Bulletin of Pharmaceutical Research 2012;2(1):5-9
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)

RESEARCH ARTICLE

FORMULATION DEVELOPMENT OF MOUTH DISSOLVING TABLETS OF A POORLY WATER SOLUBLE DRUG USING SUBLIMATION TECHNIQUE

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Received: January 04, 2012 / Revised: January 23, 2012 / Accepted: January 24, 2012

The purpose of this research was to develop mouth dissolving tablets of etoricoxib. Materials containing etoricoxib, camphor, low substituted-hydroxypropyl cellulose (L-HPC) and lactose were compressed by direct compression technique. Camphor was sublimed from the tablets by exposure to vacuum. The porous tablets were evaluated for percentage friability, wetting time and disintegration time. Sublimation of camphor from tablets resulted in superior tablets. The systematic formulation approach helped in understanding the effect of formulation processing variables. The best results for the batch D3 in terms of crushing strength; friability and disintegration were obtained, when sublimation was carried out of the tablets containing camphor as a sublimating agent at 5% and L-HPC as disintegrant at the 12% concentration. The drug release data showed that the entire drug was released within 60 min. The best batch prepared using camphor sublimation technique possessed crushing strength (kg/cm^2) of 3.5, friability (%) of 0.26, wetting time of 21 sec and disintegration time of 24 sec, respectively.

Key words: Mouth dissolving tablet, Sublimation, Camphor, Etoricoxib, Pooorly water soluble drug.

INTRODUCTION

Oral route is the most widely used route of drug administration. However, the poorly soluble drugs may show difficulty in their absorption but their solubility can be enhanced by various approaches (Sachan and Pushkar, 2011; Pabreja and Dua, 2011). The demand for orally disintegrating tablets has enormously increased during the last decade, particularly for geriatric and pediatric patients who have difficulty in swallowing conventional tablets and capsules (Dinesh Kumar *et al* 2011). To provide the patient with the most convenient mode of administration, there is need to develop a fast disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without water, anywhere, anytime (Solanki and Dahima, 2011; Basu *et al* 2011; Dahiya *et al* 2011; Parkash *et al* 2011). Such tablets are also called as "melt in mouth tablets". This is an innovative technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in seconds, without the need for water, providing optimal convenience to the patient. Innovators and inventor companies have given these tablets various names such as mouth dissolving, fast melting, fast dissolving or orodispersible. Etoricoxib is an effective anti-inflammatory agent with minimal incidences of side effects and is indicated for various conditions like osteoarthritis, rheumatoid

arthritis, acute gouty arthritis, dental pain, primary dysmenorrheal, back pain and ankylosing spondylitis (Brooks and Kubler, 2006). In present study, formulation development of the mouth dissolving tablets of etoricoxib is reported with the optimized concentration of disintegrant and the sublimating agent, in order to give fast release of a poorly soluble drug with the desired characteristics.

MATERIALS AND METHODS

The etoricoxib was obtained as a gift sample from Cadila pharmaceuticals Ltd., Ahmedabad. Primogel®, Ac-Di-Sol®, Kollidone® were obtained as gift samples from Torrent pharmaceuticals Limited, Ahmedabad.

Preparation of tablet

All the materials except lactose were passed through #100 sieve prior to mixing. The drug was properly mixed with disintegrant followed by diluent lactose. The mixture was then mixed with polyvinylpyrrolidone, Aerosil® and mannitol. The material was subjected to direct compression in hand operated single punch tablet machine (**Table 1**).

Selection of disintegrants

Various disintegrating agents such as Primogel®, Ac-Di-Sol®, Kollidone®, L-HPC, L-HPMC were used in tablets preparation (**Table 2**).

Table 1. Formula for preparation of tablet

Sr. No.	Ingredient	Quantity
1.	Disintegrant	4%
2.	Binder	7%
3.	Sweetener	20%
4.	Glidant	0.5%
5.	Drug	60 mg
6.	Diluent	q.s.

Table 2. Selection of disintegrants

S. No.	Ingredient		Quantity				
			A1	A2	A3	A4	A5
1	Disintegrant	Primogel®	10	-	-	-	-
2		Ac-Di-Sol®	-	10	-	-	-
3		Kollidone®	-	-	10	-	-
4		L-HPC	-	-	-	10	-
5		L-HPMC	-	-	-	-	10
6	Binder	PVP	7%	7%	7%	7%	7%
7	Sweetener	Mannitol	20%	20%	20%	20%	20%
8	Glidant	Aerosil	0.5%	0.5%	0.5%	0.5%	0.5%
9	Drug	Etoricoxib	60 mg	60 mg	60 mg	60 mg	60 mg
10	Diluent	Spray dried lactose up to	250 mg	250 mg	250 mg	250 mg	250 mg

Selection of sublimating agent

Sublimating agents such as menthol, camphor and thymol were used to increase porosity of the tablets in the preliminary tablet formulations (Heinemann and Rothe, 1975). After compression, tablets were subjected to sublimation using vacuum oven at 60°C till the presence of camphor could not be felt by smelling (5-10 h). Different batches were prepared by varying concentration of selected subliming agent and evaluated for friability (Koizumi *et al* 1997).

Evaluation of tablet

Crushing strength

The limit of crushing strength for a mouth dissolving tablet is usually kept in a lower range to facilitate early disintegration in the mouth. The crushing strength of the tablet can be measured using Monsanto hardness tester.

Friability of tablet
Friability of tablet is measured by using Roches friabilator.

Wetting time
Five circular tissue papers of 10 cm diameter were placed in a petri dish. Ten millimeter of water containing (%) eosin, a water-soluble dye, was added to petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time (n=3).

Modified disintegration test
For this purpose, a petri dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petri dish and the time for the tablet to completely disintegrate into fine particles was noted. The studies were carried out in triplicate (n=3).

Selection of best formulation
Etoricoxib mouth dissolve tablets with selected subliming and disintegrating agent containing required excipients were formulated and evaluated for crushing strength, friability, disintegrating time. Among these, the best formulation was selected on basis of results of evaluation parameters. After selecting suitable disintegrant and sublimating agent, different formulation were prepared and optimized.

In vitro drug release
In vitro drug release study was carried out in the dissolution test apparatus USP Type II using 900 ml of phosphate buffer pH 7.4 and 0.1 N HCl at 50 rpm and 37±0.5°C. Five millilitre of the aliquots were withdrawn at different predetermined time intervals, filtered using 0.45 μm membrane filters and was analyzed at 235 nm for phosphate buffer pH 7.4 and 233 nm for 0.1 N HCl using double-beam UV/visible spectrophotometer (Shimadzu UV-1700, Japan). Five millilitre of media was replaced in the vessel after each withdrawal to maintain the sink condition. Percent drug release was calculated using the calibration curve and was plotted against function of time to study the pattern of drug release from tablets.

RESULTS AND DISCUSSION
Mouth dissolving tablets of etoricoxib were prepared successfully and evaluated for optimum disintegrant and sublimating agent on the basis of crushing strength, friability, wetting time, disintegration time and *in vitro* drug release. The results suggested that among various disintegrants used, L-HPC emerged as the best disintegrant as it exhibited least disintegration time (38 sec) and friability (0.30%). The results of crushing strength, friability, wetting time and disintegration time for formulations A1 to A5 are summarized in **Table 3**. After selection of disintegrant, B1 to B3 were designed to find out the best subliming agent respectively. The results suggest that camphor was better subliming agent as compared to thymol and menthol (**Table 4**).
To further investigate the effect of concentration of subliming agent on tablet properties, formulations C1 to C5 were prepared using increasing concentration of camphor. The results suggested that as the concentration of camphor increased, the wetting and disintegrating time of tablets decreased with increasing friability (**Table 5**). This further indicated that camphor concentration above 10% is not desirable for the tablet formulations. Based on these results, formulations D1 to D9 were prepared by varying concentration of disintegrant and sublimating agent in order to find out the best formulation for etoricoxib mouth dissolving tablets. The results suggested that D3 displayed least disintegration time, wetting time, friability and satisfactory crushing strength and therefore selected as best the best formulation (**Table 6**). Formulation D3 was further subjected to *in vitro* drug release studies and showed 93.59% and 98.60% drug release at 60 min in 0.1 N HCl and phosphate buffer pH 7.4 as dissolution media (**Figure 1, 2**). Disintegration of D3 at various time intervals is presented in **Figure 3**.

Table 3. Evaluation parameters of formulated tablets

S. No.	Formulation code	Crushing strength (kg/cm^2)	Friability (%)	Wetting time (sec)	Disintegration time (sec)
1.	A1	3.5	0.41	68	93
2.	A2	4.0	0.46	34	50
3.	A3	4.0	0.40	25	43
4.	A4	3.5	0.30	34	38
5.	A5	4.5	1.02	78	106

Table 4. Selection of sublimating agent

Formulation	B1	B2	B3
Etoricoxib	60 mg	60 mg	60 mg
Camphor	50	-	-
Thymol	-	50	-
Menthol	-	-	50
L-HPC	10	10	10
Crushing strength (kg/cm^2)	4	4.5	4
Friability (%)	0.8	N.F.	N.F.
Wetting time (sec)	31		
Disintegration time (sec)	40		

Table 5. Optimization of sublimating agent concentration

Formulation	C1	C2	C3	C4	C5
Etoricoxib	60	60	60	60	60
Camphor	12.5	25	37.5	50	75
L-HPC	10	10	10	10	10
Crushing strength (kg/cm^2)	4	3.5	4	4	3.5
Friability (%)	0.25	0.42	0.89	1.1	1.6
Wetting time (sec)	45	21	17	13	11
Disintegration time (sec)	50	37	30	28	27

Table 6. Selection of optimized formulation

Formulation	D1	D2	D3	D4	D5	D6	D7	D8	D9
Etoricoxib	60	60	60	60	60	60	60	60	60
L-HPC	10	20	30	10	20	30	10	20	30
Camphor	12.5	12.5	12.5	18.75	18.75	18.75	25	25	25
Spray dried lactose up to	250	250	250	250	250	250	250	250	250
Crushing strength (kg/cm^2)	3.1	3.4	3.5	3.3	3.5	3.2	3.4	3.5	3.4
Friability (%)	0.25	0.22	0.26	0.14	0.15	0.16	0.42	0.46	0.40
Wetting time (sec)	40	34	21	41	35	29	33	31	30
Disintegration time (sec)	50	40	24	45	37	36	40	38	35

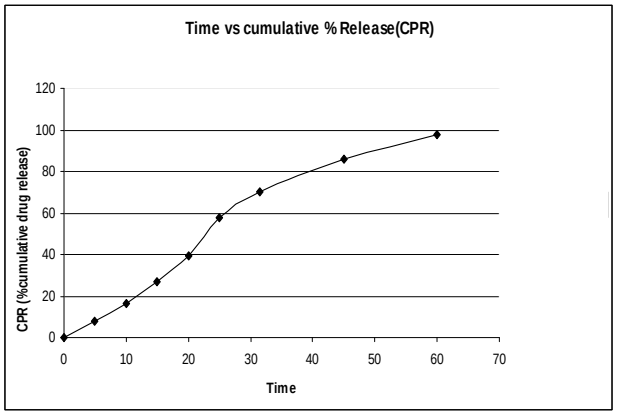


Fig. 1. Cumulative % release in phosphate buffer saline (pH 7.4) media

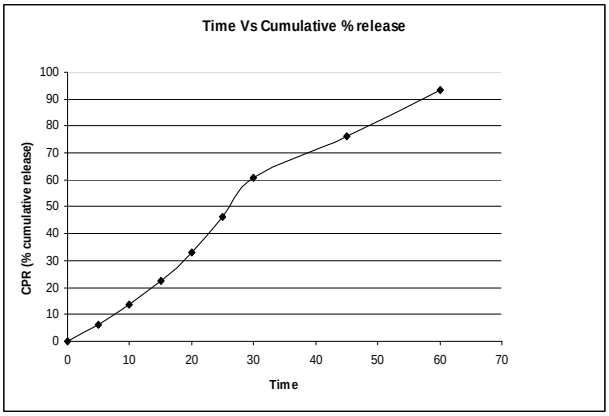
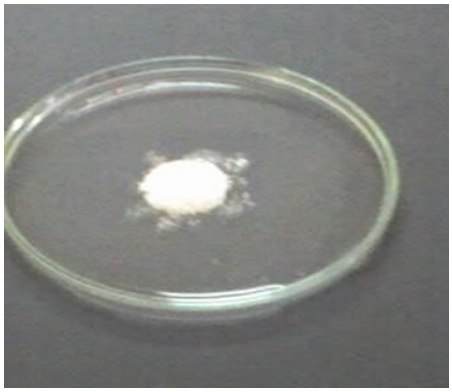
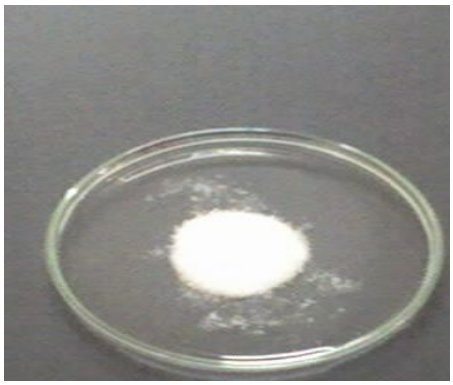


Fig. 2. Cumulative % release in 0.1 N HCl (pH 1.2) media



a) Disintegration in 8 sec



b) Disintegration in 16 sec

c) Disintegration in 24 sec

Fig. 3. Disintegration of tablet at different time intervals (sec)

CONCLUSION

The studies revealed that the type and amount of sublimating agent and disintegrant significantly affect tablet properties and are required to be optimized. Moreover, vacuum-drying technique would be an effective alternative approach compared with use of more expensive adjuvants in formulation of mouth dissolving tablets.

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