Int. J. Chem. Sci.: 8(1), 2010, 315-324

CONTROLLED RELEASE TABLETS OF ACECLOFENAC USING ETHYL CELLULOSE BY WET GRANULATION AND SOLID DISPERSION TECHNIQUE

V. LAKSHMI NARASAIAH*, RAMA DEVI, B. KALYAN, M. LAXMANA DOSS, G. SARAVANAN, S. SATYANAND and T.VENKATESWARA RAO[a]

Department of Pharmaceutics, Dr Samuel George Institute of Pharmaceutical Sciences, MARKAPUR – 523316 (A.P.) INDIA
[a]Department of Pharmaceutics, Bapatla College of Pharmacy, BAPATLA (A.P.) INDIA

ABSTRACT

The objective of the present study was to develop controlled release matrix tablets of aceclofenac by wet granulation and solid dispersion technique using ethyl cellulose as a rate controlled material. The granules and tablets were subjected to physicochemical properties and *in vitro* drug release. The physicochemical properties were found to be within the limits. The concentration of the polymer in the system was a determining factor in the control of the release rate of the drug. The *in vitro* drug release was found to be 93% for aceclofenac from solid dispersion formulation **(A7)** compared to 84% from wet granulation **(A1)**. By comparing dissolution profiles, the release pattern followed zero order kinetics and the mechanism of drug release was governed by peppas model. The 'n' values were found to be more than 1 (n > 1), which indicated that the drug release was predominately controlled by super case II diffusion.

Key words: Aceclofenac, Ethyl cellulose (EC), Solid dispersion, Wet granulation, Controlled release tablets.

INTRODUCTION

Aceclofenac is a non-steroidal anti-inflammatory drug useful in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondyltis[1,2]. The maintenance of effective drug concentration level in the body for a constant and uniform supply of drug is desired for the successful treatment of arthritis. It is rapidly and effectively absorbed after oral administration but has short biological half life of 4 hr.[3]

*Author for correspondence; Ph.: (M) +919440559245 (O) 08596224045;
E-mail: narasimhapharma21@gmail.com

A controlled release dosage form may be formulated to provide drug for an immediate release as well as gradual and continuous release of remaining doses for extended period of time.[4] The technique of solid dispersion in which a drug is incorporated into an inert carrier or matrix has been extensively used to enhance the dissolution of poorly water soluble drugs. Drug release can either be accelerated or retarded depending upon the nature of the carrier, whether hydrophilic or hydrophobic.[5]

The concentration of the polymer in the system was a determining factor in the control of the release rate of drug. Hydrophobic polymers provide several advantages ranging from good stability at varying pH values and moisture levels to established safe applications. Ethyl cellulose is a hydrophobic polymer and is used extensively as a coating material and in the preparation of matrix type controlled release tablets.[6] There are only a few reported studies of controlled released solid dispersion or matrix type wet granulated tablets that employ ethyl cellulose as a rate controlling polymer.[7, 8]

In the present work, a controlled release formulation of aceclofenac with a release rate profile greater than 12 hrs in selected *in vitro* fluids was formulated. The effect of polymer concentration and effect of different manufacturing processes (solid dispersion and wet granulation) on the dissolution of aceclofenac from ethyl cellulose controlled release formulations was studied.

EXPERIMENTAL

Materials and methods

Materials

Aceclofenac, ethyl cellulose and aerosil were gift samples from M/s Seeko Biotech Ltd, Vijayawada. Lactose (anhydrous), ethanol and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai.

Methods

Preparation of tablets by wet granulation method

The wet granulation method was used for the preparation of matrix tablets of aceclofenac, each weighing 300 mg containing 200 mg of aceclofenac. The composition of the tablet formulations are given in Table 1.

Weighed amount of aceclofenac, ethyl cellulose and lactose were geometrically mixed. Sufficient quantity of ethanol was added to get uniform wet mass. Then, sieve No.10

was used for granulation and prepared granules were kept for drying for 2 hrs in hot air oven at 40^0C. The dried granules were again passed through sieve No. 12. Sufficient quantity (1% w/w) of lubricant and glidant were added just before compression. The granules were compressed into tablets by single station compression machine (Cadmach, Ahmedabad, India) using 9 mm punches and dies.

Table 1: Formulation of tablets prepared by wet granulation method

S. No.	Ingredients	Quantity (mg)					
		A1	**A2**	**A3**	**A4**	**A5**	**A6**
1	Aceclofenac	200	200	200	200	200	200
2	Ethyl cellulose (6-20%w/w)	18	24	30	36	48	60
3	Lactose	76	70	64	58	46	34
4	Ethanol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
5	Magnesium stearate	3	3	3	3	3	3
6	Aerosil	3	3	3	3	3	3

Preparation of tablets by solid dispersion

The solid dispersion technique was used for the preparation of matrix tablets of aceclofenac, each weighing 300 mg containing 200 mg of aceclofenac. The different composition of the tablet formulations are given in Table 2.

Table 2: Formulation of tablets prepared by solid dispersions

S. No	Ingredients	Quantity (mg)					
		A7	**A8**	**A9**	**A10**	**A11**	**A12**
1	Aceclofenac	200	200	200	200	200	200
2	Ethyl cellulose (4-20%w/w)	12	24	30	36	48	60
3	Lactose	82	70	64	58	46	34

Cont…

S. No	Ingredients	Quantity (mg)					
		A7	A8	A9	A10	A11	A12
4	Ethanol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
5	Magnesium stearate	3	3	3	3	3	3
6	Aerosil	3	3	3	3	3	3

Required quantity of aceclofenac and ethyl cellulose were transferred into a beaker, ethanol was added to the beaker and stirred for 15 min until dissolved. Lactose was then added and mixed for 10 min. The beaker containing the dispersion was then incubated at 40^0C and stirred constantly until complete evaporation of the solvent. After evaporation of the solvent, the mass was passed through sieve No. 10. The obtained granules were then dried in an oven at 40^0C for 2 hrs. The dried granules were passed through sieve No. 12. Glidant and lubricant (1% w/w) were added to the above mass and blended for 2 min. The final blend was then compressed into tablets by using a single punch tablet compression machine (Cadmach, Ahmedabad, India) using 9 mm punches and dies.

Standardization of granules[9]

The angle of repose of prepared granules was determined by fixed funnel method. The loose bulk density and tapped bulk density were determined by density apparatus and the Carr's index was calculated using following equation TBD - LBD/TBD×100 and the Hausner's ratio was calculated by TBD/LBD.

Physicochemical characterization of tablets[10]

The thickness of the tablets was determined by using vernier calipers. The hardness of the tablets was determined by using Pfizer hardness tester. The friability of the tablets was determined by using Roche friabilator. Weight variation of the tablets was carried out as per the official method of IP.

Estimation of drug content

Three tablets of each formulation were collected and powdered. Powder equivalent to 100 mg of aceclofenac was weighed and sufficient quantity of methanol was added and diluted with 6.8 phosphate buffer make up the volume to 100 mL. It was allowed to sonicate for 15 min. The solution was filtered and the absorbance was measured after suitable dilutions by using Shimazdu UV spectrophotometer at 275 nm[11].

in vitro Dissolution studies

The *in vitro* dissolution study was carried out using USP Type II dissolution apparatus. The study was carried out in 900 mL of 2% w/v of SLS in 0.1N HCl for first 2 hours and next 3 to 12 hrs in 900 mL of phosphate buffer (pH 6.8). The dissolution medium was kept in thermostatically controlled water bath, maintained at 37 ± 0.5^0C. The tablet was then introduced into the dissolution jar and the paddle was rotated at 75 rpm. At different time intervals, 5 mL sample was withdrawn and analyzed by using spectrophotometer at 275 nm. At each time of withdrawal, 5 mL of fresh dissolution medium was replaced into the dissolution flask.

RESULTS AND DISCUSSION

Physical characteristics of aceclofenac granules and tablets

The results of angle of repose (between 20-30%) indicate good flow properties and this was further supported for lower compressibility index values. The Carr's index between 5-15% indicates excellent flow properties of the prepared granules (Table 3).

Table 3: Evaluations of granules prepared by wet granulation method and solid dispersions

Formulations code	Angle of repose (θ)	Loose bulk density (g/mL)	Tapped bulk density (g/mL)	Compress ibility index (%)	Hausner's ratio
A1	23.699±0.013	0.497±0.011	0.531±0.010	6.403±0.021	1.068±0.041
A2	24.139±0.022	0.477±0.021	0.508±0.011	5.731±0.032	1.061±0.012
A3	24.546±0.011	0.458±0.042	0.486±0.021	5.761±0.041	1.061±0.011
A4	25.371±0.023	0.466±0.051	0.494±0.031	5.668±0.040	1.060±0.013
A5	26.331±0.024	0.446±0.043	0.471±0.036	5.307±0.012	1.056±0.048
A6	27.613±0.030	0.469±0.041	0.497±0.062	5.633±0.011	1.059±0.054
A7	20.941±0.014	0.568±0.013	0.632±0.010	10.126±0.011	0.900±0.021
A8	21.360±0.011	0.494±0.011	0.539±0.013	8.348±0.018	1.091±0.020

Cont…

Formulations code	Angle of repose (θ)	Loose bulk density (g/mL)	Tapped bulk density (g/mL)	Compress ibility index (%)	Hausner's ratio
A9	22.603±0.016	0.486±0.014	0.527±0.017	7.779±0.017	1.084±0.019
A10	23.034±0.018	0.479±0.041	0.516±0.021	7.170±0.021	1.077±0.011
A11	23.307±0.011	0.503±0.032	0.542±0.027	7.196±0.035	1.077±0.014
A12	24.606±0.016	0.546±0.033	0.588±0.031	7.140±0.044	1.077±0.024

All values are expressed as Mean ± S.d, n = 3

All the formulations showed uniform thickness. In weight variation test, all the tablet formulations were found to be within the I.P. limits and hence, all the formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different formulations and was more than 98 %. Hardness and friability of the prepared tablets containing ethyl cellulose by both methods were satisfactory. The breaking strength ranged from 4-4.8 kg/cm^2. The tablet friability of these formulations was extremely low < 1%, indicating that the granules provided an acceptable control release (Table 4).

Table 4: Evaluations of tablets prepared by wet granulation method and solid dispersions

Formulations code	Thickness* (mm)	Hardness* (kg/cm^2)	Friability** (%)	Weight variation*** (%)	Drug content* (%)
A1	4.71±0.01	4.4 ±0.156	0.75 ±0.011	2.161±0.045	98.33±0.051
A2	4.70±0.02	4.6 ±0.114	0.88 ±0.021	2.951±0.173	98.80±0.051
A3	4.66±0.02	4.1 ±0.245	0.82 ±0.032	3.527±0.416	99.45±0.034
A4	4.72±0.02	4.3 ±0.112	0.85 ±0.010	3.367±0.174	98.23±0.069
A5	4.70±0.03	4.0 ±0.158	0.76 ±0.022	2.758±0.192	98.48±0.086
A6	4.67±0.03	4.7 ±0.312	0.72 ±0.033	4.159±0.057	98.72±0.415
A7	4.70±0.01	4.8 ±0.205	0.87±0.010	2.448±0.113	98.55±0.072

Cont…

Formulations code	Thickness* (mm)	Hardness* (kg/cm^2)	Friability** (%)	Weight variation*** (%)	Drug content* (%)
A8	4.68±0.03	4.1 ±0.212	0.84±0.021	2.364±0.136	96.51±0.065
A9	4.66±0.02	4.3 ±0.241	0.72±0.022	3.061±0.093	97.54±0.055
A10	4.71±0.03	4.4 ±0.105	0.70±0.015	3.416±0.102	96.79±0.041
A11	4.71±0.02	4.6 ±0.102	0.65±0.016	4.088±0.069	98.55±0.176
A12	4.69±0.04	4.1 ±0.232	0.73±0.024	4.126±0.087	97.62±0.124

All values are expressed as Mean ± S.d; * n = 3; ** n = 10, and *** n = 2

Drug release behavior of Aceclofenac Controlled Release Tablets

Drug release profiles of aceclofenac prepared by wet granulation and solid dispersion techniques in 0.1N HCl with 2% SLS for first 2 hrs and pH 6.8 phosphate buffer is depicted in Figs. 1 and 2.

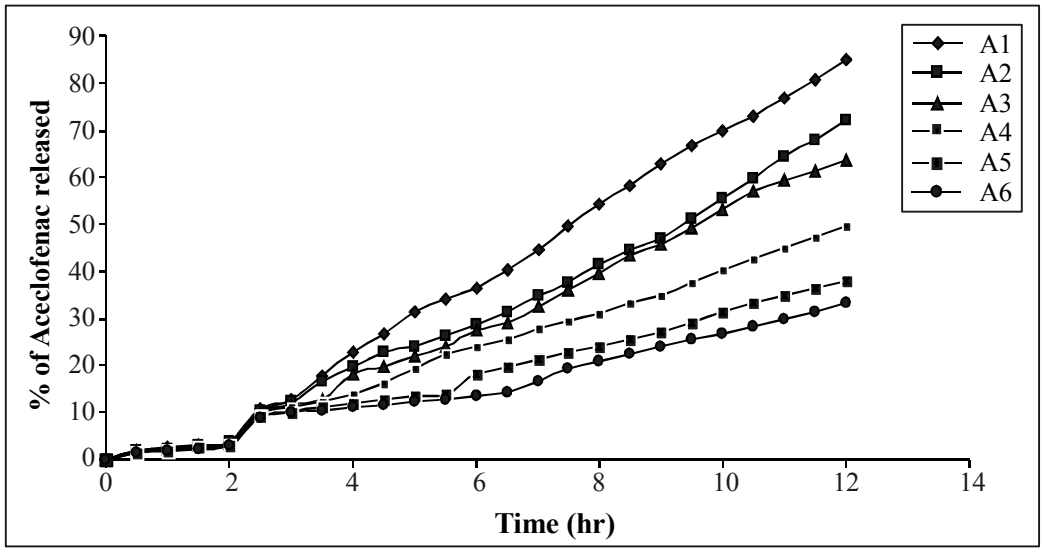

Fig. 1: Dissolution profiles of aceclofenac tablets prepared with ethyl cellulose by wet granulation method

A1: Tablets prepared with EC 6 %; **A2:** Tablets prepared with EC 8%; **A3:** Tablets prepared with EC 10%; **A4:** Tablets prepared with EC 12%; **A5:** Tablets prepared with EC 16%; **A6:** Tablets prepared with EC 20%

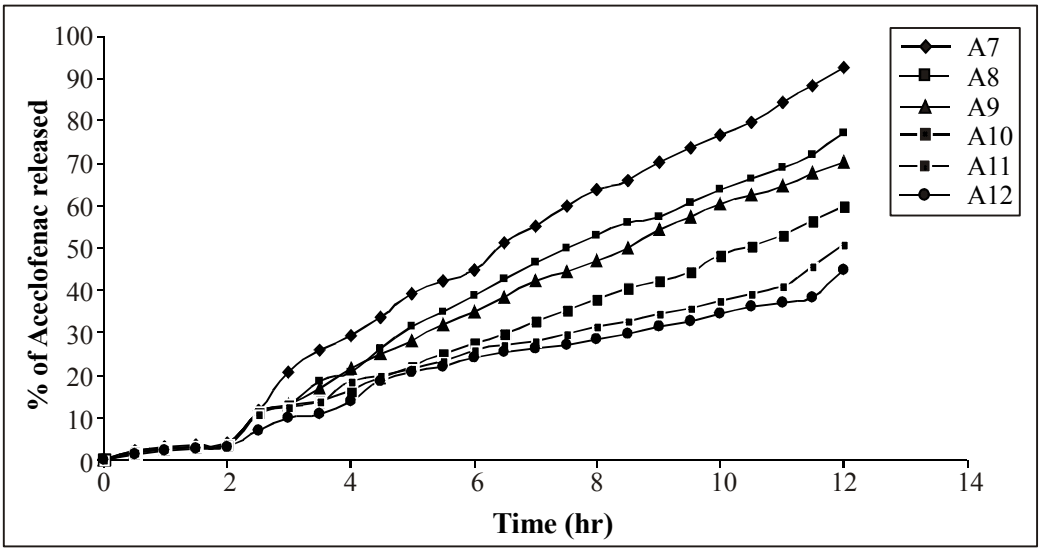

Fig. 2: Dissolution profiles of aceclofenac tablets prepared with ethyl cellulose by solid dispersions

A7: Tablets prepared with EC 4%; **A8:** Tablets prepared with EC 8%; **A9:** Tablets prepared with EC 10%; **A10:** Tablets prepared with EC 12%; **A11:** Tablets prepared with EC 16%; **A12:** Tablets prepared with EC 20%

The wet granulation formulation containing 6% EC released 84% of the drug, while the formulation containing 20% EC released 33% of the drug in 12 hr.

The solid dispersion formulation containing 4% EC released 93% of the drug, while the formulation containing 20% EC released 45% of the drug in 12 hr.

As per the above results, on increasing the concentration of ethyl cellulose content, the drug release was retarded.

The release of aceclofenac exhibited that EC is inert, insoluble cellulose ether derivative, which has excellent retardant properties.

Kinetics of aceclofenac release from controlled release formulations

The release of aceclofenac from controlled release tablet obeyed zero order kinetics and peppas mechanism. The drug release data from 12 hr controlled release formulations (wet granulation and solid dispersion) prepared with EC was plotted according the peppas equation.

Diffusion exponent of release profiles (slope) has a value for n > 1, which indicates that drug release was predominately controlled by super case II transport diffusion. The time required to get 50% drug release (T_{50}), 90% drug release (T_{90}) and the zero order release rate constant were calculated and reported in Table 5.

Table 5: Dissolution kinetics of aceclofenac tablets formulated with ethyl cellulose by wet granulation method and solid dispersions

Formulations code	Correlation coefficient (R^2)				T_{50} (hr)	T_{90} (hr)	K value (mg/hr)	n
	Zero order	First order	Matrix	Peppas				
A1	0.9881	0.9311	0.8728	0.9818	7.4	13.4	13.4328	1.3788
A2	0.9858	0.9366	0.8691	0.9824	9.2	16.6	10.8434	1.2830
A3	0.9902	0.9674	0.8809	0.9828	9.5	17.1	10.5263	1.2958
A4	0.9958	0.9841	0.9007	0.9837	12.5	22.5	8.0000	1.1894
A5	0.9945	0.9868	0.9014	0.9813	16.2	29.2	6.1644	1.0965
A6	0.9903	0.9841	0.9011	0.9761	18.9	34.0	5.2941	1.0432
A7	0.9929	0.9237	0.8970	0.9731	6.5	11.7	15.3846	1.3940
A8	0.9913	0.9651	0.8913	0.9771	7.9	14.2	12.6761	1.3569
A9	0.9932	0.9705	0.8925	0.9789	8.5	15.4	11.6883	1.3344
A10	0.9939	0.9734	0.8908	0.9832	10.6	19.0	9.4734	1.2610
A11	0.9903	0.9852	0.9187	0.9767	12.8	23.0	7.8261	1.1753
A12	0.9901	0.9887	0.9142	0.823	14.1	25.4	7.0866	1.1853

CONCLUSION

It has been demonstrated that the aceclofenac matrix tablet formulated with EC reveals suitable controlled release characteristics for 12 hrs. The proposed formulations i.e. wet granulation and solid dispersion (**A1** and **A7**) exhibits linear release profiles. Hence, it can be concluded that tablet matrix solid dispersion preparation (4% EC) provides efficiently more drug entrapment, when compared with wet granulation formulations (6% EC).

REFERENCES

1. Indian Pharmacopeia, The Indian Pharmacopeia Commission, Ghagiabad, **Vol. 2**, 681-683 (2007).
2. Sean C. Sweetman, Martindale, Pharmaceutical Press, 33, Edition, 11 (2002).
3. S. Mutalik and S. Prasanna. Arch Pharm Res, **30(2)**, 222-234 (2007).
4. Y. W. Chien, Marcel Dekker, New York, 1-11 (1982).
5. Morteza Rafiee Tehrani and Zahra Jafari Azar, Acta Pharma, **48**, 155-166 (1998).
6. Evonesghaly, Hernadez and Andres Malave, PRHS, **11(2)**, 159-162 (1992).
7. G. V. Murali Mohan Babu and K. V. Ramana Murthy, The Indian Pharmacist, **11(13)**, 63-68 (2003).
8. Jabed Iqbal, Almas Babar, and Mahammad Ashraf. Drug Dev. Ind. Pharm., **28(2)**, 129-134 (2002).
9. H. A. Liebermann, L. Lachman and J. B. Schwartz, Marcel Dekker, New York, 201-243 (1990).
10. M. E. Aulton and T. I. Wells, Churchill Livingstone London, (1988) p. 342.
11. S. Mutalik and S. Prasanna. Arch Pharm Res, **30(2)**, 222-234 (2007).

Accepted : 07.10.2009