

Research Article

Formulation and Evaluation of Aceclofenac Mouth Dissolving Tablets By Using Polyplasdone XI 10 as Super Disintegrant and Sublimation Technique

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ABSTRACT

The purpose of this investigation was to develop fast dissolving tablets of aceclofenac using Polyplasdone XL 10 (Crospovidone) as a novel superdisintegrant. Orodispersible tablets of aceclofenac were prepared by wet granulation technique using Polyplasdone XL 10 as superdisintegrant and menthol as subliming agent. Menthol was sublimed from the granules by exposing the granules to vacuum. The porous granules were then compressed into tablets. Alternatively, tablets were first prepared and later exposed to vacuum. The formulations were evaluated for hardness, friability, weight variation, thickness, wetting time, dispersion time, drug content and drug release. All the formulations showed low weight variation with dispersion time less than 70 seconds and rapid *in vitro* dissolution. Sublimation of menthol from tablets resulted in superior tablets as compared with the tablets prepared from granules that were exposed to vacuum. The results revealed that the tablets containing subliming agent had a good dissolution profile. The drug content of all the formulations was within the acceptable limits of the United States Pharmacopoeia. The optimized formulation showed good release profile with maximum drug being released at all time intervals. It was concluded that fast dissolving tablets with improved aceclofenac dissolution could be prepared by sublimation of tablets containing suitable superdisintegrant. This work helped in understanding the effect of formulation processing variables especially the subliming agent on the drug release profile. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Keywords: Mouth dissolving tablet, Aceclofenac, Subliming agent, Superdisintegrant.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as fast dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.¹⁻² NSAID has been indicated for various painful indications¹⁶ and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse

effects and thus, resulted in a greater compliance with treatment¹⁷. Aceclofenac is practically insoluble. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion). The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

In the present study, an attempt was made to develop mouth dissolving tablets of aceclofenac and to investigate the effect of subliming agent & novel superdisintegrant on the release profile of the drug in the tablets. The fundamental principle used in the development of the fast-dissolving tablet is to maximize its pore structure. Researchers have evaluated spray dried materials³ and plastic materials⁴ for development of such tablets.

Vacuum-drying⁵⁻¹⁰ and freeze-drying¹¹⁻¹⁴ techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Aceclofenac, (2-[2-[2-(2,6-dichlorophenyl)aminophenyl]acetyl]oxyacetic acid), a nonsteroidal anti-inflammatory, analgesic and antipyretic drug used in rheumatoid arthritis, post-traumatic pain, musculo-skeletal and joint disorders¹⁵

MATERIAL AND METHODS

Aceclofenac and Polyplasdone XL 10 obtained as a gift sample from Blue Cross Lab. Ltd, Nasik, India. Menthol, Calcium stearate, Aspartame, Mannitol. were purchased from authorized dealer.

METHOD

Formulation of mouth dissolving tablets of aceclofenac

The orodispersible tablets of aceclofenac were prepared using the subliming agent, menthol and Polyplasdone XL 10 as superdisintegrant, mannitol as diluent, aspartame as sweetening agent, alcoholic solution of polyvinylpyrrolidone (PVP) (10%w/v) as binder and calcium stearate with talc as flow promoter. The composition of the each batch shown in Table 1.

Table 1: Composition of different batches of mouth-dissolving tablets of aceclofenac

Name of Ingredients	Quantities (mg)				
	F1	F2	F3	F4	F5
Aceclofenac	100	100	100	100	100
Menthol	20	20	25	25	25
Polyplasdone XL 10	20	20	20	25	25
Calcium stearate	----	5	5	5	5
Mannitol	55	50	45	40	40
Total	200	200	200	200	200

*all the quantities expressed in mg. All batches contained 10% (PVP) in ethyl alcohol as a binder and 2% talc and 1% calcium stearate. Menthol was sublimed from granules in Batches F1 to F4 and from tablets in Batch F5.

The raw materials were passed through a 60-mesh screen prior to mixing. The drug and other ingredients were mixed together and a sufficient quantity of alcoholic solution of PVP (10%w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granules of the all formulations were dried in a vacuum oven (Vertex, VT4810) at 60°C for 12 h resulting in localized drying. The final moisture content of the granules was found to be between 1-2%, which was determined using an IR moisture balance. During drying, the menthol sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, calcium stearate and compressed into tablets using flat face round tooling on a Rimex-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad). Sublimation was performed from tablets instead of granules at 60°C in selected batch (F5).

Evaluation of formulated tablets

Hardness¹⁸

The crushing strength of the tablets were measured using a Erweka hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability¹⁸

Ten tablets were weighed and placed in a Roche friabilator (Electrolab, India). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets were measured as per the following formula,

Percentage friability =

$$\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight Variation

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than $\pm 7.5\%$.

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 100mg of aceclofenac was dissolved in 100ml of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 274 nm using UV-Visible Spectrophotometer (UV 160-Shimadzu, Japan).

***In vitro* dispersion time¹⁹**

In vitro dispersion time of prepared tablet was done by dropping the tablet in 10ml measuring cylinder containing 6ml of simulated salivary fluid (pH 6.8). Time required for complete dispersion of tablet was measured.

Dissolution Study

In vitro release of aceclofenac from tablets was monitored by using 900 ml of simulated intestinal fluid, SIF (USP phosphate buffer solution, pH 7.4) at $37 \pm 0.5^\circ\text{C}$ and 75 rpm using programmable dissolution tester [Paddle type, model TDT-08L, Electrolab, (USP),

India]. 5ml Aliquots were withdrawn at one minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were assayed spectrophotometrically (UV-1700, Shimadzu, Japan) at 274 nm.

Thickness

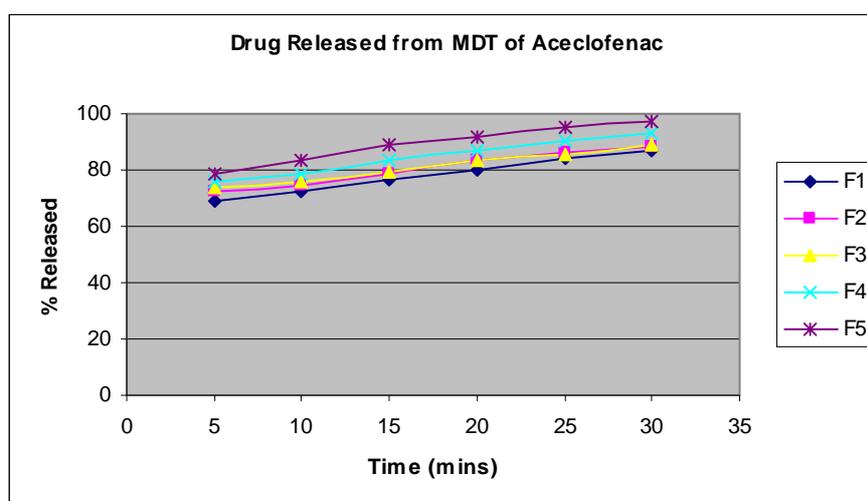
Thickness of tablet was determined by using vernier calliper (Mitutoya, Model CD-6 CS, Japan).

Wetting time²⁰

A piece of circular tissue paper (8cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 10ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted. The results are tabulated in Table 2.

Table 2: Evaluation of mouth-dissolving tablets of aceclofenac

Parameters	F1	F2	F3	F4	F5
Hardness (kg/cm ²)	3.1±0.30	3.4±0.68	2.9±0.51	3.1±0.63	3.6±0.10
Friability (%)	0.743	0.629	0.637	0.688	0.574
Weight variation (mg)	204±3	199±2	203±3	197±1	200±1
Thickness (mm)	3.5±0.03	3.4±0.07	3.6±0.05	3.4±0.06	3.5±0.01
Wetting time (s)	38.2±2.5	39.3±1.5	43.6±2.2	39.1±2.0	29.4±1.5
<i>In vitro</i> dispersion time (s)	68.3	62.1	56.2	53.7	41.8
Drug content	99.24±3.24	98.44±2.54	98.60±3.04	98.93±1.81	99.42±1.27
Drug release in 5min (%)	69.03	72.17	73.72	75.54	78.37
Drug release in 30min (%)	86.81	88.11	88.73	93.26	97.25

**Fig. 1: In vitro release profile of various Aceclofenac formulations**

RESULTS AND DISCUSSION

Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were omitted from the study as they are expected to cause an unacceptable feeling of grittiness in the mouth. Among the soluble diluents, mannitol was selected as a diluent considering its advantages in terms of easy availability and negative heat of dissolution. Table 2 shows that all the formulated tablets exhibited low weight variation. Addition of a subliming agent had no pronounced effect on hardness and increased friability of the tablets. The wetting time, *in vitro* dispersion time of the tablets were also considerably reduced in tablets (Table 2). The drug content of all the formulations was found to be between 98.4-99.5% which was within the acceptable limits as per USP XXVII. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of Polyplasdone XL 10 in bringing about faster disintegration. Tablets with lower friability may not break during handling on machines and/or shipping. The use of a sublimation agent resulted in increased friability probably due to increased porosity. In the first few attempts (F1-F4), sublimation of menthol was performed from granules prior to compression into tablets. Batches F1 to F4 showed good mechanical integrity, but the disintegration time was a little longer than the arbitrarily chosen value of less than 50 seconds. In Batch F5, sublimation was performed after compression rather than directly from granules. The results shown in Table 2 reveal that sublimation of menthol from tablets resulted in faster disintegration. The compaction process might have caused breakage of porous granules and subsequent reduction in porosity. The low value of wetting time and disintegration time indicate that the porosity of tablets of batch F5 would be greater than batches F1 to F4. *In vitro* release studies were carried out using USP XXIII tablet dissolution test apparatus paddle method at $37\pm 1^{\circ}\text{C}$, taking 900 ml of simulated intestinal fluid (SIF) as dissolution medium. Speed of rotation of the paddle was set at 75 rpm. Aliquots of 5 ml were withdrawn after 1, 3, 5, 6, 8, 10, 30 min and analyzed spectrophotometrically at 274 nm. The *in vitro* dissolution profile (Fig.1) indicated faster and maximum drug release from formulation F5. Formulation F5 prepared by direct sublimation of menthol from final tablets showed release 78.37% drug at the end of 5 min when compared to tablets prepared by sublimation of menthol from granules. The rapid drug dissolution might be due to easy breakdown of particles due to porous structure formation

after sublimation of menthol and rapid absorption of drugs into the dissolution medium.

CONCLUSION

From the study, it can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets using Polyplasdone XL 10 as superdisintegrant, disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability. Vacuum-drying technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of mouth dissolving tablets.

REFERENCES

1. Chang R, Guo X, Burnside B and Couch R. A review of fast dissolving tablets. Pharm Tech North Am. 2000; 12:52-8.
2. Bi Y, Sunada H, Yonezawa Y, Danjo K and Iida K. Preparation and evaluation of compressed tablets rapidly disintegrating in the oral cavity. Chem Pharm Bull. 1996;44:2121-7.
3. Mishra DN, Bindal M, Singh SK and Kumar SG. Spray dried excipient base: A novel technique for the formulation of orally disintegrating tablets. Chem Pharm Bull. 2006;54: 99-102.
4. Fu Y, Jeong SH, and Park K. Fast-melting tablets based on highly plastic granules. J Control Release. 2005; 109:203-10.
5. Omaira AS, Mohammed AH, Nagia AM and Ahmed SZ. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS Pharm Sci Tech. 2006;7:55.
6. Gohel M, Patel M, Amin A, Agrawal R, Dave R and Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS Pharm Sci Tech. 2004;5:36.
7. Suresh S, Pandit V and Joshi HP. Preparation and evaluation of mouth dissolving tablets of salbutamol sulphate. Ind J Pharm Sci. 2007;69: 467-9.
8. Heinemann H and Rothe W. Preparation of porous tablets. US patent. 3885026. 1975.
9. Knistich A, Hagen E and Munz HD. Production of porous tablets. US patent 4134843. 1979.

10. Roser BJ and Blair J. Rapidly soluble oral dosage forms, methods of making the same and composition thereof. US patent 5762961, 1998.
11. Ahmed IS and Fatahalla FA. Pilot study of relative bioavailability of two oral formulations of ketoprofen in healthy subjects, a fast dissolving lyophilized tablet as compared to immediate release tablet. *Drug Dev. Ind. Pharm.* 2007;33:505-11.
12. Ahmed IS, Nafadi MM and Fatahalla FA. Formulation of fast dissolving ketoprofen tablet using freeze-drying in blister technique. *Drug Dev. Ind. Pharm.* 2006;32:437-42.
13. Corveleyn S and Remon JP. Formulation and production of rapidly disintegrating tablets by lyophilization using hydrochlorothiazide as a model drug. *Int J Pharm.* 1997;152:215-25.
14. Remon JP and Corveleyn S. Freeze-dried rapidly disintegrating tablets. US patent. 6010719, 2000.
15. Setty CM, Prasad DVK, Gupta VRM and BSA. Development of fast dispersible aceclofenac tablets: Effects of functionality of superdisintegrants. *Ind J Pharm Sci.* 2008;70(2):180-185.
16. Hinz B, Auge D, Rau T, Rietbrock S, Brune K and Werner U. Simultaneous determination of aceclofenac and three of its metabolites in human plasma by high-performance liquid chromatography. *Biomed Chromatogr.* 2003;17:268-75.
17. Legrand E. Aceclofenac in the management of inflammatory pain. *Exp. Opin. Pharmacother.* 2004;5:1347-57.
18. Marshall K, Lachman N and Liberman HA. The theory and practice of industrial pharmacy. 3rd Ed, Varghese Publishing House, Mumbai. 1987;66-69.
19. Kimura S, Imai T and Otagiri M. Pharmaceutical evaluation of ibuprofen syrup containing low molecular weight gelatin. *J Pharm Sci.* 1992;81:141-144.
20. Yunxia B, Yorinobu Y, Kazumi D and Akinobu O. Preparation and evaluation of oral tablet rapidly dissolving in oral cavity. *Chem Pharm Bull.* 1996;44(11):2121-2127.