Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 3, 2013

Research Article

FORMULATION AND EVALUATION OF ALCOHOL RESISTANT DOSAGE FORMS OF DICLOFENAC SODIUM

TRIPURA SUNDARI P*, R.S. GAUD

SPP SPTM, SVKM's NMIMS, Vile Parle West, Mumbai 400056. Email: tripurakrishna@gmail.com

Received: 07 May 2013, Revised and Accepted: 21 Jun 2013

ABSTRACT

Objective: The present work is focused on the Formulation and Evaluation of Alcohol Resistant Dosage Forms of Diclofenac sodium by various polymers.

Methods: Oral controlled release pellet formulations of diclofenac were prepared using extrusion spheronization technique. Pellets provide specific advantages in controlling the drug release and increasing the absorption of the active ingredient. The major drawback for these systems is dose dumping which is very prominent in presence of alcohol. In the present study, attempt was made to prepare alcohol resistant pellet formulations of diclofenac. Diclofenac is used as a model drug which is an NSAID. Various polymers like Eudragit RSPO, RLPO and cellulose acetate butyrate were used for preparing the pellets. The prepared pellets were studied for different flow properties and drug release studies.

Results and discussion: The in vitro drug release studies were carried out in phosphate buffer as well as in phosphate buffer containing 5% and 10% alcohol. Drug release from the pellets was by non fickian diffusion mechanism and was comparable with that of marketed preparations. The pellets also had shown resistance to alcohol dose dumping.

Keywords: Diclofenac, Pellets, Eudragits, Cellulose acetate butyrate, Alcohol resistance.

INTRODUCTION

Development of controlled release drug delivery systems provide a uniform concentration or amount of drug at absorption site, maintained plasma concentration within a therapeutic range, minimizes the side effects and reduces the frequency of drug administration. A considerable attention has been focused on the development of novel drug delivery systems because of their obvious advantages such as ease of administration, controlled release of drug at predetermined rate, effectiveness in the treatment of chronic conditions and better patient convenience due to simplified dosing schedule. A number of design options are available for the preparation of controlled release formulations to modify oral absorption by matrix pellet.

Pelletization [1,2] is a term used to define agglomeration of drug substances in either powder or granule form resulting in the form of semi spherical and spherical agglomerates having good flow properties. Generally, the particle sizes of the resulting pellets are between 0.5 and 1.5mm depending on the preparation technique.

Pellets [3] provide a reduction in the dosage regimen and gastrointestinal irritation, moreover controlling the drug release and increasing the absorption of the active ingredient. One of the advantageous properties of the pellet formulations is being good candidate for the delivery of the drug substances due to minimizing the dose dumping effect [4-7]. The reproducibility of the release characteristics from pellet formulations is also much better when compared to the single-unit dosage forms. They are suitable systems for film coating because of the low surface area-volume ratio, resistance to external factors such as moisture, air and light.

Extrusion-spheronization is the most commonly used method for pellet production. Use of suitable excipients and fillers can be made to produce pellets of desirable quality. Different excipients from a variety of sources have been evaluated for the formation of spherical pellets. In spheronizer, a plate (diameter 10-1000 cm) rotates within the confines of a cylinder. The extruded, cylindrically shaped particles are broken into uniform lengths almost instantaneously and are gradually transformed into spherical shapes.

Diclofenac is a non steroidal anti inflammatory drug (NSAID) with antipyretic and analgesic actions. It is primarily available as the sodium salt. It is a yellowish hygroscopic crystalline powder; soluble in alcohols and insoluble in chloroform and in dilute acid. It is bound to the plasma proteins with a ratio of 99% having a half life value of 2hrs. The dose of diclofenac is 50mg three times a day or 100mg in extended release dosage forms.

The objectives of the present study was to formulate, characterize, *in vitro* drug release from blend of MCC/Lactose [8-11] pellets loaded with diclofenac [12] and to achieve the controlled and alcohol resistant drug release system.

MATERIALS AND METHODS

Materials

The active substance diclofenac is obtained as gift sample from Dr. Reddys labs, Hyderabad. The polymers used in the coating Eudragit RLPO and Eudragit RSPO were obtained as gift sample from Evonik industries, Mumbai. Cellulose acetate butyrate was purchased from Signet chemicals, Mumbai. All other chemicals used in the study were of pharmacopeial standards.

Preparation of Microcrystalline cellulose (MCC)/Lactose based matrix pellets by extrusion- spheronization method

The pellets were prepared by using extrusion/spheronization pelletization technique. Required amount of Diclofenac, lactose, MCC and binder were passed through sieve No.40 prior to pelletization and mixed uniformly in a planetary mixer. Water is added drop wise to bind the mixture to obtain dough mass, which was extruded using a piston extruder (1mm orifice, Umang, India). The extrudates were immediately spheronized for 4 min at a rotational speed of 1400 rpm and an air velocity of 1 kg/cm^2. The pellets were dried at 40^{o}C for 2 h in a tray dryer (Labultima, India). The formulae used for the preparation of pellets is given in table no.1. The prepared pellets were coated with polymers in the ratios specified in table no 2 and 3. The parameters of the fluidizer were adjusted according to table no 4 for coating the pellets.

Characterization and evaluation of pellets

Measurement of micromeritic properties, granule density and friability of pellets

The flow properties were investigated by measuring the angle of repose, Carr's index (I %), Hausner ratio, Friability (%) of drug loaded pellets. The results were given in table no 5.

Determination of drug entrapment efficiency

Pellets equivalent to 100mg of Diclofenac were dissolved in 10 ml of methanol & sonicated for 5 min. Then volume was made up to 100 ml with buffer of pH 6.8 and filtered. From this filtered stock solution, 2 ml was diluted to 10 ml with buffer (10 ppm). Then absorbance was measured at 285 nm to calculate drug entrapment efficiency.

In vitro drug release studies

The release of diclofenac from prepared pellets was studied in phosphate buffer of pH 6.8 (900 ml) using an 8 station dissolution rate test apparatus (Campbell electronics) with a paddle stirrer at 50 rpm speed and at temperature 37 ± 0.5°C. At regular intervals, the sample (10 ml) was withdrawn and replaced with same volume of fresh medium. The samples withdrawn were filtered through a 0.45 µm membrane filter and were assayed at 285 nm for estimating diclofenac concentration using UV spectrophotometer. Finally, corresponding drug content in the samples was calculated from the calibration curve to determine the drug release pattern.

RESULTS AND DISCUSSION

Extrusion spheronization technique was employed for the preparation of Diclofenac pellets. The pellets prepared by using the formula F1 were coated with insoluble polymers like Eudragit [13] RLPO and RSPO in 9:1 ratio to different weight gains viz., 5, 10 % w/w and with cellulose acetate butyrate at 1, 2, 5 % w/w. The prepared pellets were evaluated for different flow properties like tapped density, granule density, angle of repose, Carr's index and Hausner's ratio. The flow properties have shown that the pellets were free flowing.

Table 1: Formulae of Different Diclofenac Pellets Prepared

Ingredients	Amounts (g)		
	F1	F2	F3
Diclofenac	33	33	33
MCC	33	33	33
Lactose	30	24	24
Carbopol	4	--	--
PVPK30	--	10	--
Starch	--	--	10
Purified water	q.s	q.s	q.s
Total weight (g)	100	100	100

Table 2: Composition of Coating Solution with Eudragits

Ingredients	Amounts	
	P1	P2
Eudragit RSPO	9 g	9 g
Eudragit RLPO	1 g	1 g
PEG	1.1 g	1.1 g
IPA:Acetone (1:1)	100 g	100 g
% wt gain	5%	10%

Table 3: Composition of Coating Solution with Cellulose Acetate Butyrate

Ingredients	Amounts		
	P4	P5	P6
CAB	1 g	1 g	1 g
PEG	1.1 g	1.1 g	1.1 g
Acetone	100 g	100 g	100 g
% wt gain	1%	2%	5%

Table 4: Optimized FBP parameters

S. No.	Parameters	Values
1	Fluidized air	0.2-0.4 bar
2	Atomized air	1-1.2 bar
3	Temperature	38.5 ^{o}C
4	RPM	3-4
5	Spray type	Bottom spray

Diclofenac release from the coated pellets was studied in phosphate buffer of pH 6.8 using paddle at 50 rpm. The diclofenac release from the pellets was slow and sustained for more than 6 hrs and depended on the coating thickness. As the thickness of the coat was increased release rate was decreased. A linear relationship was observed between coating thickness and release rate (Ko) as shown in table no 6.

Table 5: Flow Properties of the Prepared Pellets of Diclofenac

	Yeild (%)	Average Size (µm)	Angle of Repose (θ^0)	Tapped Density (g/cm^3)	Granule Density (g/cm^3)	Carr's Index (%)	Hausner Ratio (%)	Friability (%)	Drug Loading (mg)	Encapsulation Efficiency(%)
P1	92.30	1105	26.63	1.081	0.987	8.6	1.09	0.03	4.44	88.8
P2	94.17	1221	25.13	1.068	1.021	4.4	1.04	0.04	4.60	92.0
P3	91.23	1158	26.32	1.057	1.011	4.3	1.04	0.05	4.45	89.0
P4	92.36	1213	25.98	1.052	1.032	1.9	1.01	0.04	4.70	94.0
P5	94.07	1093	26.81	1.038	0.985	5.1	1.05	0.03	4.75	95.0

Table 6: Kinetic Parameters for the Prepared Pellets and the Marketed Products

Formulation	r^2 value				K_0(mg/hr)	K_1(Hr^1)	n in Peppas
	Zero order	First order	Higuchi	Peppas			
P1	0.9975	0.8689	0.966	0.9852	14.22	0.4527	0.6915
P2	0.9865	0.9322	0.8899	0.9761	11.68	0.198	0.9767
P3	0.9776	0.8411	0.9791	0.9961	15.25	0.4958	0.7106
P4	0.9845	0.9235	0.6655	0.9921	11.65	0.1928	0.9921
P5	0.9859	0.9687	0.8879	0.9747	6.006	0.0747	0.9376
Dicloran	0.9759	0.9869	0.9718	0.9970	12.46	0.2346	0.7259
Voveran	0.9359	0.9635	0.9903	0.9941	16.02	0.4579	0.5568

Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from the formulations followed zero order kinetics. When the release data was analysed as per Peppas equation, the release exponent 'n' was between 0.5 and 1 with the pellets indicating non fickian diffusion as the release mechanism. Plots of percent released versus square root of time were found to be linear (r > 0.9350 except P4 formulation) indicating that the drug release from the pellets was diffusion controlled.

The in vitro dissolution profiles of the prepared pellets were compared with two marketed preparations as shown in figure 1. The studies shown that the drug release profile from formulations P2 and P4 were comparable with Dicloran.

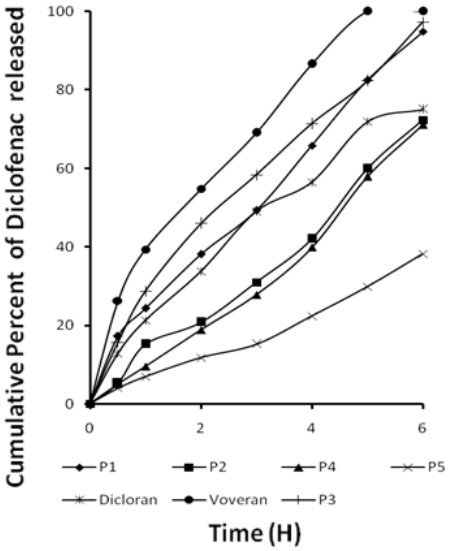

Fig. 1: Dissolution Profile of Prepared Pellets of Diclofenac and Marketed Preparations in Phosphate Buffer

The two formulations namely P2 and P4 were further studied for drug release characteristics in dissolution medium containing 5% and 10% alcohol. The results were shown in figures 2 and 3. When compared to marketed preparation the drug release from the prepared pellets was slow and sustained without dose dumping in presence of alcohol.

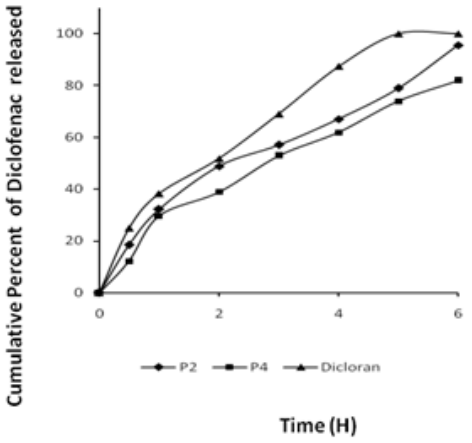

Fig. 2: Dissolution Profile of Prepared Pellets of Diclofenac and Marketed Preparations in Phosphate Buffer Containing 5% Alcohol

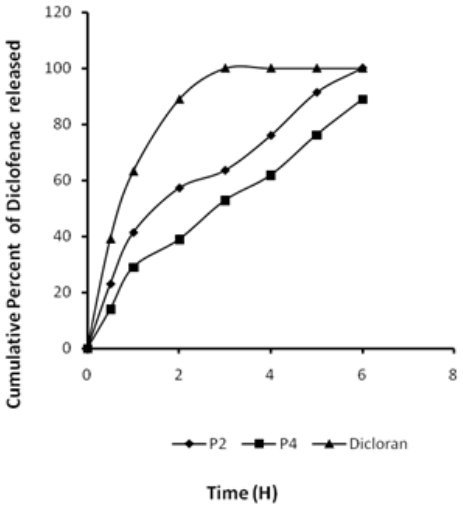

Fig. 3: Dissolution Profile of Prepared Pellets of Diclofenac and Marketed Preparations in Phosphate Buffer Containing 10% Alcohol

CONCLUSION

Sustained release pellets of diclofenac could be prepared by extrusion spheronization technique which is industrially feasible method. Diclofenac release from the coated pellets was slow and extended over longer periods of time and depended on the coating thickness. Drug release from the pellets was by non fickian diffusion mechanism and was comparable with that of marketed preparations. The pellets also had shown resistance to alcohol dose dumping.

REFERENCES

1. Masazumi K, Hiroaki N. Development of controlled release matrix pellets by annealing with micronized water-insoluble or enteric polymers, J. Contr. Rel., 2002; 82: 335-343.
2. Ponghanaghakul T, Puttipipatkhachorn S. Alginate-magnesium aluminum silicate film: Effect of plasticizer film properties, drug permeation and drug release from coated tablets. Int. J. Pharm., 2007; 333: 34-44.
3. Mustafa SinanKaynak, H. SüheylaKaş, LeventÖner, Formulation of Controlled Release Glipizide Pellets Using Pan Coating Method Hacettepe University Journal of the Faculty of Pharmacy 27; 2:2007, 93-106.
4. Kibbe AH. Hands on book of Pharmaceutical Excipients. 3rd ed. London: Association of Pharmaceutical society of Great Britain. 2000.
5. Kleinebudde P. The crystallite-gel-model for microcrystalline cellulose in wet granulation, extrusion and spheronization. Pharm. Res., 1997; 14: 804-809.
6. Gowda DV, Rajesh N, Afrasim M, Shivakumar HG, Siddaramaiah H. Controlled release behaviour of nifedipine from the pellets of gellucire/ microcrystalline cellulose blends. Int. J. Pharm Tech. Res., 2010; 2: 1215-1226.
7. Rajesh KS, Khanrah A, Biswanath S. Release of ketoprofen from alginate microparticles containing film forming polymers. J. Sci. Ind. Res., 2003; 27: 965-989.
8. Mannion, Richard, O., Euro-Celtique S.A., Opioid controlled release formulations resistant to alcohol extraction of the opiod. European patent2319499A1. 2011 May 11.
9. Welgang R, Abbott laboratories, Abuse resistant melt extruded formulation having reduced alcohol interaction, US patent20100172989, 2010 Jul 8.
10. Florence G, Flamel technologies, Multi microparticulate pharmaceutical forms for oral administration, US Patent 20110104266, 2011 Jan 11.
11. Catherine H, Ethypharm, Alcohol resistant oral pharmaceutical form based on microgranules,US Patent 20110177138, 2011 Apr 1.
12. Krunal B, Priyal RP, Formulation and evaluation of diclofenac sodium injection using 2- hydroxyl propyl beta cyclodextrin, Int J Pharm Pharm Sci, 2011; 3(5): 250-252.
13. EL Nabarawi M.A, Makkya.M, development and characterization of ketorolac tromethamine(KT) orobuccal films, Int J Pharm Pharm Sci, 2011; 4(4): 186-193.