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Formulation and evaluation of Ketorolac Tromethamine fast dissolving tablets

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ABSTRACT

Fast dissolving tablets were highly accepted drug delivery system. Fast dissolving tablets were dissolved/disintegrated in the mouth within a matter of few seconds without need of water. The aim of the present study was to prepare and evaluate fast dissolving tablets of ketorolac tromethamine using a combined approach of subliming agent and superdisintegrant. Fast dissolving tablets were prepared by direct compression technique. The prepared tablets were dried under vacuum for camphor sublimation that results porous structure in the tablet. This porous structure results faster disintegration and drug release. The tablets were evaluated for weight variation, friability, hardness, In vitro disintegration time, wetting time, In vitro drug release profile. The porous structure of the tablet was observed under scanning electron microscopy (SEM).The obtained results showed that low weight variation, good hardness, acceptable friability. All the formulation disintegrated within 11-60 sec. The formulation containing subliming agent and superdisintegrants showed better performance in disintegration and drug release profile.

Key words: Fast dissolving tablets (FDTs), Ketorolac tromethamine, subliming agents, superdistegrants.

INTRODUCTION

Tablets are most commonly preferred dosage forms because of its convenience in terms of self administration, production, marketing, accurate dosing [1]. Problem of these dosage forms was difficulty in swallowing, especially in case of pediatric and geriatric patients. To avoid this, a novel drug delivery system known as fast dissolving tablets (FDTs) has been developed. FDTs can be taken orally without the need of water, dissolves or disperses in the saliva, shows rapid onset of action, increased bioavailability makes these tablets popular. FDTs are also suitable for

patient groups such as mentally disable, bedridden, Patients while traveling little or no access of water [2, 3].

Different approaches for the development of fast dissolving tablets are, by using super disintegrates namely croscarmellose sodium, crospovidone, sodium starch glycolate. Another approach, Maximizes the porous structure of tablet by sublimation technique. Vacuum drying has been used to form porous structure of the tablets [11-15], which absorbs dissolution medium rapidly, results the fast disintegration of tablet [4-6].

Ketorolac tromethamine [(+/-)-5(benzoyl)-2,3- dihydro-1N-pyr rolizine-1-carboxylic acid tris hydroxymethylaminomethane salt] is a class of nonsteroidal anti-inflammatory drug (NSAID), commonly used to decrease the postoperative pain associated with the surgical treatment of spine deformities, to treat moderate to severe pain, including pain after surgery and inexpensive, safe, and well tolerated [7] . The mechanism in this is the inhibition of prostaglandin synthesis by competitive blocking of the enzyme cyclooxygenase (COX), ketorolac is a non-selective COX inhibitor [8].

MATERIALS AND METHODS

Materials

Ketorolac tromethamine was obtained from Dr.Reddy's Laboratories (Hyderabad, India).Croscarmellose sodium, were gifts from Recon Health Care Ltd (Bangalore, India). Camphor, Ammonium bicarbonate and Menthol were obtained from Laser Industries (Ahmedabad, India), spray dried mannitol Ranbaxy Fine Chemicals Ltd, (New Delhi, India). Aerosil, Aspartame was obtained from S.D.Fine chemicals Pvt. (Mumbai, India).

Preparation of ketorolac tromethamine tablets

Fast dissolving tablets of Ketorolac tromethamine were prepared using the subliming agents, camphor, ammonium bicarbonate, menthol. Crosscarmellose sodium as superdisintegrants, spray dried mannitol as diluents, aspartame as sweetening agent, the drug and other ingredients were mixed together by using a glass mortar and pestle, and then passed through sieve no. 60. Then directly compressed by using 7 mm punch of rotary tablet machine (CADMACH 16 station rotary tablet press). Dried at 60°C for 24 hours to facilitate sublimation of camphor. A porous structure was obtained. The end point of drying was indicated by constant weight of tablet. Table 1 outlines the composition of various Fast dissolving formulations.

Evaluation of compressed tablets

Weight Variation

Twenty tablets from each formulation was randomly selected and weighed using a Shimadzu digital balance. The mean ± standard deviation (*SD*) and relative standard deviation (*RSD*) were recorded.

Thickness Variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital verneir calipers. The mean ± *SD* and *RSD* values were calculated.

Table 1: Formulation of Ketorolac tromethamine fast dissolving tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Ketorolac Tromethamine	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Croscarmellose sodium	3	6	9	-	-	-	-	-	-	-	-	-	6	6	6
Camphor	-	-	-	10	15	20	-	-	-	-	-	-	10	15	20
Ammonium bicarbonate	-	-	-	-	-	-	10	15	20	-	-	-	-	-	-
Menthol	-	-	-							10	15	20	-	-	-
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sparydried Mannitol	85	82	79	78	73	68	78	73	68	73	78	68	72	68	63

Hardness and Friability

Hardness was measured using the Monsanto hardness tester (Campbell Electronics, Maharashtra).The friability of 20 tablets was measured utilizing Roche friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss was calculated.

Content Uniformity

The formulations were assayed for drug content. Ten tablets were randomly selected from each formulation and pulverized to a fine powder. Weigh the required quantity of powder equivalent to a single dose were taken in triplicate and assayed for the drug content utilizing a UV-Visible spectrophotometer (Eleco lab, India) at a wavelength of 322 nm.

Wetting Time

Five tissue papers were placed in a petri dish of 10 cm diameter. 10ml of water was added to the petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time[3]. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch.

***InVitro* Disintegration Time**

In vitro disintegration time of the mouth dissolving tablets was determined following the procedure; 10 mL of water was placed in a Petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the Petri dish and the time required for the tablet to completely disintegrate was noted[12]. Measurements were carried out in replicates (n=6) and mean ± *SD* values were recorded.

***InVitro* Release Studies**

Release studies of ketorolac tromethamine of different formulations were performed according to USP XVIII apparatus II, paddle method utilizing a dissolution system (Systronic India ltd, India). Paddle speed was maintained at 50 rpm and 600 mL of water was used as the dissolution medium. Samples (5 mL) were collected at predetermined time intervals (5, 10, 15, 30, 45 and 60min) and replaced with equal volume of fresh medium, filtered through a filter paper and

analyzed with a UV-Visible spectrophotometer at λ_{max} 322 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved.

Scanning Electron Microscopy (SEM)
The surface morphology and pores of the tables were examined by SEM. The samples were placed on double sided adhesive tapes and scanning electron photographs was taken at 35 X magnification.

RESULTS AND DISCUSSION

Formulation rationale
The objective of fast dissolving tablets was that, it dissolves/disintegrates in the saliva within a few seconds. To achieve such a formulation most of excipients are selected and required to be water soluble. Among the soluble diluents spray dried mannitol was selected as diluents, because narrow particle size distribution that allows it to be free flowing and easily mixed with other ingredients. Preliminary trials conducted using different superdisintegrants like croscarmellose sodium (CCS), Crospovidone (CP), Sodium starch glycolate (SSG). Among them only CCS (F1 to F3) was selected for further study. To study effect of disintegration time various subliming agents like camphor, menthol, ammonium bicarbonate used at different levels (F4 to F12). The subliming time (5-10h) depending upon the amount of subliming agent. These subliming agents responsible for the porous structure in tablets. The porous structure responsible for faster water uptake. Camphor containing tablets exhibited faster disintegration as compared to tablets containing ammonium bicarbonate and menthol [9]. To study effect of disintegration time, combination of camphor and CCS was used at different levels. These studies showed greater decreased disintegration time when compared to single CCS and camphor. But the use of subliming agents results in increased friability due to porous structure. Colloidal silicon dioxide (Aerosil) was added. It helps to restore the bonding properties of exicipients, and act as lubricant[10]. Aspartame was included to increase the taste for the formulations.

Weight, thickness variation and Hardness
All the formulations showed low weight variation, thickness was found be 2-3 mm and hardness was up to 3 kg/cm^2.

Friability
All formulations were evaluated for friability by using Roche friabilator. The subliming agents showed increased friability due to increased porosity. So, aerosil was incorporated helps in decrease in the friability due to its restoring the bonding properties of exicipents[10].After incorporation of aerosol the friability was within the limits.

Content Uniformity
Uniformity of drug content was estimated for all the formulations. The results indicated that drug was uniformly distributed and were given in the Table 2.

Wetting time
Wetting time was determined for all the formulations. Wetting time was decreased when the concentration of superdisintegrants and subliming agents increased. The formulation containing CCS (6%), camphor (15%) showed less wetting time when compared to other formulations.

InVitro Disintegration time

Disintegration time was an important criterion for selecting the optimum fast dissolving formulations. The formulations were evaluated for disintegration time. Among these formulations combination of CCS (6%), camphor (15%) showed less disintegration time due to porous nature and wicking action.

Table 2: Evaluation of fast dissolving tablets of ketorolac tromethamine

Formulation codes	Weight Variation (mg)	Thickness	Hardness	Disintegration Time (sec)	wetting time (sec)	friability	Content uniformity
F1	99.98±0.89	2.56±0.56	2.26±0.36	70±0.76	69±1.25	0.6±0.06	98.89±0.19
F2	98.26±0.88	3±0.26	3.13±0.21	55±1.12	50±1.36	0.5±0.12	99.02±0.75
F3	98±0.46	2.56±0.56	3.06±0.14	61±0.29	58±0.98	0.6±0.29	97.15±1.36
F4	99±1.03	2.44±0.24	2.33±0.11	42±1.39	36±0.24	0.8±0.60	102±0.63
F5	98.56±1.29	3.01±0.35	3.14±0.46	30±1.26	25±0.36	0.7±0.32	100±1.26
F6	98.12±1.06	2.96±0.4	4.47±0.96	35±0.98	26±0.14	0.9±0.34	96.36.±2.06
F7	98±0.56	2.90±0.36	3.49±0.73	53±0.76	35±1.25	0.9±0.19	101±0.60
F8	99.23±0.25	3.03±0.09	2.36±0.19	44±0.46	39±0.98	0.8±0.54	100±0.25
F9	97.96±1.25	2.29±0.68	3.87±0.79	38±0.14	26±1.36	0.8±0.37	97.2±1.36
F10	98.34±1.23	2.36±0.36	2.49±0.83	59±1.36	46±1.24	0.7±0.09	99.34±1.93
F11	97.99±2.03	3.06±0.56	2.41±0.98	40±1.24	35±1.44	0.9±0.06	101.5±0.23
F12	99.99±0.36	3.12±0.76	3.47±0.60	32±0.36	26±0.16	0.8±0.36	99.01±0.96
F13	99±0.45	2.98±0.36	2.26±0.25	25±0.14	18±0.06	0.9±0.34	99.47±0.46
F14	98.80±1.06	3.01±0.9	3.24±0.32	12±0.78	9±1.36	0.8±0.25	98±1.56
F15	99.14±0.89	2.98±0.34	3.36±0.40	18±0.43	12±0.14	0.9±0.14	101±0.82

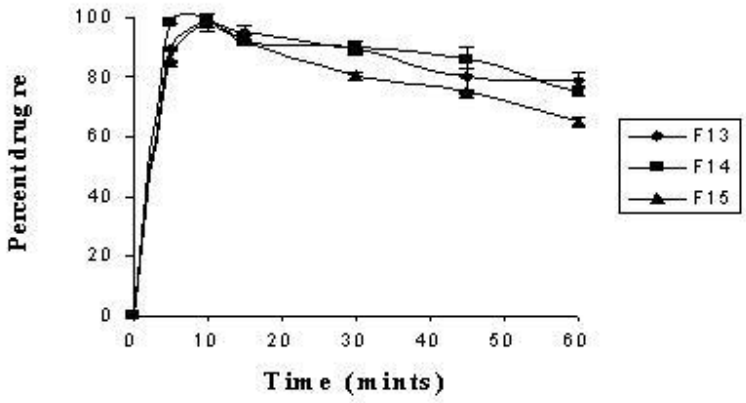

Fig 1: In-vitro drug release profile for the formulations F13, F14, F15.

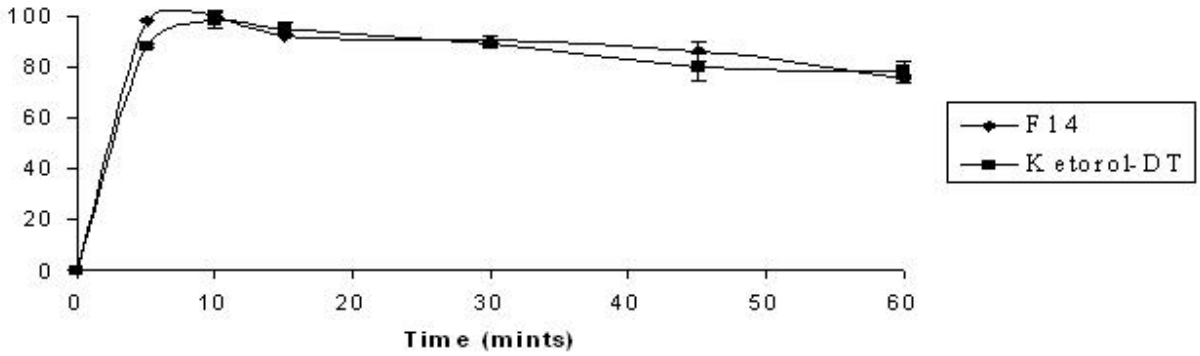

Fig 2: In-vitro drug release profile for Formulation F14 and Ketorol – DT.

***In Vitro* Release Studies**

Dissolution studies were performed by using dissolution USP apparatus II with a paddle speed of 50 rpm. An increase in superdisintegrants concentration resulted increase in cumulative drug release. All the formulations released about 90% within 15 mints. Among the all formulations optimized was selected Figure 1. The optimized formulation was compared with marketed Ketorol-DT Figure 2. The results indicated that The optimized formulation showed greater release than the marketed Dispersible tablets.

Scanning Electron Microscopy (SEM)

The SEM photographs of the tablets of without subliming agents and superdisintegrants and optimized formula showed that the porous structure was observed in the tablets Figure 3.

Fig 3: SEM photographs for A) Without camphor and Superdisintegrates B) optimized formula.

CONCLUSION

Oral route is the most convenient route of drug administration can be made as an ideal route by overcoming certain drawbacks. Fast dissolving tablets by using a combined approach of subliming agent and superdisintegrant solved the problems encountered in the administration of

drug by oral route. The results showed low weight variation, good hardness, and acceptable friability. All the formulation disintegrated within 11-60 sec. The release profile reveled that optimized formulation showed greater release than the commercial Ketorol-DT. This combined approach was alternative for the preparation of fast dissolving tablets.

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