Optimizing Fast Dissolving Dosage Form of Diclofenac Sodium by Rapidly Disintegrating Agents

V. SHENOY, S. AGRAWAL AND S. PANDEY*
Department of Pharmaceutics, College of Pharmaceutical Sciences, MAHE, Manipal-576 119.

Accepted 25 October 2002
Revised 18 September 2002
Received 8 April 2002

Fast dissolving tablets of diclofenac sodium were prepared using direct compression after incorporating superdisintegrants such as cross linked carboxymethylcellulose, sodium starch glycolate and cross linked povidone in different concentrations. All the formulations were evaluated for the influence of disintegrants and their concentrations on the characteristics of fast dissolving tablet mainly in terms of disintegration time and dissolution rate. Tablets containing cross-linked carboxymethylcellulose showed better disintegrating character along with rapid release (90% drug release in 10 min.). No appreciable difference was found between the formulations containing other two superdisintegrants. The concentration of the superdisintegrants had also an effect on disintegration time and *in vitro* dissolution. There seems to be a trend towards use of higher level of disintegrants producing rapid disintegration and faster dissolution. The resulting tablets were also evaluated for its hardness and friability and were found to be independent of disintegrant concentration.

Fast dissolving tablets are gaining prominence as new drug delivery systems. These dosage forms dissolve or disintegrate in oral cavity within a minute without the need of water or chewing. These are not only useful in administration of drugs in pediatric and geriatric patients but in patients suffering from dysphagia, leading to improved patient compliance[1]. Several approaches have been employed to formulate fast dissolving tablets which involve tablet molding[2], increasing porosity by freeze drying[3], sublimation[4], spray drying[5,6], disintegrants addition[7] and use of sugar-based excipients[8,9].

Disintegrants can help to facilitate drug dissolution and consequently can improve bioavailability. Despite a long and proven record of starch as a disintegrant, it possesses disadvantages when used in direct compression formulation[10]. The relatively high levels required and the lack of compressibility often weaken the tablet structure. Therefore the development of new disintegrants that are effective at lower levels and help in rapid disintegration is of great importance in formulations for direct compression. A number of disintegrants, known as superdisintegrants like cross linked carboxymethyl cellulose (Ac-di- sol®), sodium starch glycolate (Explotab®) and crospovidone (Polyplasdone XL®) markedly improve tablet disintegration by swelling and exerting sufficient pressure in the tablet to break it apart into small segments[11]. The efficacy of these superdisintegrants in any fast dissolving dosage forms depends upon its selection, its concentration used, on method of incorporation[12], on steps used for preparation and/or physico-chemical characteristics of the formulations.

In this study, an effort is made to formulate fast dissolving tablets of diclofenac sodium using different superdisintegrants. The tablets were prepared by direct compression method. Diclofenac sodium is an acidic NSAID, generally used in the treatment of acute inflammatory conditions where a rapid onset of action is desired. Diclofenac has a pKa of 4 and high salivary solubility, hence it is appropriate to formulate it as fast dissolving tablet for the oral cavity.

Diclofenac Sodium was obtained from Sarabhai Chemicals, Mumbai. Mannitol was purchased from Qualigens Fine Chemicals, Mumbai. Microcrystalline cellulose (directly com-

***For correspondence**
E-mail: s.pandey@cops.manipal.edu

pressible), cross linked carboxymethyl cellulose (Ac-di-sol®), sodium starch glycolate (Explotab®) and crospovidone (Polyplasdone XL®) were obtained as gift samples from SPARC, Baroda. All other ingredients and chemicals used were of analytical grade, obtained commercially and used as such.

Diclofenac sodium tablets each containing 25 mg of drug were prepared as per the formulae given in Table 1. Ac-di-sol, Explotab and Polyplasdone XL were tried as superdisintegrants and microcrystalline cellulose (MCC) as directly compressible ingredient[13]. Drug, mannitol and MCC were triturated thoroughly in a glass mortar using a pestle. Superdisintegrants were incorporated in the powder mix and finally magnesium stearate (1 mg) and talc (1 mg) were added as lubricant. The powder mix was weighed individually (108 mg) and compressed with 9 mm flat face punches using a Cadmach single punch tableting machine.

Disintegration testing (6 tablets) was performed for the tablets at 37° in Sorenson's buffer (pH 6.2) medium in disintegration time testing machine[14] (Thermonik, Campbell electronic, Mumbai). Weight loss through friability was determined for 10 tablets after 4 min in a Roche friabilator (Thermonik, Campbell electronic, Mumbai) at 25 rpm[15]. The hardness of 6 tablets was determined using a Pfizer hardness tester and results are presented as a mean±S.D. Dissolution testing was performed by modified USP paddle method at 50 rpm. The test was carried out at 37° in 650 ml of Sorenson's buffer (pH 6.2) as the dissolution medium. Aliquots were withdrawn at different time intervals, filtered and analysed spectrophotometrically at λ_{max} 276 nm for diclofenac sodium against appropriate blank. To maintain a constant volume of release medium, a volume of fresh medium equivalent to the volume of sample withdrawn was added immediately after withdrawal of the sample.

Most of the tablet dosage forms formulated for oral administration are either swallowed or chewed which will allow the drug release in biological milieu. Pediatric and geriatric patients, in particular may have difficulties in swallowing and chewing tablets. Tablets that rapidly disintegrate upon contact with saliva in the buccal cavity could resolve these problems and so there is an increased interest in fast dissolving tablets for buccal, sublingual and oral administration. Worldwide there are few fast dissolve products on the market but very few published scientific articles are available discussing the technology. Use of superdisintegrants in fast dissolving tablet formulations is one of the simplest approaches to achieve. The choice of superdisintegrants and their concentration are the two important factors to formulate these products. Here we have made an attempt to explain the influence of few superdisintegrants in different concentrations to design fast dissolving tablet formulations, which can be prepared by direct compression technique using some compressible vehicles. Table 1 shows different tablet formula-

TABLE 1: COMPOSITION OF PREPARED FAST DISSOLVING TABLETS OF DICLOFENAC SODIUM.

Formulations (mg)	Drug (mg)	Mannitol (mg)	MCC (mg)	Ac-di-sol (mg)	Explotab (mg)	Polyplasdone XL
Control	25	47	36	-	-	-
IA	25	41	36	6	-	-
IB	25	38	36	9	-	-
IC	25	35	36	12	-	-
IIA	25	41	36	-	6	-
IIB	25	38	36	-	9	-
IIC	25	35	36	-	12	-
IIIA	25	41	36	-	-	6
IIIB	25	38	36	-	-	9
IIIC	25	35	36	-	-	12

Drug, mannitol and MCC were mixed thoroughly, superdisintegrants were incorporated in the powder mix along with magnesium stearate and talc, weighed individually and punched into tablets using the Cadmach single punch tableting machine.

tions used in this study. Ten formulations were prepared and each formulation (except control) contained one of the three superdisintegrants in different concentrations. The method of preparation, amount of drug and other tableting excipients were kept constant to avoid the influence of these on results.

The disintegration time in 37° Sorenson's buffer (pH 6.2) for the control batch with no disintegrants was around 160 min. The tablet formulations containing disintegrants had disintegration time of less than 1 min (Table 2) indicating the efficacy of superdisintegrants. Among the three disintegrants used, Ac-di-sol demonstrated best disintegration power in these formulations. Tablets containing Ac-di-sol disintegrated faster when compared to others. Formulation IIC containing 12 mg of Ac-di-sol gave the least disintegration time of 41±2 s. This can be attributed to the extent of water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration. There was no significant difference in the disintegration time of tablets containing Explotab and Polyplasdone XL. This might be again attributed to their mechanism, which may comprise capillary action with a secondary burst effect[16]. The result also showed decrease in disintegration time as the concentration of superdisintegrants increases from 6 mg to 12 mg (Table 2). This can be correlated to tablet matrix pore size distribution created by the use of superdisintegrants. Higher levels of disintegrants probably made larger pores with continuous network or skeleton providing enough pressure within a matrix for faster disintegration[17].

The influence of the disintegrants and their different concentrations on tablet hardness and friability is shown in Table 2. Tablet hardness and friability was found to be fairly uniform for all the formulations and was well within the approved range (Indian Pharmacopoeia, 1996). Disintegrants and their different levels did not show any appreciable impact on these physical parameters, as they are independent of disintegrants and their concentration.

Dissolution for the control batch with no disintegrants was very slow with only 6.2% released in 10 min. and about 20% in 40 min. Tablets containing disintegrants released more than 75% of the drug at the end of 10 min. Ac-di-sol containing formulations produced faster rate of dissolution than other disintegrants (Figs. 1, 2 and 3). Tablets that contained Ac-di-sol dissolved much faster and releasing about 90% of the drug in 10 min. In general, the disintegration power of Explotab and Polyplasdone XL appeared to be equal. The results clearly show the effect of increasing concentration of superdisintegrants on dissolution rate of tab-

TABLE 2: INFLUENCE OF SUPERDISINTEGRANTS CONCENTRATIONS ON THE CHARACTERISTICS OF FAST DISSOLVING TABLETS.

Formulations	Hardness (kg/cm²)*	Disintegration time (sec.)*	% Friability
Control	3.0±0.2	960±21	0.87±0.02
IA	3.2±0.2	48±2	0.91±0.02
IB	3.4±0.4	45±1	0.89±0.01
IC	3.1±0.2	41±2	0.88±0.01
IIA	3.2±0.2	59±3	0.89±0.04
IIB	3.1±0.4	55±1	0.88±0.02
IIC	3.4±0.2	52±2	0.91±0.04
IIIA	3.4±0.4	58±1	0.89±0.01
IIIB	3.2±0.4	55±2	0.94±0.03
IIIC	3.4±0.2	51±1	0.82±0.02

*Each value is the mean±standard deviation of six tablets. IA to IIIC represents various formulations prepared. 'A' represents all the formulations containing 6 mg of superdisintegrants. Similarly 'B' and 'C' represent 9 mg and 12 mg of superdisintegrants, respectively. 'I' represents formulations containing Ac-di-sol, 'II' and 'III' represents for Explotab and Polyplasdone XL, respectively.

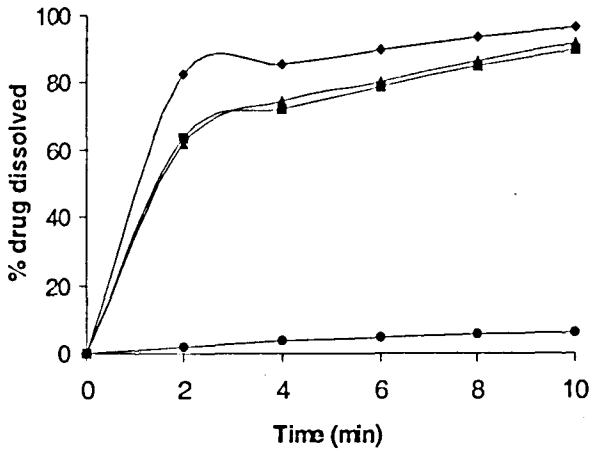

Fig. 1: Comparative dissolution profile of diclofenac sodium from fast dissolving tablets containing 12 mg of superdisintegrants

Dissolution testing was performed by modified USP paddle method at 50 rpm taking Sorenson's buffer (pH 6.2) as the dissolution medium. The super disintegrants used in the formulations are (-◆-) Ac-di-sol, (-■-) Explotab, (-▲-) Polyplasdone XL. (-●-) represents control preparations without any superdisintegrants.

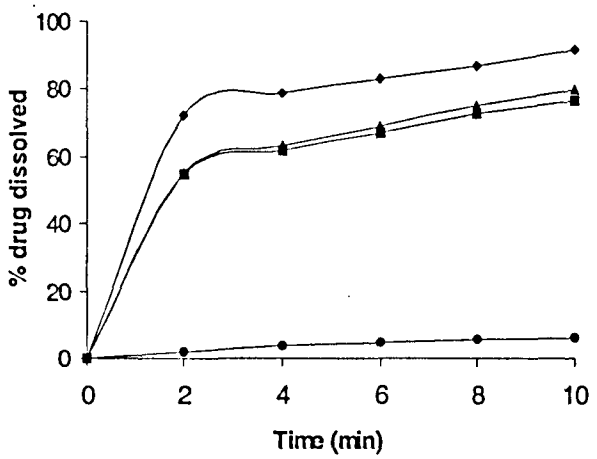

Fig. 3: Comparative dissolution profile of diclofenac sodium from fast dissolving tablets containing 6 mg of superdisintegrants

Dissolution testing was performed by modified USP paddle method at 50 rpm taking Sorenson's buffer (pH 6.2) as the dissolution medium. The super disintegrants used in the formulations are, (-◆-) Ac-di-sol, (-■-) Explotab, (-▲-) Polyplasdone XL. (-●-) represents control preparations without any superdisintegrants.

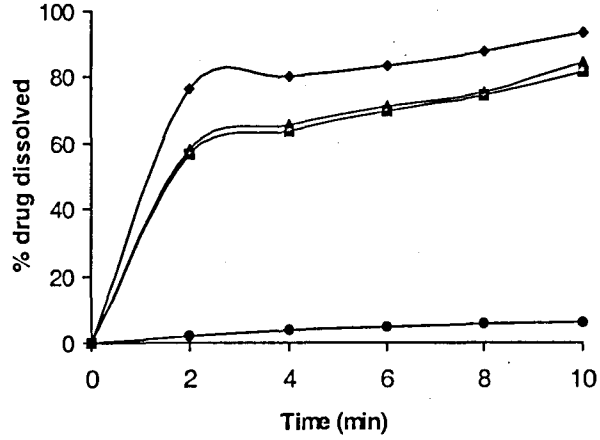

Fig. 2: Comparative dissolution profile of diclofenac sodium from fast dissolving tablets containing 9 mg of superdisintegrants

Dissolution testing was performed by modified USP paddle method at 50 rpm taking Sorenson's buffer (pH 6.2) as the dissolution medium. The super disintegrants used in the formulations are (-◆-) Ac-di-sol, (-■-) Explotab, (-▲-) Polyplasdone XL. (-●-) represents control preparations without any superdisintegrants.

lets. Formulations with higher concentration of disintegrants showed increased dissolution rate. Rapid disintegration with Ac-di-sol formulations and tablets having higher levels of superdisintegrants, as shown earlier might be one of the probable cause for their faster dissolution. Another reason could be that in the presence of disintegrants, the matrix might have distorted resulting higher surface area, allowing the superdisintegrants to readily pick up water and thereby rendering rapid rate of dissolution.

In conclusion, Ac-di-sol was found to be better suited for the formulation of fast dissolving tablets of diclofenac sodium when compared to other superdisintegrants used in the study. Formulations containing Ac-di-sol have exhibited excellent disintegrating character and consequently the rapid dissolution even at concentrations as low as 6 mg.

REFERENCES

1. Habib, W., Khankari, R. and Hontz, J., **Crit. Rev. Ther. Drug Carr. Syst.,** 2000, 17, 61.
2. Masaki, K., **US Patent No.** 5,466,464, 1995.
3. Remon, J.P. and Corveleyn, S., **US Patent No.** US6,010,719, 2000.
4. Seager, H., **J. Pharm. Pharmacol.,** 1998, 50, 375.
5. Allen, L.V. and Wang, B., **US Patent No.** US5,635,210, 1997.
6. Allen, L.V., Wang, B. and Davies, J.D., **US Patent No.** US5,

635,210, 1997.
7. Ito, A. and Sugihara, M., **Chem. Pharm. Bull.,** 1996, 44, 2132.
8. Visavarungroj, N. and Remon, J.P., **Int. J. Pharm.,** 1990, 62, 125.
9. Chang, R., Guo, X. and Burnside, B.A., **Pharm.Technol.,** 2000, 24, 52.
10. Shangraw, R.F., Mitrevej, A. and Shah, M.A., **Pharm.Technol.,** 1980, 4, 49.
11. Kuchekar, B.S., Bhise, S.B. and Armugam, V., **Indian J. Pharm. Edu.,** 2001, 35, 150.
12. Gordon, M.S., Chatterjee, B. and Chowhan Z.T., **J. Pharm. Sci.,** 1990, 79, 43.
13. Munoz-Ruitz, A., Gallego, R., Del pozo, M. and Jimenez-Castellanos, M.R., **Eur. J. Pharm. and Biopharm.,** 1994, 40, 36.
14. Indian Pharmacopoeia, Ministry of health and family welfare, Govt. of India, Delhi, 1996, 736.
15. Lachmann, L., Liberman, H.A. and Kanig, J.L. Eds., In; The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese Publishing House, Mumbai, 1987, 293.
16. Shangraw, R.F., Mitrevej, A. and Shah, M., **Pharm. Technol.,** 1980, 4, 49.
17. Ganderton, D. and Fraser, D.R., **J. Pharm. Pharmacol.,** 1970, 22, 95S.

Immunostimulant Activity of *Kalayak ghrita*

S. V. FULZELE*, P. M. SATTURWAR, S. B. JOSHI AND A. K. DORLE
Department of Pharmaceutical Sciences, Nagpur University Campus
Amravati road, Nagpur-440 010.

Accepted 29 October 2002
Revised 13 September 2002
Received 15 February 2002

The focus of the present study is to investigate the immunostimulant effect of *Kalayak ghrita*, an herbal formulation. The study of this formulation in respect to humoral and cell-mediated immune response showed that oral administration of *Kalayak ghrita* enhanced the antibody titre as well as foot pad swelling response to the antigenic challenges with sheep red blood cells. The herbal formulation belongs to the *Panchgavya* class of ayurvedic formulations in which one or more of the five bovine products (milk, ghee, curd, urine and dung) are used along with herbs. The formulation was administered at doses 50, 100, 150 and 200 mg/kg/day to healthy rats. Results of the present study suggest a dose-dependent immunostimulant effect of *Kalayak ghrita* in rats.

The field of medicine has witnessed a global resurgence of interest in traditional systems of therapy over the past few years. Apprehensions concerning the toxicity and safety of modern/synthetic drugs have played a prominent role towards promoting research in developing safer drugs for clinical therapy[1]. Emphasis is also laid on the integration of traditional medicine with the modern health practices[2,3]. With increasing understanding of disease management, it has become necessary to provide scientific basis/rationale for the clinical utility of such medicinal agents of traditional systems. A lot of focus is being given for conducting studies that substantiate the claims of traditional formulations[4]. The present study attempts to investigate the claimed immunostimulant effect of an herbal formulation belonging to *Panchgavya* class of medicinal agents.

Panchgavya is a term used in Ayurveda to describe the five important products of bovine origin such as milk, curd, ghee, urine and dung. Several formulations based on *Panchgavya* are reported in ancient Ayurvedic texts. *Panchgavya* are used either alone or in combination with herbs for the treatment of several diseases[5-7]. In the present manuscript we have investigated the immunostimulant activity of *Kalayak ghrita* (KG), an herbal formulation in experimental animals. The ingredients of KG are *Berberis*

***For correspondence**
E-mail: fsuniket@yahoo.com