspheres, followed by dissolution in phosphate buffer, pH 7.4 till complete release of drug. Periodically samples were withdrawn and filtered through Whatman filter paper and the concentration of aceclofenac was measured spectrophotometrically at 275nm¹⁴.

RESULTS AND DISCUSSION

Drug entrapment efficiency was found to be in the range of 78.15% to 90.1% and the mean particle size of the microspheres significantly increased with increasing Eudragit S100 and Eudragit L100 concentration and was in the range of 80 µm to 118.66 µm as shown in Table 3.

Effect of drug polymer ratio on responses: Response plots (Figure 1 and Figure 2) indicates that on increasing the concentration of drug-polymer ratio, the particle size was increased. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles. As the ratio of drug-to-polymer increases, encapsulation efficiency increased; this is due to higher ratio of drug-to-polymer, which would produce large size droplets with decrease surface area, here diffusion of drug from such microspheres will be slow, resulting in higher encapsulation efficiency.

Effect of stirring speed on responses: Response plots (Figure 1 and Figure 2) indicates that on increasing stirring speed, particle size was decreased and formations of microspheres were irregular in shape. The fact that high shearing rate required for emulsification caused the breakdown of the viscous drug polymer solution into fine globules resulting in small microspheres. The stirring speed has negative effect on % drug entrapment i.e. as the stirring speed was increased the % drug entrapment was decreased.

Design Expert tool was used for selection of optimized formulation. The tool offers the possibility to vary each variable simultaneously and presents possible optimum selections with their respective value. According to the desired criteria of higher drug entrapment efficiency, F7 was selected as the optimized formulation.

The floating test was carried out to investigate the floating ability of the prepared microsphere. Floating Microsphere were dispersed in 0.1 N HCl containing Tween 80 (0.02% w/v). Tween 80 was added to counteract the downward pulling at the liquid surface by lowering surface tension. Floating ability of different formulations was found to be differed according to the polymer ratio. Microspheres of Batches F1, F2, F4 and F7 remained floating for more than 6 hrs as shown in Table 4. The floating properties of microspheres may be attributed to their low density.

To simulate the pH variation of the GI tract, dissolution studies were performed first at pH 1.2 for time equivalent to floating time (round figure-hours) and then subsequently medium was replaced with fresh pH 7.4 having maintained temperature of 37±0.2°C. In pH 1.2 all the formulation showed 3-4% cumulative drug release. The low amount of drug release at gastric pH is also advantageous to reduce gastric irritation caused by NSAIDs. After this lag time, complete drug was released within 60-90 minutes in phosphate buffer pH 7.4 in which Eudragit S100 and Eudragit L100 got dissolved. The microspheres showed excellent lag at acidic pH, which may be due to insolubility of the drug and polymer as shown in Figure 3.

CONCLUSION

Novel floating-pulsatile microspheres containing aceclofenac were prepared by emulsion solvent diffusion technique. A 3² factorial design was employed to assess the effect of independent variables (drug to polymer ratio and stirring speed) on the constructed batches. Acceptable particle size and high drug entrapment efficiency were selected as the response variables for the optimized formulation. Drug to polymer ratio of 1:3 and stirring speed of 500 rpm yielded the desired responses for the optimized batch (F7).

Overall, the buoyant microspheres provided lag phase while showing gastroretention in the acidic medium, while a pulsatile drug release in the alkaline pH would be beneficial for chronotherapy of rheumatoid arthritis. The developed system offers a simple and novel technique for pulsed release of drugs in the small intestine. Such work can be further extended using various excipients for a variety of drugs suitable for chronopharmaceutical drug delivery. This approach suggested the use of floating pulsatile microspheres as promising drug delivery for site and time specific release of Aceclofenac acting as per chronotherapy of rheumatoid arthritis.

Above technology employed for the preparation of floating microspheres is relatively simple and the manufacturing process can be easily adopted in an industrial setup and on commercial scale.

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Table 1: Coded units of 3² Factorial design

Variables	Low (-1)	Medium (0)	High (1)
Drug to polymer ratio	1:1	1:2	1:3
Stirring speed (rpm)	500	700	1000

Table 2: Formulation of floating microspheres of aceclofenac: F₁-F₉

Sr.no.	Formulation code	Drug (mg)	Polymers		Stirring Rate (rpm)
			Eudragit S100 (mg)	Eudragit L100 (mg)	
1.	F1	500	250	250	500
2.	F2	500	250	250	700
3.	F3	500	250	250	1000
4	F4	500	500	500	500
5	F5	500	500	500	700
6	F6	500	500	500	1000
7	F7	500	750	750	500
8	F8	500	750	750	700
9	F9	500	750	750	1000

Table 3: Particle size and drug entrapment efficiency of floating microspheres of aceclofenac: F₁-F₉

Formulation code	Particle size μm	% Drug Entrapment Efficiency
F1	109±0.5	84.89 ± 0.005
F2	86±2.5	80.88 ± 0.01
F3	80±1	78.15 ± 0.02
F4	112.66±0.57	89.20 ± 0.01
F5	104±0.57	87.60 ± 0.04
F6	89±1	80.7 ± 0.04
F7	118.66±1.15	90.1 ± 0.04
F8	106.33±1.52	86.28 ± 0.01
F9	98.33±1.52	85.11 ± 0.02

Table 4: Floating time of microspheres: F₁-F₉

Formulation code	Floating time(min)
F1	7.5±0.25
F2	6.5±0.5
F3	4.5±0.28
F4	7.5±0.25
F5	5.5±0.25
F6	4±0.25
F7	6±0.5
F8	4±0.25
F9	3.5±0.25

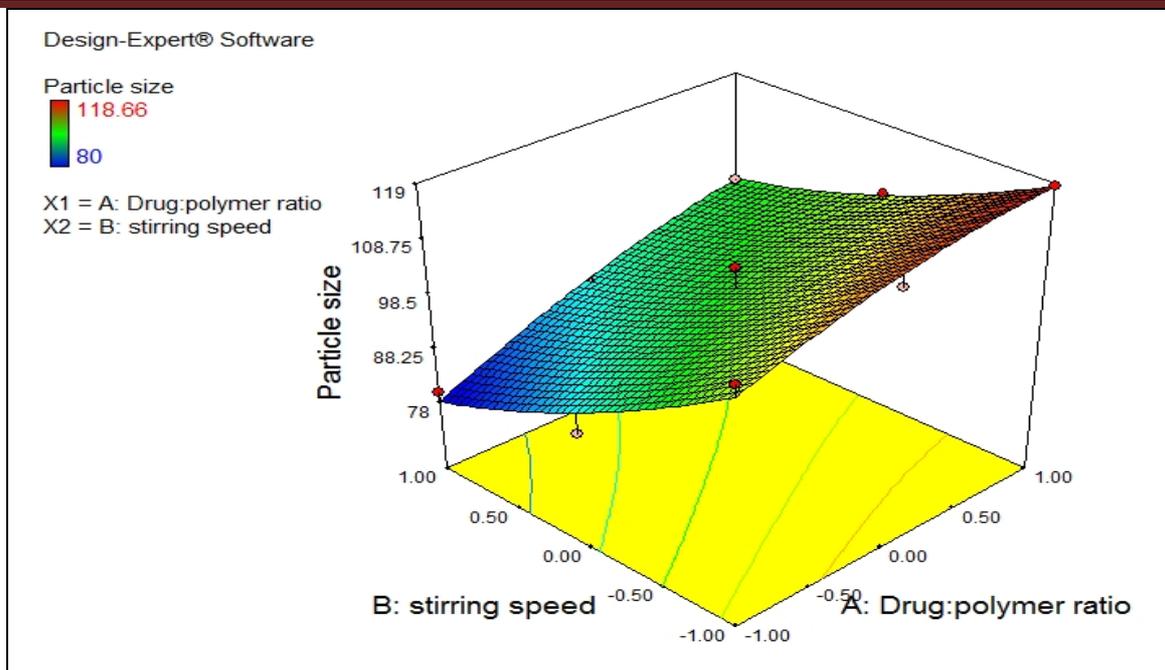


Figure 1: Response Surface Plot for Particle size

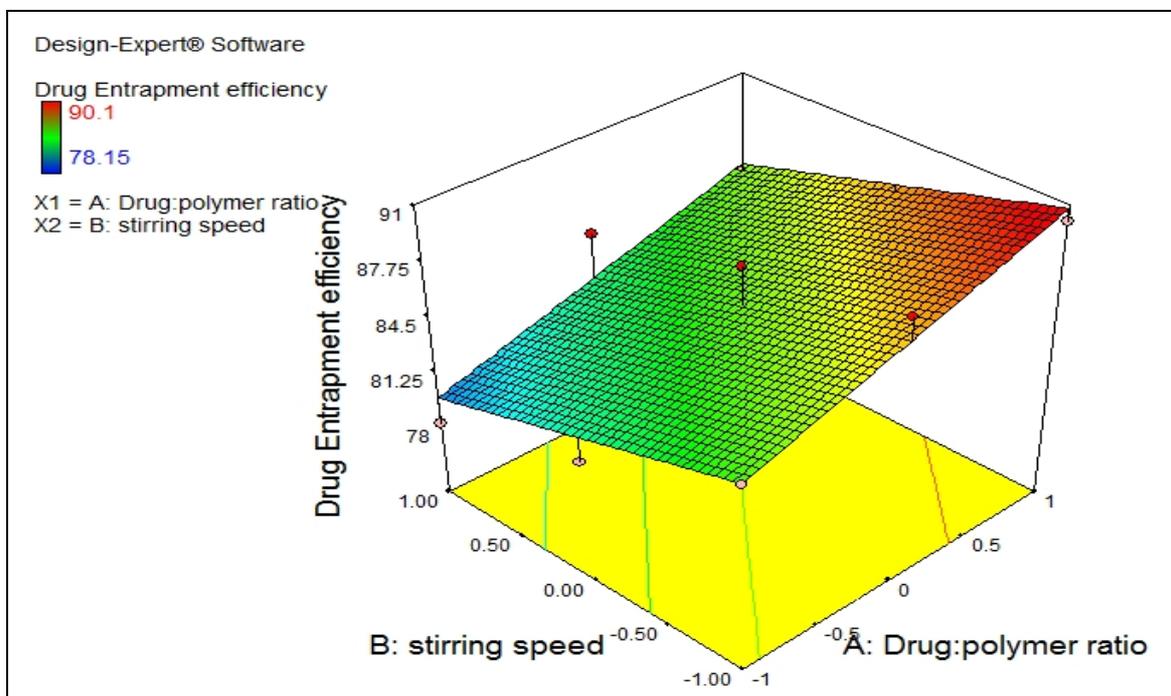


Figure 2: Response Surface Plot for Drug Entrapment Efficiency

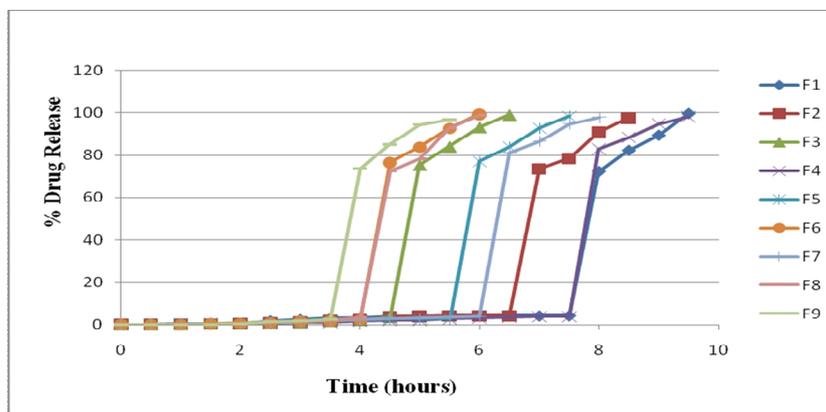


Figure 3: In vitro drug release profile of floating aceclofenac microspheres, formulation F1 to F9