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Research Article

Effect of Different Parameters on the Release of Diclofenac Modified Tablets

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ABSTRACT
In the present study the influence of designing and development of sustained release (SR) matrix tablets of diclofenac sodium were investigated. The aim was to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance. Sustained release matrix tablets of diclofenac sodium, were developed by using different drug: gum ratios, using Xanthan gum as matrix former, microcrystalline cellulose as diluent and Polyethylene Glycol (PEG 6000) as release modifier. Formulated tablets were evaluated for friability, hardness, thickness and their relation to the amount of gum: drug ratio and drug release. The drug release was evaluated in different pH, rotation speed and stirrer. All the formulations showed compliance with pharmacopeial standards. Formulation consisting of drug: Gum ratio of 1:0.12 showed sustained release of drug for 12 hours with 89.67% release. The release pattern showed constant kinetics. Thus, (Xanthan Gum) can be used in as effective matrix former.

Keywords: Xanthan gum- hydrophilic matrix - sustained release, diclofenac sodium.

INTRODUCTION

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release (CR) drug delivery systems[1]. Although the matrix system is the most innumerable method used in the development of controlled release (CR) formulations, there are a lot of parameters which control the release of the drug from it. Beside, long-term therapy for chronic disease conditions, multiple administration is inconvenient to the patients[2]. Therefore, improving drug delivery system by maintenance of a steady drug plasma concentration is the aim of many studies to improve therapeutic efficiency by sustain release the drug[3].

The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms[4]. Also the matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behaviour[5]. In fact, a matrix is defined as a well-mixed composite of one or more drugs with a gelling agent i.e. hydrophilic polymer[6] such as Xanthan Gum. Xanthan gum is a high molecular weight extracellular polysaccharide, produced on commercial scale by the viscous fermentation of gram negative bacterium *Xanthomonas campesteris*[7]. Its high gelling capacity is of particular interest in the field of controlled release[8]. On coming in contact with aqueous medium it hydrates at solid-liquid interface and form vicious layer which retards the release of the drug[8,9]. It is used in thickening, suspending and emulsifying water based systems and fabrication of matrices. The appropriate drug/gelling agent ratio can play a role in prolonging and controlling the release of drug that is dissolved or dispersed[10]. Diclofenac sodium is a most widely used NSAID, useful in the treatment of rheumatic disorders[11]. It is characterized by rapid systemic clearance and thus warrants the use of a SR formulation for prolonged action[9,12]. Various experimental reports indicated diclofenac sodium as a good candidate for SR formulation[12]. Few SR formulations of diclofenac sodium (100 mg) are also available commercially.

The aim of the present study was to investigate the effect of the following parameters in sustaining the release of sodium diclofenac: drug/gum ratio, physical properties of the formulations such as friability, hardness and thickness, inclusion of some additives in the formulation such as microcrystalline cellulose (MCC) as diluent and Polyethylene Glycol (PEG) as release modifier, swelling index and different dissolution conditions such as change in pH, rotation speed and stirrer. Drug release from Xanthan matrix usually is preceded by polymer erosion or hydration, or a combination of both processes, depending on the drug/diluent ratio[12]. That is why the release kinetics

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Table 1: Composition of Diclofenac Sodium SR Matrix Tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Diclofenac Sodium IP	100	100	100	100	100	100
Xanthan gum	12	16	20	24	28	12
Microcrystalline Cellulose	86	82	78	74	70	74
PEG	-	-	-	-	-	12
Magnesium stearate	02	02	02	02	02	02
Total Weight	200	200	200	200	200	200
Drug /Gum ratio	1/0.12	1/0.16	1/0.20	1/0.24	1/0.28	1/0.12

Table 2: Physical properties of Diclofinac Sodium SR Matrix Tablets.

Formulation	Hardness (Kg/ cm^2)	Friability (%)	Thickness (mm)± SD	Batch code Average weight (mg)± SD	% Drug Content mg ± SD
F1	5.50±1.10	0.20	4.59±0.02	201 ± 3.43	100.1216
F2	5.50±1.50	0.27	4.48±0.04	204±2.44	99.1534
F3	5.45± 1.35	0.33	4.41±0.07	209±2.36	99.5632
F4	5.40± 1.27	0.36	4.51±0.07	208±4.52	100.02563
F5	5.45± 1.10	0.40	4.46±0.04	209±4.01	99.2345
F6	3.00± 0.20	0.50	4.41±0.06	208±3.52	100.4562

Table 3: Formula for investigating the kinetics Function Equation.

Function	Equation
Zero order	% diss = Kt
First order	% diss = 100 { 1- e-kt}
Higuchi	% diss = Kt 0.5
Korsmeyer- Peppas	Q = Kptn

and mechanism of drug release were also investigated by using various release kinetics model equations.

MATERIALS AND METHODS

Materials

Diclofenac sodium (DS), the pharmacopoeial grade of Xanthan gum (XG), (USP/NF, viscosity of 1% aqueous solution is 1350 cps at 25°, particle size less than 14.28 µm) was obtained from. Global Company,Dubai, UAE, ., Polyethylene glycol (PEG) was obtained from Dubai Pharmacy store, UAE, ; microcrystalline cellulose (MCC) Avicel PH101® from Julphar Co.,RAK,UAE; and magnesium stearate from Dubai Pharmacy store, UAE,. All chemicals used were of analytical grade, and procured from commercial source.

Methods

Preparation of SR matrix tablets

SR matrix tablets of diclofenac sodium were prepared by using different drug:gum ratios viz. 1:0.12, 1:0.16, 1:20, 1:0.24, 1:0.28 , as per the formula given in Table 1. Xanthan Gum (XG) was used as matrix-forming material, while microcrystalline cellulose(MCC) was used as diluent. Magnesium stearate was incorporated as lubricant. All ingredients were passed through a # 100 sieve, weighed, and blended. The lubricated formulations were compressed by a direct compression technique, using 8 mm flat faced punches.

Preparation of modified tablets by incorporation of (PEG 6000)

Formulation F6 was modified by incorporating 12 mg of PEG 6000, to develop new formula F6 Table -1, to observe the effect of PEG 6000 on drug release. Firstly, a physical mixture of drug and PEG 6000 was heated to temperature 70 C°, till it was converted into a fluid state. It was allowed to cool, and was then dried at room temperature. This mixture was then blended with XG, diluted with MCC, and finally the lubricated formulation was compressed directly with 8 mm flat faced punch, and evaluated [13,14].

Estimation of diclofenac

Diclofenac content of the tablets was estimated by UV spectrophotometric method based on the measurement of absorbance at 276 nm in phosphate buffer of pH 6.8. The method was validated for linearity, precision and accuracy. The method obeyed Beer's Law in the concentration range

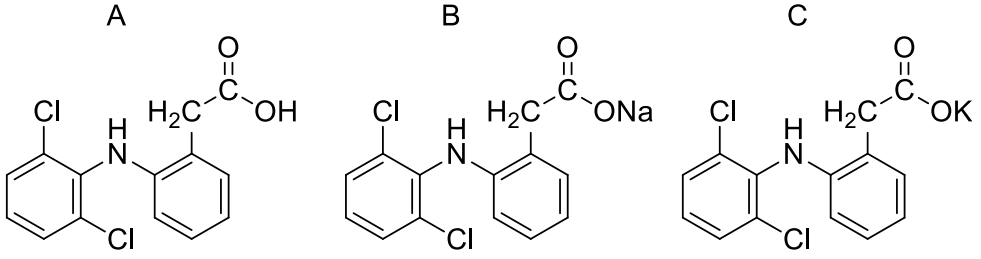

Figure 1: A Diclofenac, B: Diclofenac Sodium, C: Diclofenac Potassium

Table 4: Drug release kinetics from different matrix tablets (using Higuchi, zero order and first order release).

Formulation	Higuchi model		Zero order release		First order release	
Code	K	r^2	K	r^2	K	r^2
F1	26.77	0.9831	8.6982	0.9755	0.0981	0.9757
F2	24.49	0.9822	7.916	0.9710	0.274	0.974
F3	23.07	0.9827	7.4919	0.9741	0.263	0.9733
F4	22.08	0.9848	7.155	0.9718	0.292	0.9634
F5	21.04	0.9858	6.8239	0.9752	0.269	0.976
F6	19.568	0.9776	6.4581	0.9707	0.303	0.9545

Table 5: Determination of drug release mechanism using Peppas exponential model equation.

Formulations	n
F1	0.6741
F2	0.6652
F3	0.6223
F4	0.6277
F5	0.6215
F6	0.6985

0-10 µg/ml. When a standard drug solution was assayed repeatedly (n=6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8%, respectively[15].

Evaluation of physical properties

All the batches were evaluated for weight variation, hardness, friability, thickness and drug content as per USP XXIV monograph. The weight variation was determined by taking 20 tablets using an electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 10 tablets in a friability tester for 4 minutes at 25 rpm. Thickness was measured and SD was determined[15,16].

In-vitro drug release study

In vitro drug release was studied using USP I apparatus, with 900 ml of dissolution medium maintained at 37±1° for 12 h, at 50 rpm. 0.1 N HCl pH 1.2 was used as a dissolution medium for the first 2 h, followed by pH 6.8 phosphate buffer for further 10 h., 5ml of sample was withdrawn after every hour and was replaced by an equal volume of fresh dissolution medium of the same pH. Collected samples were analyzed spectrophotometrically at 276 nm; cumulative percent drug release was calculated. The study was performed in triplicate.

the effect of

dissolution variables including pH (1.2, 6.8), rotation speed (50,100 rpm), stirrers (paddle, basket) on drug release[17,18].

Analysis of release data

Mathematical modelling

The release profile of the drug obtained was analysed using different kinetic models Table-2 such as zero order,

first order, Higuchi, Korsmeyer- Peppas equation is used in order to evaluate the release mechanism from the matrices[19].

Swelling Index

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation F1, F3 and F5 was studied. One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 6.8. At the end of 1 h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 2 h, weights of the tablet were noted, and the process was continued till the end of 12 h, % weight gain by the tablet was calculated by formula;

$[(X_t - X_0) / X_0]_X 100$

$S.I = \{(X_t - X_0) / X_0\}_X 100$, where, S.I = swelling index, X_t = weight of tablet at time't' and X_0 = weight of tablet at time t = 0.[20]

Accelerated stability studies

Stability study was carried out to observe the effect of temperature and relative humidity on optimized formulations (F1-F6), by keeping at 4° (in refrigerator), room temperature (28°), and at 45°, at RH 75±5%. In air tight high density polyethylene (HDP) bottles for three months. Physical evaluation and *in vitro* drug release was carried out after every 1 month[16].

RESULTS AND DISCUSSION

Evaluation of physical properties

Hardness of the formulated tablets was in the range of 6-7 kg/sq.cm and the percent weight loss in the friability test was found to be less than 0.4 %, in all the formulated tablets. The content of diclofenac in all the matrix tablets was within 100±5% of the labelled amount. As such all the formulated matrix tablets prepared were of good quality with regard to hardness, friability and drug content (Table-2). All the formulations met the pharmacopoeial requirement range and all values were well within acceptable limits.

Effect of dissolution variables on drug release

Dissolution studies were conducted at two pH conditions acidic pH 0.1N HCl and pH 6.8 buffer and the effect of pH and time was studied in all formulations. It showed that the tablet dissolved in alkaline medium as compared to acidic pH (Figure-1). From this it could be concluded that all the batches showed pH dissolution dependent. The increase in the percentage release may be due to decrease in the amount of polymer as hydration is a function of amount of polymer present[21].

Concerning the rotation speed, a slight positive influence was observed, as stirring speed increases, the thickness of hydrated gelatinous layer surrounding the intact tablet core decreases, resulting in slight increase in the rate of drug release from matrix tablet (Figure-2). Our results were in disagreement with that obtained by Vazquez MJ, and et al[22] who reported a positive influence of rotation speed in drug release.

Regarding the effect of using different stirrers, there was no significant difference observed between basket method

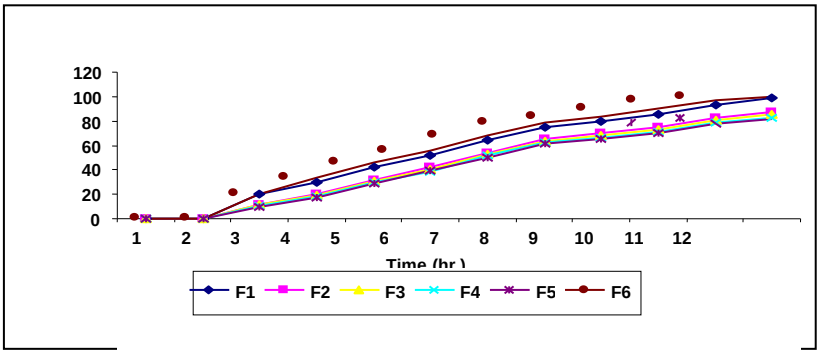

Figure 2: *In Vitro* dissolution profiles of diclofenac sodium Formulations F1-F6.

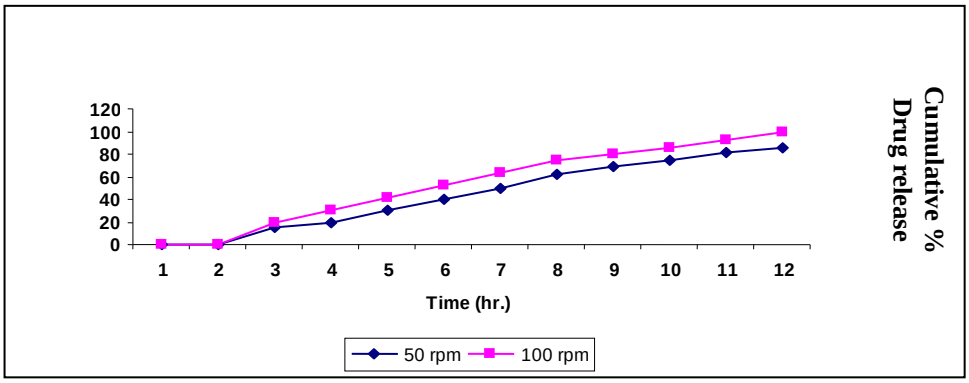

Figure 3: Effect of speed of rotation on in vitro dissolution of formulation F1 at 50rpm and 100rpm.

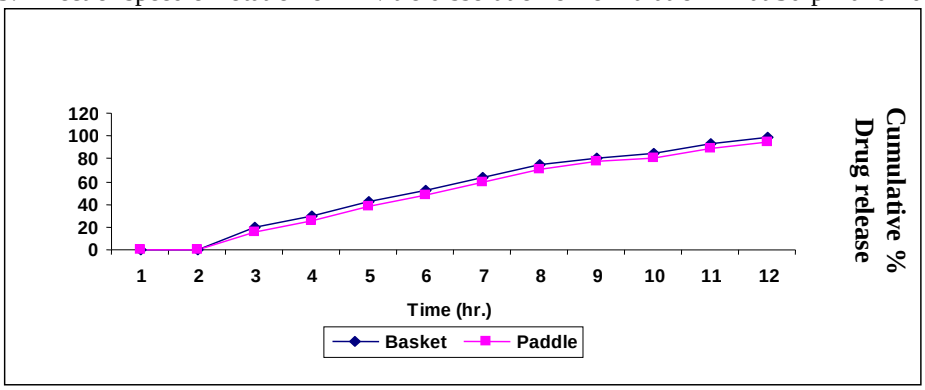

Figure 4: Comparative dissolution study of formulation F1 using basket and paddle apparatus.

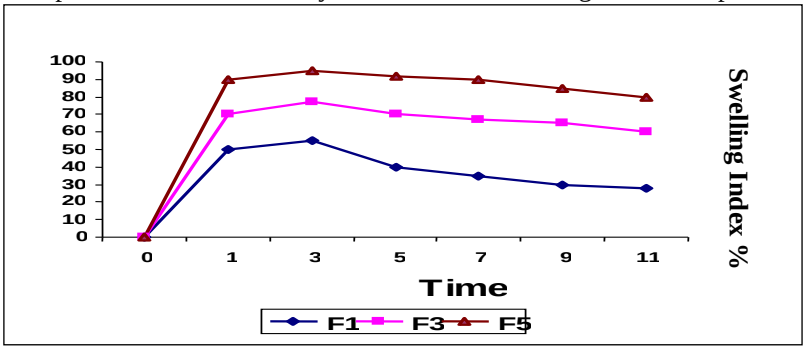

Figure 5: Relationship between Swelling Index and time of formulations F1,F3 and f5.

and paddle method at the same experimental conditions (P >0.05), when data was analyzed using student 't' test (Figure-3). That finding is in agreement with Efentakis M.[23].

The incorporation of PEG 6000 (6% of weight of tablet) in formulation F6, the release was sustained observed in 12 h (Figure 1). Thus, there was no significant increase in drug release. This may be attributed to the little amount of PEG. Sankar, C has been reported that incorporation of drugs

into a water soluble carrier such as PEG has frequently improved drug dissolution rate and bioavailability[24].

Swelling Studies

The swelling index was calculated with respect to time (Figure 4). The swelling index was increased with time, because weight gain by tablet was increased proportionally with rate of hydration up to 3 h. Later on, it decreases gradually due to the dissolution of outermost gelled layer of tablet into dissolution medium. The relationship between swelling index gum concentration and drug release decrease was observed. It has been observed that as gum concentration increases, swelling index increases and the cumulative percent drug release decreases. The reason attributed to the slow erosion of the gelled layer from the tablets containing higher amount of xanthan gum[22,23].

The pattern of drug release from hydrophilic polymeric matrices involves solvent penetration, hydration and swelling of the polymer, diffusion of the dissolved drug in the matrix, and erosion of the gel layer[24,25]. Initially, the diffusion coefficient of drug in the dehydrated polymer matrix was low; it increased significantly as the polymer matrix imbibes more and more water and forms a gel, as time progressed (Fig. 4). That is attributed to the hydration rate of the polymer matrix, and thereby the gel formation which depends significantly on polymer proportion, viscosity, and to a lesser degree on polymer particle size[26]. In order to investigate the release mechanism, the data were fitted to models representing zero-order, first-order and Higuchi's square root of time (Table-3)[25,27]. It had been found that all the fabricated tablets followed Higuchi release kinetics. The diffusion was non-Fickian mechanism, which indicates the drug release through diffusion and relaxation, that was similar to study reported by Sankar, C and et al[25].

Accelerated stability studies

Accelerated stability conditions did not appear to have any effect on the rate of drug release. All formulations were stable physically and chemically within the limits.

CONCLUSION

Diclofenac sodium release from different gum concentrations formulations studied was generally linear. Accelerated stability conditions did not appear to have any effect on the rate of drug release. However, PH of the dissolution medium had a significant effect on the release while the rotation speed, the apparatus method and additives have little effect on drug release from xanthan gum matrices .These parameters should be properly controlled to avoid variations in rate of drug release among production of matrix sustained release tablets.

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