

PREPARATION OF MICROSPHERES OF DICLOFENAC SODIUM BY IONOTROPIC GELATION TECHNIQUE

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ABSTRACT

Diclofenac sodium is a non-steroidal anti-inflammatory drug used in the treatment of arthritis. Treatment with NSAIDs is observed to have gastro intestinal side effects and the formulation of Diclofenac sodium using biodegradable and biocompatible polymer in the form of microspheres is expected to decrease GI side effects. In the present study, different microsphere formulations of Diclofenac Sodium were formulated by Ionotropic Gelation Technique using sodium alginate as carrier and Eudragit S100 as release modifying agent. Microspheres of Diclofenac Sodium prepared in this study were evaluated for flow properties, drug entrapment efficiency and drug release from tablets. Of the various formulations prepared, formulation F4 was found to show satisfactory results. Drug release data was fitted into various kinetic models and was found to be following Michaelis Menten release. Sustained release microspheres of diclofenac sodium were successfully prepared using Ionotropic Gelation Technique and the Tablets containing drug polymer ratio of 1:2 were found to sustain the release of the active substance for 12 hours when examined in pH 7.5 phosphate buffer. These results demonstrate the suitability of the prepared microspheres of Diclofenac sodium as sustained release dosage form.

Keywords: Ionotropic gelation, Sustained release, Diclofenac sodium, Sodium alginate

INTRODUCTION

Diclofenac sodium is a Non-Steroidal Anti-inflammatory Drug used in the treatment of arthritis. It has a short half life of about 1 to 2 hours and requires multiple dosing. Generally 100 to 200 mg of drug in divided doses is prescribed to be administered twice or thrice a day for chronic pain associated with arthritis and this leads to fluctuation in drug blood levels and causes dose related side effects. To overcome the limitations of conventional therapy, sustained/controlled release dosage forms are designed which are able to maintain steady state drug plasma levels 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 [1]. Sustained release preparations are useful to reduce the dosage frequency to improve patient convenience [2]. Diclofenac sodium with its low oral bioavailability and short plasma half life is an ideal candidate for formulation as a sustained release drug delivery system. The most frequent adverse side effects of Diclofenac sodium on long term administration are gastro-intestinal disturbances, peptic ulceration and perforation [3]. In order to eliminate the gastrointestinal adverse effects of this drug, several swellable controlled-release pharmaceutical dosage forms have been developed [4]. From literature survey, it is evident that multiple unit systems are better distributed and tend to cause lesser GIT irritation. The SR formulations of NSAIDs have been proved to minimize the side effects [3]. Furthermore, administration of NSAIDs incorporated multiparticulates can avoid undesired intestinal retention of polymeric material, which can occur in case of a single unit form, particularly on chronic dosing [5].

When orally administering Diclofenac sodium conventional formulation, it was difficult to achieve the desired clinical effect, because it elicited patients' incompliance of administration in the early morning to coordinate the rhythm of rheumatoid arthritis, due to rapid absorption of the conventional formulation (Gang et al., 2004). Therefore, the present study was designed to formulate microspheres of Diclofenac sodium using Ionotropic gelation technique in continuation to earlier studies but using hydrophilic drug carrier along with release retarding polymer to develop a suitable drug delivery system.

Microencapsulation has been a common technique in the production of controlled release dosage forms [6]. Microencapsulation is a process by which solids, liquids or even gases may be enclosed in microscopic particles formation of thin coatings of wall material around the substances [7].

Recently, aqueous polymeric dispersions have played a great role in replacing organic solvents in the coating of solid dosage forms with soluble polymers. These polymeric dispersions form a homogenous film on drying and provide a diffusion controlled release of the drug from the polymer matrix [8].

Microspheres are characteristically free flowing powders consisting of protein or synthetic polymers which are biodegradable in nature and ideally having particle size less than 1000m [9].

Microparticles play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects [10].

The objective of the present study was to develop microspheres of Diclofenac sodium by Ionotropic Gelation Technique using hydrophilic carrier to sustain the release so as to reduce the frequency of dosing and to improve patient compliance.

MATERIALS AND METHODS

Chemicals: Diclofenac Sodium, Eudragit S 100, Sodium alginate and Calcium chloride were provided by Dr. Reddy's Laboratories Limited.

In Ionotropic gelation technique, the preparation of drug containing microparticles is based on the principle of coalescence of colloidal polymer particles. Ionotropic gelation of the anionic polysaccharide sodium alginate with oppositely charged calcium ions forms microparticles. Subsequent curing step induces the fusion of colloidal polymer particles into a homogenous matrix. During the coating and drying process, the colloidal polymer particles coalesce and fuse into a homogenous film [11]. It is a cost effective technique that establishes intimate contact of the drug with the release retardant.

Alginate is a natural biopolymer which has been used widely due to its non-toxic, biodegradable and biocompatible nature. Alginate is a linear copolymer of p-o-mannuronic acid and u-L-guluronic acid linked by (1-4)-glycosidic bonds [12].

Alginate gelation takes place when divalent cations, interact ionically with blocks of guluronic acid residues, resulting in formation of three-dimensional network [13].

Sodium alginate is soluble in water and forms a reticulated structure which is cross-linked with divalent calcium chloride to form insoluble meshwork. Alginate's unique property of forming water insoluble calcium alginate gel through ionotropic gelation with calcium ions is a simple, mild and eco-friendly condition to

encapsulate drugs. Another important property of alginate beads is their re-swelling ability. This property is sensitive to the environment pH [11]. Alginate has a property of coating on the drug core and also acts as release rate retardant [14].

Polymethacrylate copolymers are widely used as coating materials in oral pharmaceutical formulations [7]. Eudragit S 100 is a Type B methacrylic acid which is soluble only above pH 7.0 and thus resistant to gastric fluid [15].

Diclofenac Sodium, one of the most useful NSAID, is a practically insoluble compound in acidic solution ($pK_a = 4.0$), but dissolves in intestinal fluid and water [16]. It is a benzene acetic acid derivative. The chemical name is 2- [(2,6-dichlorophenyl)amino] benzene acetic acid, monosodium salt [17].

Preparation of Microspheres

Microspheres of Diclofenac sodium were prepared by ionotropic gelation method using Sodium alginate, Eudragit S100 and calcium chloride. Weighed quantity of drug and polymer were added to 50 ml of sodium alginate solution with stirring at about 300 rpm. The resultant solution was then added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 30 minutes. The obtained microspheres were filtered and washed with purified water and then dried for 6 hours at 40°C.

Preparation of microspheres was optimized based on entrapment efficiency and release data.

The dried microspheres were sifted through mesh 30 ASTM.

Tablets were compressed so that each tablet contained microspheres equivalent to 100 mg of drug.

Hardness was maintained at 4-5 kp and tested for friability. The tablets were found to meet the friability limit of 0.1% w/w.

Dissolution studies

Dissolution studies of different formulations were carried out in the following conditions,

Apparatus: USP II

Media: Acid stage: 0.1 N Hydrochloric acid for 2 hours

Buffer stage: 0.05 M pH 7.5 Phosphate buffer for 12 hours

RPM: 75

Time points: 1, 2, 4, 6, 10 and 12 hours in buffer stage.

UV Wavelength: 276 nm

Details of composition of various formulations prepared are mentioned in the below table.

Drug entrapment efficiency

Encapsulation efficiency = (actual drug loading / theoretical drug loading) X 100 %

Drug loading depends on the solubility of the drug in the external phase. Stirring time becomes very critical for water soluble drugs as they may diffuse into the gelation medium leading to decreased efficiency of encapsulation of the drug.

Table 1: It shows the composition of the prepared formulations

Formulation code	Drug: Eudragit S100	Sodium alginate solution (% w/v)	Calcium chloride solution (% w/v)
F1	1:1	4	5
F2	1:2	4	5
F3	2:1	2	5
F4	1:2	2	5
F5	2:1	3	5

Flow property

Flow of microspheres was studied by assessing angle of repose. Prepared microspheres were allowed to fall freely through a funnel fixed at 1 cm above a flat surface until the microspheres touched the tip of the funnel.

$$\theta = \tan^{-1}(H/R)$$

H - height of cone

R - radius of microspheres on surface.

Dissolution

An aliquot of sample was withdrawn at suitable time intervals and the same amount of volume was replaced with fresh dissolution medium.

Kinetics

To understand the kinetics of drug release, dissolution data of the formulations was fitted to various release models.

RESULTS AND DISCUSSION

Particle size decreases by increasing the stirring speed of calcium chloride solution and increases by increase in the sodium alginate concentration.

With increase in the concentration of sodium alginate, drug entrapment efficiency and particle size were found to increase.

The percentage entrapment efficiency was found to be between 40 and 85 depending upon the process parameters. The microspheres obtained by longer exposure to the crosslinking agent have shown lower entrapment efficiency but sustained the release of Diclofenac sodium.

Angle of repose obtained for different formulations was between 29 and 37°.

Release of diclofenac sodium from the tablets was studied for a period of 12 hours in phosphate buffer after 2 hours exposure in acid media.

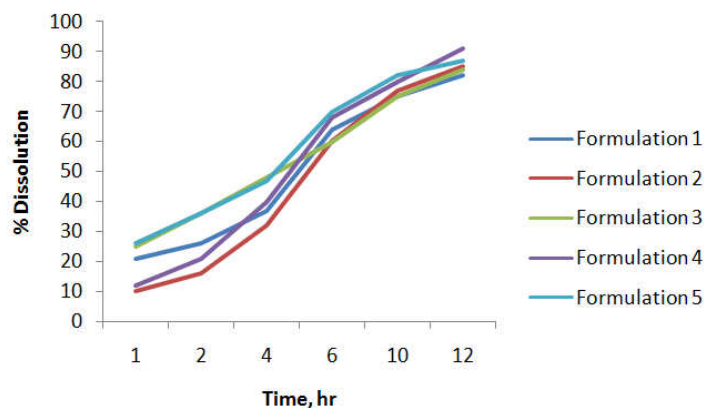


Fig. 1: It shows In vitro Dissolution profile of the prepared formulations

Table 2: It shows % drug release data observed for various formulations in buffer stage

Time, hr	Formulation 1	Formulation 2	Formulation 3	Formulation 4	Formulation 5
1	21	10	25	12	26
2	26	16	36	21	36
4	37	32	48	40	47
6	64	60	60	68	70
10	75	77	75	80	82
12	82	85	84	91	87

The release was observed to be slow and extended.

Due to low solubility of sodium alginate and diclofenac sodium being practically insoluble in acidic medium, there was no observable release of diclofenac sodium in 0.1 N HCl.

Among the formulations, suitable sustained release till 12 hours was obtained with formulation F4.

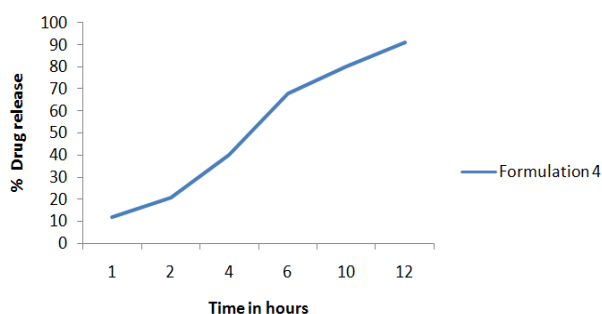


Fig. 2: It shows the invitro Dissolution profile of the finalized formulation, F4

The release was observed to be sustained in a slow and uniform manner in the presence of release retardant than with sodium alginate alone.

The following parameters have been studied for different models to understand the best fit model.

Root Mean Square Error (RMSE),

Akaike Information Criterion (AIC): It is a measure of relative goodness of fit of a statistical model.

Bayesian Information Criteria (BIC) or Schwarz Criterion: It is based in part on the likelihood function and is closely related to AIC.

Coefficient of Determination (R^2): The highest R^2 value determines the best fit model.

The minimum value of AIC and BIC denotes the best fit model [18].

Drug release data of F4 was best fitted to Michaelis Menten model. The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance is not constant as it is with linear pharmacokinetics, but is concentration or dose-dependent.

Table 3: It shows the drug release kinetics of different formulations [18]

Model	Parameters	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Zero order	RMSE	5.63	5.74	3.12	6.98
	AIC	3.55	3.57	2.84	3.81
	BIC	3.51	3.53	2.8	3.76
	R^2	9.44	9.61	9.77	9.44
First order	RMSE	9.62	1.5	6.24	1.56
	AIC	4.19	4.73	3.67	4.77
	BIC	4.15	4.68	3.63	4.73
	R^2	8.98	8.67	9.01	8.36
Korsemeyer Peppas	RMSE	4.72	5.47	8.29	6.49
	AIC	3.34	3.51	1.25	3.72
	BIC	3.29	3.47	1.21	3.68
	R^2	9.59	9.83	9.99	9.83
Weibull model	RMSE	4.99	3.67	2.54	3.65
	AIC	3.41	3.03	2.59	3.03
	BIC	3.36	2.98	2.55	2.99
	R^2	9.48	9.81	9.84	9.86
Hixson Crowell	RMSE	7.88	1.05	0	1.15
	AIC	3.95	4.29	3.41	4.41
	BIC	3.91	4.25	3.36	4.37
	R^2	9.17	9.09	9.33	8.82
Michaelis Menten	RMSE	1.01	6.55	5.71	4.7
	AIC	4.25	3.73	3.56	3.33
	BIC	4.21	3.69	3.52	3.29
	R^2	8.97	9.82	9.78	9.95
Hills equation	RMSE	6.06	4.89	4.03	5.14
	AIC	3.64	3.38	3.15	3.44
	BIC	3.59	3.34	3.1	3.4
	R^2	9.3	9.64	9.54	9.6

CONCLUSION

Sustained release formulation of Diclofenac Sodium was successfully prepared using sodium alginate in combination with Eudragit S100 by Ionotropic Gelation Technique. The *in vitro* dissolution data showed sustained release of the formulation up to 12 hours. The microspheres were prepared without the use of organic solvents. Microspheres of Diclofenac sodium decrease the incidence of side effects and also improve patient compliance by reducing the number of dosings and by reducing the fluctuations of drug in the blood.

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