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Formulation and evaluation of diclofenac microspheres for sustained drug delivery

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ABSTRACT

In the present work, Diclofenac sodium microspheres using Sodium alginate along with Ethylcellulose, Eudragit and HPMC as copolymers were formulated to deliver Diclofenac sodium via oral route. Diclofenac sodium microspheres were prepared by ionotropic gelation technique by using different polymers. The prepared diclofenac microspheres were different evaluation parameters were examined for particle size, drug entrapment efficiency and in viro drug release studies. Diclofenac sodium microspheres drug release mechanism showed that the drug release from the formulations followed zero order kinetics with higuchis model of drug release

Keywords: Diclofenac Sodium, Sodium alginate, Ethylcellulose, Eudragit, Ionotropic gelation technique

INTRODUCTION

Microspheres are small spherical particles , with particle size range 1 to 1000µm. Microspheres are also known as microparticles [1, 2]. Microspheres can be manufactured from various natural and synthetic polymers.

Diclofenac sodium is a non steroidal anti inflammatory drug used in the treatment rheumatoid arrtheritis. It has a short half life of about 1 to 2 hrs [3]. To overcome the limitations of conventional therapy, sustained / controlled release dosage forms are designed which are able to maintain steady state drug plasma leads for extended periods of time as a result of which the variations of the drug levels in the blood and drug related side effects are minimized [4, 5].

Objective behind the preparation of microspheres were increase the residence time in stomach with lesser direct contact with gastric mucosa [6, 7].

MATERIALS AND METHODS

Diclofenac Sodium, Sodium alginate (SD fine –chem pvt, Mumbai) HPMC(SD fine –chem pvt, Mumbai), Ethylcellulose(SD fine –chem pvt, Mumbai), Tragacanth(SD fine –chem pvt, Mumbai), Eudragit(SD fine –chem pvt, Mumbai), Methanol(SD fine –chem pvt, Mumbai), Calcium chloride(SD fine –chem pvt, Mumbai)

METHODOLOGY [8,9,10]

Method of preparation

Ionotropic gelation technique

Diclofenac microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polyatomic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate polymer were dispersed in purified water (100 ml) to form a homogeneous polymer mixture. The drug were added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (5% w/v) aqueous solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

Table no 1: Preparation of Diclofenac sodium microspheres

Ingredients	F1	F2	F3	F4	F5
Drug	500 mg	500 mg	500 mg	500 mg	500 mg
Sodium alginate	1000mg	-	-	500 mg	500mg
HPMC k100	-	-	-	-	500mg
Ethylcellulose	_	-	1000mg	500	-
Eudradit	-	1000mg		-	-
Methanol	5 ml	5 ml	5 ml	5 ml	5 ml
$Cacl_2$	5 gms	5 gms	5 gms	5 gms	5 gms

RESULTS AND DISCUSSION

Evaluation of Microspheres

Evaluation of microspheres can be done by determining its particle size distribution, drug entrapment efficiency and percentage yield.

Percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula,

Percentage yield = {The weight of microspheres / (The weight of polymer + drug)}*100

Particle Size Analysis

Particle size of the microspheres was determined by optical microscopy. The eye piece micrometer was calibrated with the help of a stage micrometer. The particle diameters of more than 50 microspheres were measured randomly. The average particle size was determined by using Edmondson's equation.

$$D = \Sigma nd / \Sigma n$$

Where, n = Number of microspheres checked; D = Mean of the size range

Drug Entrapment Efficiency

Microspheres were crushed using a glass mortar by pestle and equivalent to 5 mg of Diclofenac weighed. These microspheres were suspended in 25 ml of phosphate buffer pH 6.8. After 24 h, the solution was filtered; 1 ml of the filtrate was pipette out and diluted to 10 ml and analyzed for the drug content using UV Visible1spectrophotometer at 243 nm. The drug entrapment efficiency was calculated using the following formula:

% Drug entrapment efficiency = (Practical Drug content / Theoretical Drug content) X100

Drug release studies

In vitro drug release studies were carried out for all formulations in Franz diffusion cell. Microspheres equivalent to 10 mg of Diclofenac sodium were poured into 5 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions. The necessary dilutions were made with 7.4 pH buffer and the solution was analysed for the drug content spectrophotometrically using UV-Visible spectrophotometer at 243 nm against an appropriate blank. Three trials were carried out for all formulations. From this cumulative percentage drug release was calculated and plotted against function of time to study the pattern of drug release.

Table no 2 Evaluation parameters of Microspheres

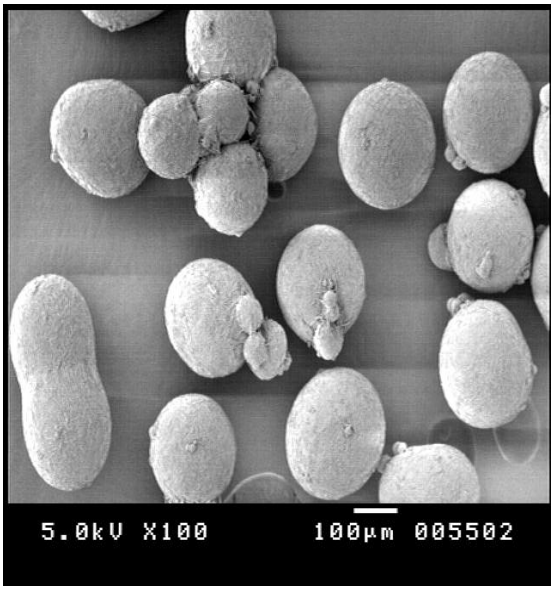
Formulation code	% yield	Particle size	Drug Entrapment Efficiency
F1	85.85	88.39	49.97
F2	79.55	93.64	49.01
F3	88.33	96.72	49.93
F4	84.23	85.24	48.26
F5	85.23	87.24	49.27

RESULTS AND DISCUSSION

Formulation F1 containing sodium alginate and maximum percentage of drug loading about 49.97% these microspheres are small in size which results more loss of drug from surface during washing of microspheres.

Surface topography by scanning electron microscopy (SEM)

SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of un entrapped drug in dispersion medium.



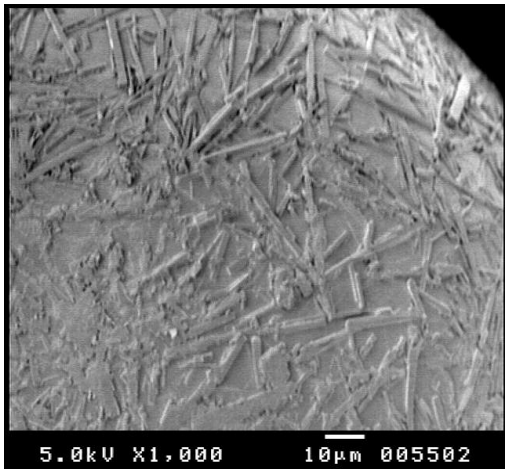


Figure no 1: SEM photograph of Diclofenac microspheres at 100x and 1000x magnification.

Table no 3: Average Particle Size analysis for formulation F1-F5

S.No	Formulation	Average particle size
1	F1	612
2	F2	616
3	F3	621
4	F4	631
5	F5	656

In vitro drug release studies

The in vitro release studies of all the sustained release microspheres formulated (F1-F5) were performed using Franz diffusion cell apparatus at 37.5±0.5 in 7.4 Phosphate buffer and samples were withdrawn and analyzed by using UV spectrophotometry at 243nm. The results were shown in table

The release profile of formulations F1-F5 comprising various polymers like HPMC K 100, sodium alginate, ethylcellulose and with different l concentrations were shown in **table**. Formulations F1, F2, F3, F4 and F5exhibits release rates of 99.826%, 95.743%, 80.256% , 88.312% and 81.908 % .The results of the in-vitro dissolution studies of formulations F1 to F5and shown in table .The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of % CDR for formulations F1 to F5.

Table no 4 : Drug release studies of all formulations

TIME (hours)	F1	F 2	F3	F4	F5
1	63.519	35.185	37.449	34.225	57.421
2	69.471	52.680	53.109	53.109	53.109
3	75.628	76.452	57.949	67.229	58.910
4	86.990	84.521	63.232	73.541	63.124
5	91.907	85.845	65.664	75.143	65.129
6	94.432	87.997	68.725	78.613	69.907
7	97.520	90.159	70.979	80.812	70.153
8	99.826	91.508	73.656	83.612	76.612
9	----------	95.743	80.256	88.312	81.908

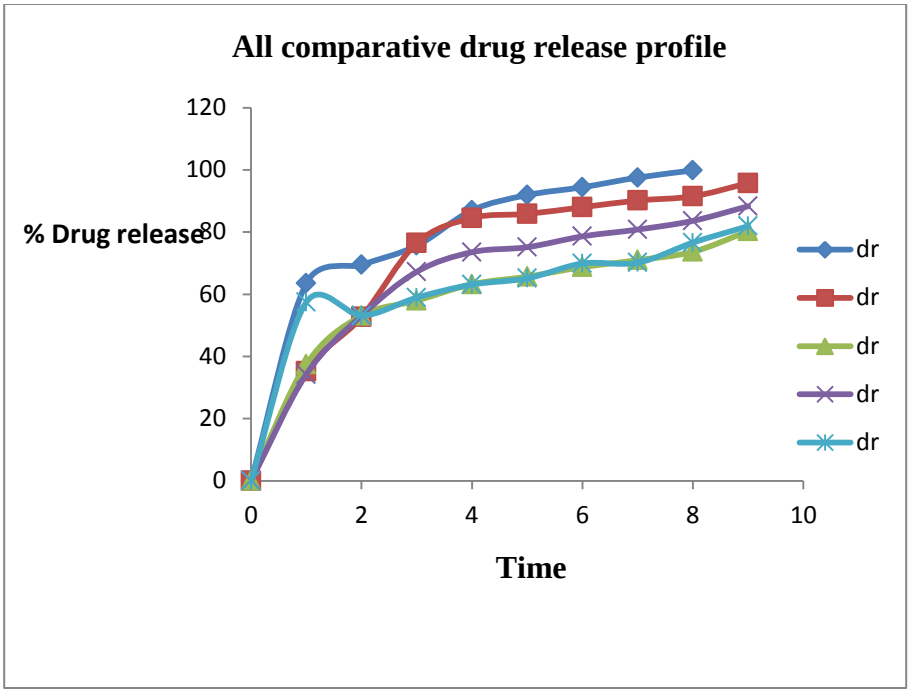


Figure no 2: Drug release studies of all formulations

Optimized formulation Containing sodium alginate showed maximum release at 8hours. This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

In vitro drug release studies

Table no 5: kinetic models

S.NO	time	log T	Square root of Time	%CR	%Drug remaining	log %CR	LOG% DRUG RETAINED	cube root of %drug remaining
0	0	0	0	0	100	0	2	4.642689
1	1	0	1	5.73	92.17	0.765668	1.973813	4.549564
2	2	0.30102	1.413214	6.21	94.79	0.857835	1.966501	4.527242
3	3	0.467121	1.632051	8.4	96.4	0.929417	1.961411	4.516064
4	4	0.60306	2	9.52	92.27	0.987566	1.954592	4.476037
5	5	0.69797	2.235068	10.31	88.6	1.013837	1.953792	4.37542
6	6	0.768151	2.44849	62.4	26.5	1.859729	1.440809	3.12206
7	7	0.835098	2.64751	79	10	1.94839	1.061393	2.23298
8	8	0.91329	2.828326	98.6	0.6	1.987259	-0.39674	0.736706

Table no 6: Correlation coefficient values for release kinetics of sustained release microspheres

Drug Kinetics	Optimised Formula
First-Order	0.689
Zero-Order	0.762
Higuchi	0.561
korsermeyer peppas	0.657

Zero order kinetics

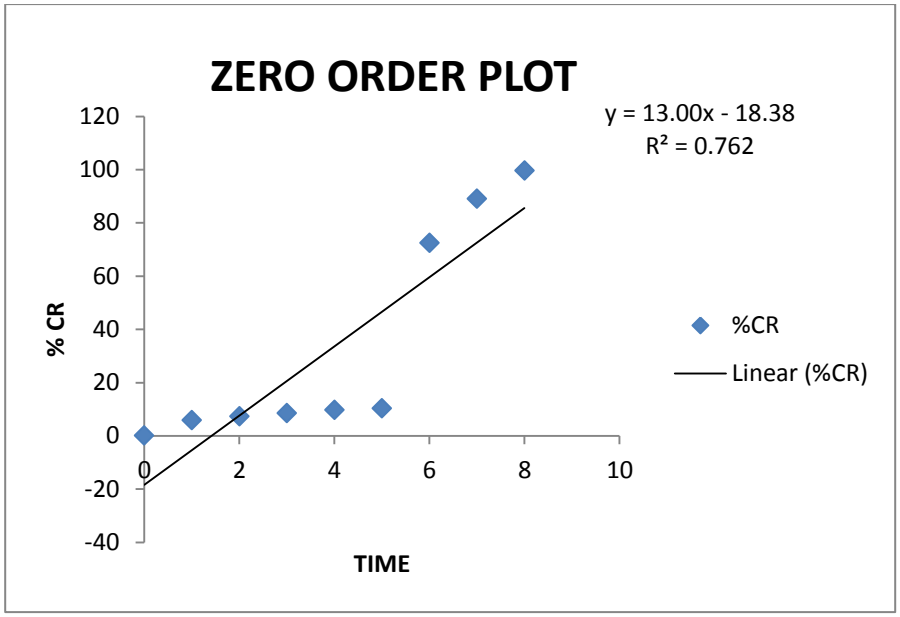


Figure 3: Zero Order Plot For Optimized Formulation:

First order kinetics

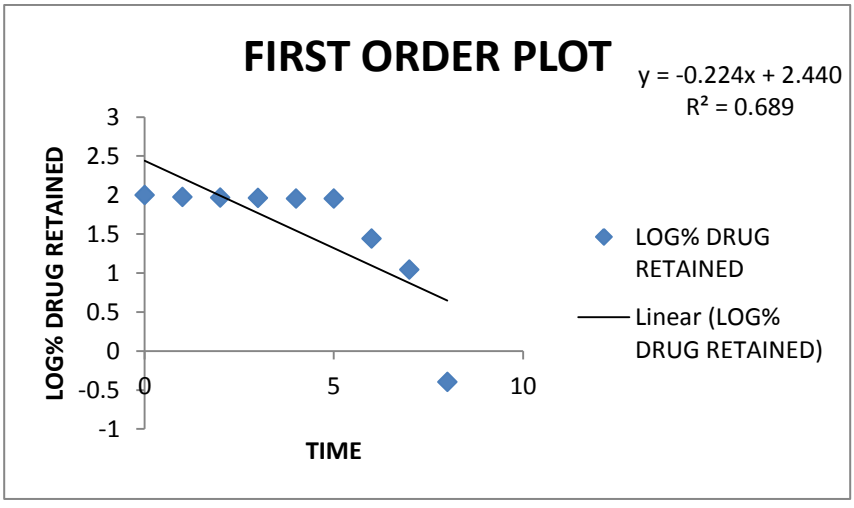


Figure 4: First Order Plot for Optimized Formulation

Higuchi Model

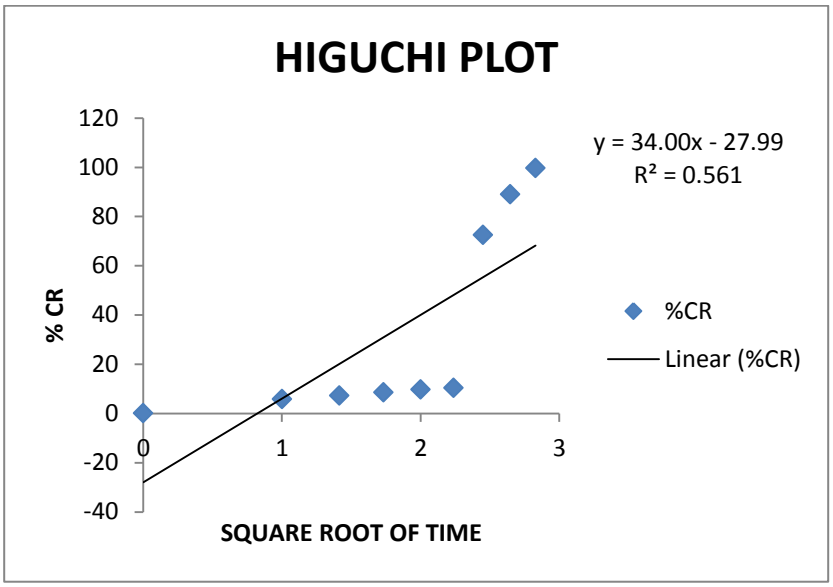


Figure 5: Higuchi Plot for Optimized Formulatio

Korsmayer Peppas equations

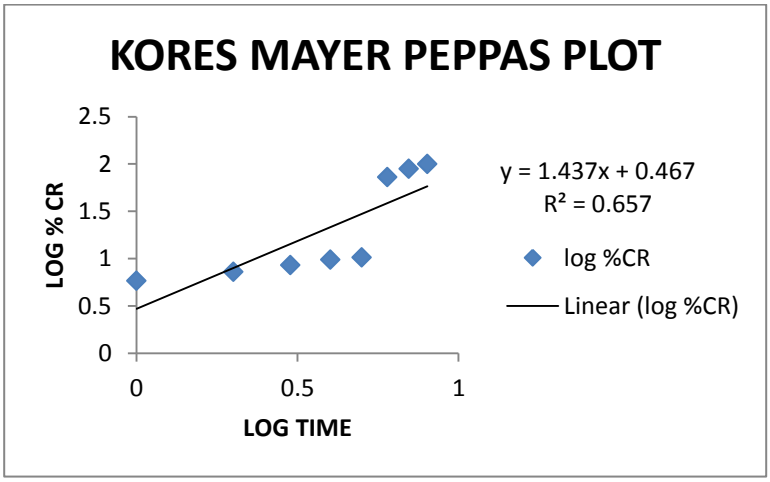


Figure 6: Kores Mayer Peppas Plot For Optimised Formulation

Hixon Crowell erosion equation

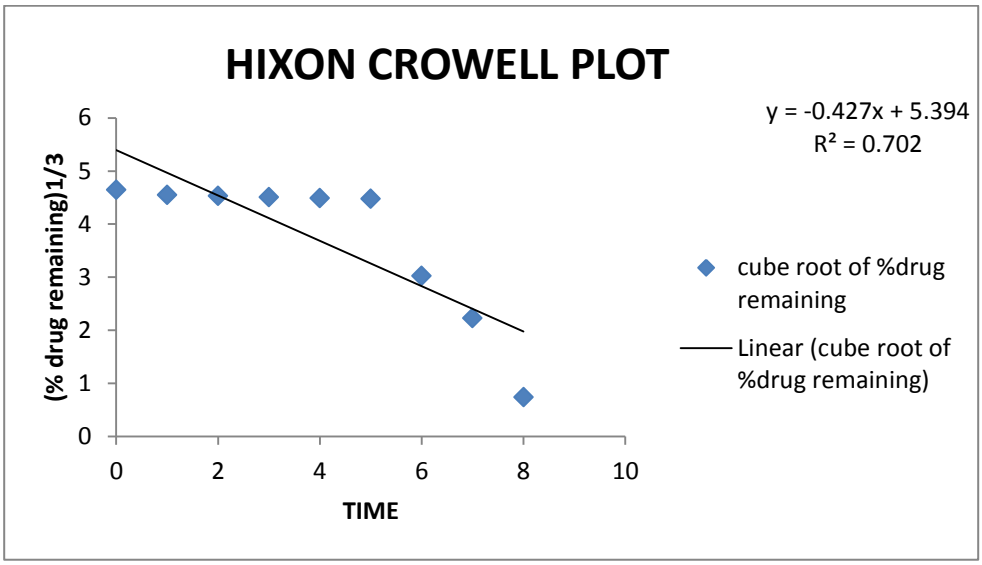


Figure 7: Hixson Crowell Plot for Optimized Formulation

Table no 6: Correlation coefficient values for release kinetics of sustained release microspheres

Drug Kinetics	Optimised Formula
First-Order	0.8587
Zero-Order	0.8587
Higuchi	0.9415
korsermeyer peppas	0.9756

CONCLUSION

Rationale of the present study was to prevent extensive metabolism of the drug and consequently to increase the oral bioavailability of the drug in the form of sustained release microspheres.

Attempt has been made to prepare sustained release microspheres of Diclofenac Sodium, a highly water soluble drug. These microspheres are used to treatment of rheumatoid arthritis. The microspheres were prepared by Ionotropic gelation technique method using Ethylcellulose, Eudragit, Sodium alginate, HPMC polymers as retarding polymers and evaluated for parameters like percentage yield, particle size, entrapment efficiency and the effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on evaluated parameters. Microspheres morphology was evaluated by SEM.

The yield and entrapment efficiency was high for Sodium alginate microspheres were Particle size, entrapment efficiency and production yield were influenced by the type of polymer, polymer concentration, stirring speed and combination of polymers. *In vitro* dissolution of optimized formulations of various Polymer in pH 7.4 formulations are releasing the drug up to 8 hrs.

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