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FORMULATION AND EVALUATION OF FLOATING PULSATILE DRUG DELIVERY SYSTEM OF DICLOFENAC

L. Satyanarayana*, N. Sandeepthi

Department of Pharmaceutics, Omega College of Pharmacy, Edulabad, Ghatkesar, Medchal, Telangana, India.

***Corresponding author E-mail**: satyadna_l@yahoo.co.in

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ABSTRACT

The Chronopharmacotherapy are the drug administration is synchronised with circadian rhythms Formulation development of Microspheres is more reliable formulation as compare to single type dosage formulation due to it avoids dose dumping, as per required drug release profile is achieved For microspheres many polymers are used such as albumin, gelatine, starch, Eudragit**,** Polyacrylamide (PAM) these material loading capacity is high. Micro sponges which are Spherical are called as micro-balloons. Due to its hollow structure it shows good floating properties. In these systems use of Carbon-dioxide (CO_2) as gas generating system which are used for floating purpose. The objective of present investigation is to prepare and evaluate a floating pulsatile drug delivery system of Diclofenac. The strategy adopted for microspheres containing Diclofenac as a material were prepared by emulsion solvent diffusion technique. Drug and polymer were mixed in dichloromethane and ethanol at 1:1 ratio. The drug and polymer solution were poured in water 50% w/v polyvinyl alcohol maintained at 30-40 ^{0}C and the solution was stir at 500rpm using mechanical stirrer, The microspheres obtain were washed repeatedly with water until free from poly vinyl alcohol. The developed formulations were evaluated yield of floating microspheres particle size and shape, drug entrapment efficiency in-vitro evolution of floating ability, in-vitro drug release study. On the basis of these evolution parameters it was found that optimised floating pulsatile release formulation F7 showed higher drug entrapment efficiency floating time 6.8 minutes and the drug and polymer 3^2 1:3 ratio the particle size was increased.

INTRODUCTION:

Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy". Chrono pharmaceutics principally contains of Chronobiology of disease and pharmaceutical agents. Chronobiology principally accommodates mechanism and biological rhythms study. "Pulsatile drug delivery systems are gaining importance as they deliver a drug at time and site specific manner resulting in improved therapeutic efficacy as well as compliance". The major Advantages are

System developed is reproducible type and resident time is very short, Person to person variability is less, Bioavailability is improved by this system, It reduces adverse drug reaction of drug molecule, Less irritation in body parts, In GI drug dumping problem not observed, Development various approaches available, Stability of formulation is improved, These formulation improvement patient compliance, Drug release profile is unique, Patent extension can possible by these approaches. Chronotherapeutics refers to a treatment method in which *in-vivo* drug availability is timed in relation to our body's natural rhythms (circadian rhythms) to produce maximum health benefits. It is becoming increasingly evident that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. For example, researchers have reported that asthma is worst in the early morning hours between 4 a.m. to 6 a.m., when cortisol levels in the body are low and histamine concentrations are at their highest level. In such circumstances Chronotherapeutics plays a prominent role, where the intention is that the formulation is administered in the evening, which provides treatment for disease in which symptoms are experienced in the early morning hours. The principal advantage of Chronotherapeutics pharmaceuticals is to provide optimum plasma levels of drug, resulting in maximum health benefits and minimize the undesired ones. As a consequence there is reduction of dose requirement and this is likely to improve the patient compliance. In the present study an attempt is made to develop Chronotherapeutics formulations containing Non-steroidal anti-inflammatory drug (Diclofenac). Instead of normal trial and error method, a standard statistical tool of optimization technique is adopted to identify the potential contribution of various formulation variables in the development of Chronotherapeutics formulations for anti-asthmatic drugs.

The main objective of the present study is to carry out formulation of floating- pulsatile drug delivery system of Diclofenac and to evaluate it for:

- Selection of drugs, polymers and other excipients.
- Characterisation of drug, polymer and excipients for the intended work.
- Carry out compatibility studies for the selected drug, polymer and excipients by FTIR.
- Development of floating pulsatile delivery formulation of Diclofenac.
- Characterisation of the formulation for various *in vitro* parameters.
- Statistical assessment of all the results by QbD approach.
- To carry out short term stability studies on the most satisfactory formulation as per ICH guidelines.

Preparation of Microspheres:

Microspheres containing Diclofenac 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 in to 200ml of water containing .50%w/v polyvinyl alcohol, maintained between 30-40 ^{0}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 ^{0}C.

Table 1: Formulation of Diclofenac Floating Microspheres

Coded units of 3^2 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

Formulation of floating microspheres

Sl. No.	Formulation Code	Drug(mg)	Polymers		Stirring Rate (rpm)
			Eudragit RS100 (mg)	Eudragit RL100 (mg)	
1	F1	50	25	25	500
2	F2	50	25	25	700
3	F3	50	25	25	1000
4	F4	50	50	50	500
5	F5	50	50	50	700
6	F6	50	50	50	1000
7	F7	50	75	75	500
8	F8	50	75	75	700
9	F9	50	75	75	1000

Table 2: Excipients Compatibility Study

Sr. No.	Drug + Excipients	Drug: Excipients (Ratio)	After one week 40°C/75%RH	After Two weeks 40°C/75%RH	After Four weeks 40°C/75%RH
1.	Drug	-	No colour change	No colour change	No colour change
2.	Drug + Eudragit RS100	1:5	No colour change	No colour change	No colour change
3.	Drug + Eudragit RL100	1:5	No colour change	No colour change	No colour change
4.	Drug + All excipients	5:5	No colour change	No colour change	No colour change

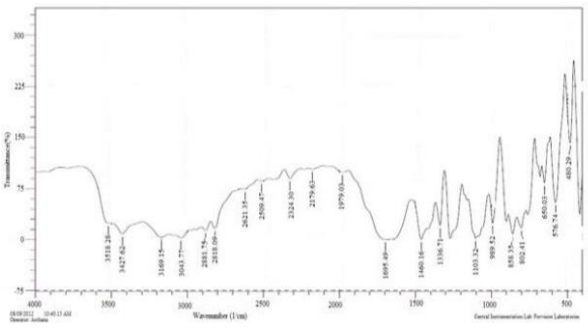


Figure 1: (FT-IR) of pure drug

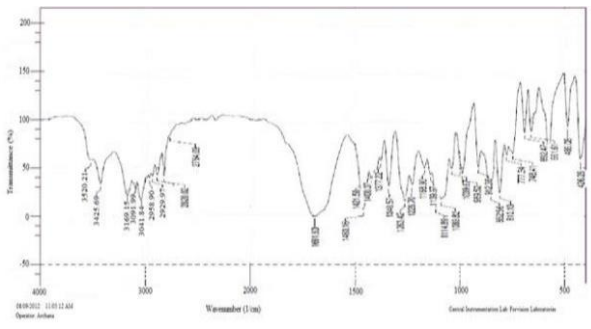


Figure 2: (FT-IR) of Drug with Polymeric Mixture

Table 3: Standard Calibration Curve for Diclofenac in 0.1N HCl

Concentration (µg/ml)	UV absorbance (mean ± S.D.)
2	0.090±0.02
4	0.170±0.03
6	0.233±0.12
8	0.314±0.21
10	0.386±0.18

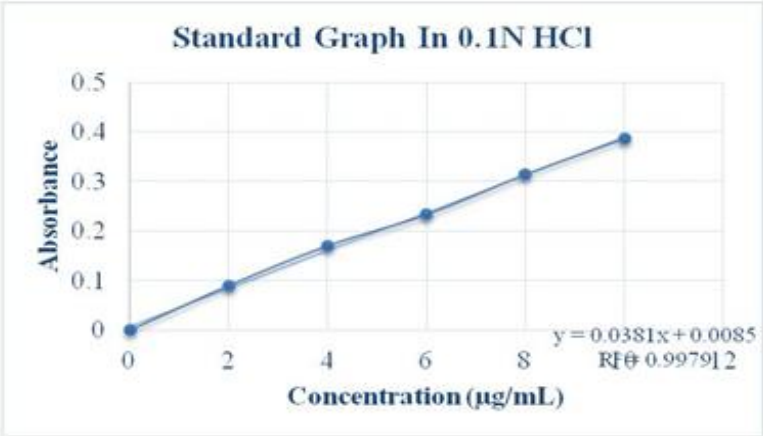


Figure 3: Standard Graph in 0.1NHCl

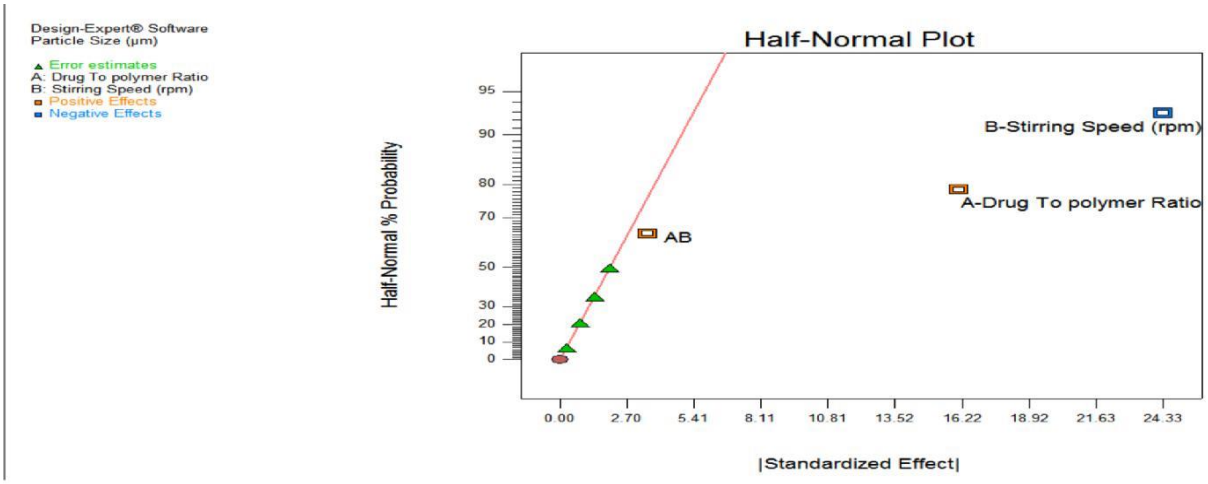
Table 4: Evaluation of Diclofenac PDDS

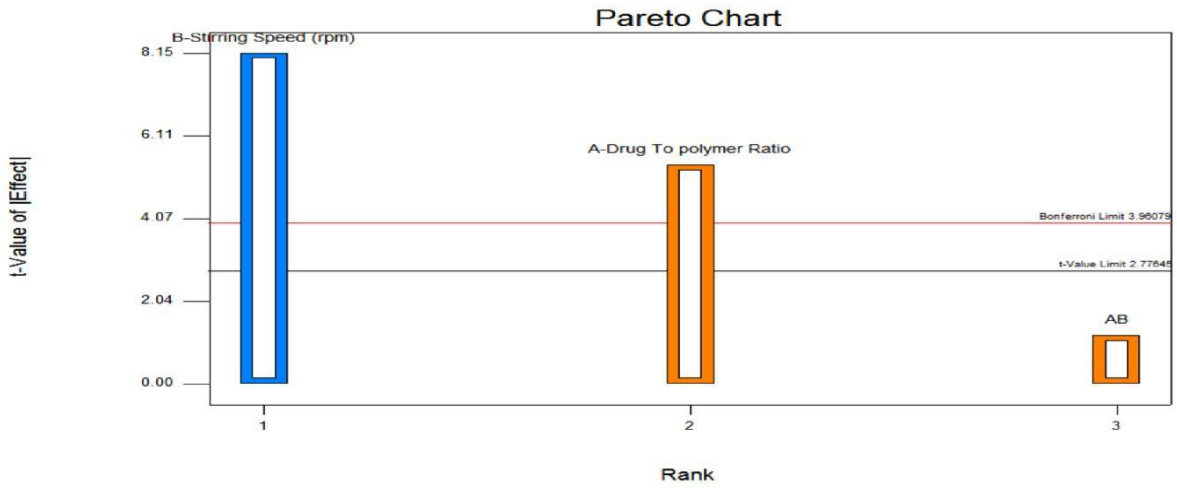
Formulation Code	Particle Size (µm)	% Drug Entrapment efficiency	Floating Time (min)
F1	110 ± 0.7	83.76 ± 0.005	7.2 ± 0.25
F2	85 ± 3.2	79.86 ± 0.01	6.4 ± 0.48
F3	79 ± 1.5	77.20 ± 0.02	4.2 ± 0.28
F4	114.25 ± 0.63	89.20 ± 0.01	7.3 ± 0.68
F5	102.5 ± 0.64	87.60 ± 0.04	5.3 ± 0.42
F6	89.8 ±1.28	80.7 ± 0.04	4.2 ± 0.25
F7	108.66 ± 1.20	95.1 ± 0.04	6.8 ± 0.46
F8	106.33 ± 1.52	86.28 ± 0.01	4.9 ± 0.25
F9	97.33 ± 1.64	84.11 ± 0.05	3.5 ± 0.25

Data Analysis

Response 1:- Particle Size (µm)

Half Normal Plot and Pareto Chart:





Experimental Design:

Factorial design was employed during the construction of batches. It was applied for two factors with three levels for each. Thus 3^2 factorial designs were employed to assess the effect of independent variables 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 the table.

To simulate the pH variation of the GI tract, dissolution studies were performed first at pH1.2 For Time Equivalent To Floating Time (4hrs) and then subsequently medium was replaced with fresh pH7.4 having maintained temperature of 37±0.2°C. In pH1.2 all the formulations showed 0% 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 min in phosphate buffer pH7.4 in which Eudragit RS100 and Eudragit RL100 got dissolved. The microspheres showed excellent lag at acidic pH, which may be due to in solubility of the drug and polymer.

CONCLUSION

Novel floating pulsatile microspheres containing Diclofenac were prepared by emulsion solvent diffusion technique. A 3^2 factorial design was employed to assess the effect of independent variables (Drug to polymer

ratio and stirring speed) on the designed batches. Acceptable particle size and high entrampment efficiency were selected as the response variables for the optimised formulation. Drug to polymer ratio of 1:3 and stirring speed of 500rpm yielded the desired responses for the optimised 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 benificial for chronotherapy of rheumatoid arthritis. This approach suggested the use of floating pulsatile Microspheres as promising drug delivery for site and time specific release of Diclofenac acting as per chronotherapy of rheumatoid arthritis.

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