www.sphinxsai.com

PharmTech

International Journal of PharmTech Research
CODEN(USA): IJPRIF ISSN : 0974-4304
Vol.1, No.2, pp 210-214 , April-June 2009

Development and Characterization of Orodispersible Tablets of Aceclofenac by Sublimation Technique

Ravi Kumar*[1], M. B. Patil[2], Sachin R. Patil[1], Mahesh S. Paschapur[3], Mahalaxmi.R[4]

[1] Department of Pharmaceutics, K.L.E.S's College of Pharmacy, Ankola-,India,
[2] Department of Pharmacognosy, K.L.E.S's College of Pharmacy, Ankola-,India,
[3] Department of Pharmacology, K.L.E.S's College of Pharmacy, Ankola-,India,
[4] Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal, India.

Abstract: The purpose of this investigation was to develop fast dissolving tablets of aceclofenac using camphor as a subliming agent. Orodispersible tablets of aceclofenac were prepared by wet granulation technique using camphor as subliming agent and sodium starch glycolate together with crosscarmellose sodium as superdisintegrants. Camphor was sublimed from the granules by exposing the granules to vacuum. The porous granules were then compressed in to tablets. Alternatively, tablets were first prepared and later exposed to vacuum. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, *in vitro* and *in-vivo* dispersion, mouth feel and *in vitro* dissolution. All the formulations showed low weight variation with dispersion time less than 55 seconds and rapid *in vitro* dissolution. Sublimation of camphor 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 XXVII. 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 subliming agent. 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, super disintegrant, Camphor.

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].

The fundamental principle used in the development of the fast-dissolving tablet is to maximize its pore structure. Researchers have evaluated spray dried materials[3] and plastic materials[4] for development of such tablets. Vacuum-drying[5-10] and freeze-drying[11-14] 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-(2,6-dichlorophenyl)aminophenyl]acetyl]oxyacetic acid), a nonsteroidal antiinflammatory drug

(NSAID) has been indicated for various painful indications[15] and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatment[16]. Aceclofenac is practically insoluble. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. Clear aceclofenac-loaded soft capsules have been prepared to accelerate the absorption[17]. 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 on the release profile of the drug in the tablets.

Material and Methods:

Aceclofenac (Aristo Pharmaceuticals Ltd, Mumbai, India), croscarmellose sodium, sodium starch glycolate, and microcrystalline cellulose (Maple Biotech Pvt Ltd., Pune, India), aspartame (Ranbaxy, New Delhi, India). Crospovidone (Concertina Pharma Pvt., Ltd, Hyderabad, India). Camphor, sodium saccharin, mannitol, polyvinyl pyrollidone (PVP), talc and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai, India.

Method

Formulation of mouth dissolving tablets of aceclofenac

The orodispersible tablets of aceclofenac were prepared using the subliming agent, camphor, sodium starch glycolate and crosscarmellose sodium as superdisintegrants, mannitol as a diluent, sodium saccharin as sweetening agent, alcoholic solution of PVP (10%w/v) as binder and magnesium stearate with talc as a flow promoter. The composition of the each batch shown in Table 1.

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

Ingredients*	F1	F2	F3	F4	F5	F6
Aceclofenac	100	100	100	100	100	100
Camphor	--	--	12.5	12.5	25	25
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5
Crosscarmellose sodium	--	15	--	15	---	15
Sodium starch glycolate	15	--	15	--	15	---
Colloidal silicon dioxide	--	--	--	--	2.5	2.5
Mannitol q.s.	250	250	250	250	250	250

*all the quantities expressed in mg. All batches contained 10% polyvinylpyrrolidone in ethyl alcohol as a binder and 2% talc and 1% magnesium stearate. Camphor was sublimed from granules in Batches F1 to AF5 and from tablets in Batch F6.

The raw materials were passed through a 100-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 formulations containing either of the superdisintegrants but without camphor (F1 or F2) were dried in a tray dryer (Tempo instruments and equipments, Mumbai) at 60^0C for 30 min. resulting in localized drying.

Other granular formulations (F3 to F6) contained a subliming agent and were dried at room temperature, 20-22 ^{0}C for 8hrs. The final moisture content of the granules was found to be between 3-4%, which was determined using an IR moisture balance. During drying, the camphor sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, magnesium stearate and compressed into tablets using flat face round tooling on a Rimek-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad). Sublimation was performed from tablets instead of granules at 60º C in selected batch (F6).

Evaluation of formulated tablets:

Hardness [18]

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability[18]

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 was measured as per the following formula,

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

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 ±7.5% (USPXX).

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 time[19]

In vitro dispersion time was measured by dropping a tablet in a 10ml measuring cylinder containing 6ml of buffer solution simulating saliva fluid (pH7.4).

Dissolution Study

In vitro release of aceclofenac from tablets was monitored by using 900 ml of SIF (USP phosphate buffer solution, pH 7.4) at 37±0.5° 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 dial caliper (Mitutoya, Model CD-6 CS, Japan).

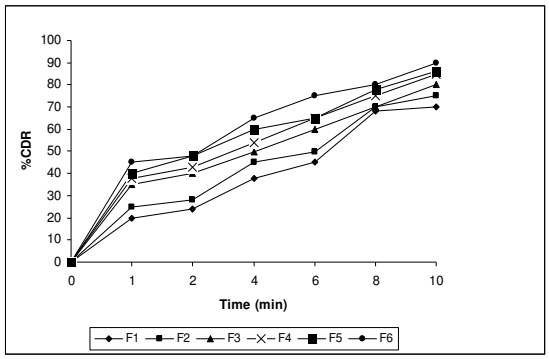
Wetting time[20]

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 9ml of buffer solution simulating saliva pH 7.4. 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 aceclofena

Formulation	Hardness (kg/cm^2) n = 6	Friability (%) n =10	Drug content (%) n = 4	*In vitro* dispersion time (s)	Wetting time (s)	Weight varriation (mg)	Thickness (mm)
F1	4.8±1.6	0.457	98.23±3.24	160	95±2.5	253±2	4.6± 0.19
F2	4.5±0.42	0.535	99.23± 2..68	150	75±2.0	252±1	4.6±0.07
F3	3.8±1.4	0.583	98. 6±3.23	115	45±1.5	255±2	4.28±0.05
F4	3.5±0.56	0.683	98.47± 1.26	90	35±1.4	254±3	4.6±0.03
F5	4±0.41	0.486	99.1± 2.32	75	25±1.2	249±3	4.43±0.01
F6	3.5±0.63	0.354	97.4±1.32	45	15± 1.3	249±1	4.38±0.05

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 containing camphor (Table 2). The drug content of all the formulations was found to be between 97.4 - 99.1% which was within the acceptable limits as per USP XXVII. The batches F3 and F5 were prepared using camphor at different concentrations to study its effect on disintegration time. The sublimation time (0.5-8 hours) depended on the amount of camphor present initially (0%, 5%, or 10%). Batch F5, containing 10% camphor, showed the least disintegrating time. The results shown in Table 2 indicate that concentration-dependent disintegration was observed in batches prepared using camphor as a subliming agent. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of crospovidone in bringing about faster disintegration. It is worthwhile to note that as the concentration of camphor increased, the wetting decreased. Tablets with lower friability (≤0.5%) 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. It was decided to incorporate colloidal silicon dioxide, extragranularly, at a level of 1% to decrease the friability of the tablets (batches F5 and F6). Addition of colloidal silicon dioxide resulted in appreciable decrease in friability and marginal decrease in disintegration time. Colloidal silicon dioxide helps to restore the bonding properties of the excipients.

In the first few attempts (F1-F5), sublimation of camphor was performed from granules prior to compression into tablets. Batches F1 to F5 showed good mechanical integrity, but the disintegration time was a little longer than the arbitrarily chosen value of less than 50 seconds. In Batch F6, sublimation was performed after compression rather than directly from granules. The results shown in Table 2 reveal that sublimation of camphor 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 F6 would be greater than batches F1 to F5. The granules required 4 hours of vacuum drying, whereas the tablets required 8 hours of vacuum drying. The longer drying time was required in the case of tablets probably because of the decreased surface area and porosity.

In vitro release studies were carried out using USP XXIII tablet dissolution test apparatus paddle method at 37±1 ^{o}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, 2, 4, 6, 8, 10 min and analyzed spectrophotometrically at 274 nm. The *in vitro* dissolution profile (Fig.1) indicated faster and maximum drug release from formulation F6. Formulation F6 prepared by direct sublimation of camphor from final tablets showed release 90.12% drug at the end of 10 min when compared to tablets prepared by sublimation of camphor from granules. The rapid drug dissolution might be due to easy breakdown of particles due to porous structure formation after sublimation of camphor and rapid absorption of drugs into the dissolution medium, and slope values signify that the release rate follows first order kinetics

Conclusion:

From the study, it can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets 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, 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, Iida K. Preparation and evaluation of compressed tablets rapidly disintegrating in the oral cavity. Chem Pharm Bull (Tokyo) 1996;44:2121-7.
3. Mishra DN, Bindal M, Singh SK, 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, Park K. Fast-melting tablets based on highly plastic granules. J Control Release 2005;109:203-10

5. Omaima AS, Mohammed AH, Nagia AM, Ahmed SZ. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS PharmSciTech 2006;7:55.

6. Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS PharmSciTech 2004;5:36.

7. Suresh S, Pandit V, Joshi HP. Preparation and evaluation of mouth dissolving tablets of salbutamol sulphate. Indian J Pharm Sci 2007;69:467-9.

8. Heinemann H, Rothe W. Preparation of porous tablets. US patent 3 885 026. May 20, 1975.

9. Knistch A, Hagen E, Munz HD. Production of porous tablets. US patent 4 134 843. January 16, 1979

10. Roser BJ, Blair J. Rapidly soluble oral dosage forms, methods of making the same and composition thereof. US patent 5 762 961, June 9, 1998

11. Ahmed IS, 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 Develop Ind Pharm 2007;33:505-11.

12. Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of fast dissolving ketoprofen tablet using freeze-drying in blister technique. Drug Develop Ind Pharm 2006;32:437-42.

13. Corveleyn S, 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, Corveleyn S. Freeze-dried rapidly disintegrating tablets. US patent 6 010 719, January 4, 2000.

15. Hinz B, Auge D, Rau T, Rietbrock S, Brune K, 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.

16. Legrand E. Aceclofenac in the management of inflammatory pain. Exp Opin Pharmacother 2004;5:1347-57

17. Yong CS, Oh YK, Lee KH, Park SM, Park YJ, Gil YS, *et al.* Trials of clear aceclofenac- loaded soft capsules with accelerated oral absorption in human subjects. Int J Pharm 2005;302:78-83.

18. Marshall K, Lachman N, Liberman HA. The theory and practice of industrial pharmacy, 3rd Ed, Varghese Publishing House, Mumbai, 1987, pp *66-69.*

19. Kimura S, Imai T, 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, Akinobu O. Preparation and evaluation of oral tablet rapidly dissolving in oral cavity. Chem. Pharm. Bull. 1996; 44(11): 2121-2127.

*****