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KETOROLAC TRIMETHAMINE FAST DISSOLVING TABLETS - FORMULATION AND EVALUATION

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ABSTRACT

Ketorolac trimethamine is a class of Non steroidal anti-inflammatory drug (NSAID), commonly used to decrease the post-operative pain associated with the surgical treatment of spine deformities to treat moderate to severe pain, including pain after surgery. Ketorolac was inexpensive, safe, and well tolerated. It is a non-selective COX inhibitor the mechanism of action includes the inhibition of prostaglandin synthesis by competitively blocking the enzyme cyclo-oxygenase. Conventional ketorolac tablets which are available in market are not suitable for acute inflammatory conditions where quick onset of action is required. Besides, the conventional tablets also show poor patient compliance particularly by the geriatric and pediatric patients who experience difficulty in swallowing, and by those who are bed ridden or who are traveling and do not have an easy access of water. To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without need of water, anytime, anywhere. Such tablets are called as fast dissolving tablets in mouth. The present investigation is aimed to formulate fast dissolving tablets of ketorolac trimethamine. The results showed low weight variation, good hardness and acceptable friability. The release profile revealed that optimized formulation (f10) showed greater release than the commercial ketorolac.

Keywords: Ketorolac trimethamine, Fast Dissolving tablet, Disintegrants.

1. 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 taken orally without the need of water, dissolves or disperses in the saliva, shows rapid onset of action, increased bioavailability makes these tablets popular (Biradar SS, 2006) (Shu T, 2002). FDTs are also suitable for patient groups such as mentally disable, bed ridden, Patients while traveling and have little or no access of water. Different approaches for the development of fast dissolving tablets are, by using super disintegrates namely croscarmellose sodium, crosprovidone 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, which absorbs dissolution medium rapidly, resulting in the fast disintegration of tablet. Ketorolac trimethamine 5 (benzoyl)-2,3- dihydro-1N-pyr rolizine-1-carboxylic acid trishydroxymethylaminomethane salt] is a class of non-steroidal 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 it was inexpensive, safe, and well tolerated (Kaushik D, 2004). Ketorolac is a non-selective COX inhibitor[8].The mechanism of action is the inhibition of prostaglandin synthesis by competitively blocking the enzyme cyclo-oxygenase (COX) (Seager H, 1998)(Fini Adamo, 2007).

2. MATERIALS AND METHODS

2.1 Formulation of ketorolac trimethamine: Ketorolac trimethamine, Mannitol and Aspartame were mixed with disintegrant for 15 minutes using porcelain mortar, and then passed through sieve no: 60. The obtained blend was then mixed with camphor, talc, and magnesium stearate for 5 minutes and directly compressed by using g 7 mm round flat faced punch of rotary tablet machine. Compressed force was kept constant for all formulations. The Magnesium stearate level was fixed at 1% w/w for all formulation (Bi YX, 1999) (Sallam E, 1998) (Bi YX, 1996).

Table no 1 Formulation Table of ketorolac fast dissolving tablets by direct compression

Ingredients	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ketorolac trimethamine	10	10	10	10	10	10	10	10	10	10
Ac-Dil-Sol (HPMC Brand name)	5	6	-	-	-	-	-	-	-	-
Polyplasdone	-	-	5	6	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	5	6	-	-	-	-
Camphor	-	-	-	-	-	-	10	15	-	-
Camphor (and)ac-dil-sol	-	-	-	-		-	-	-	15	21
Mannitol	80	83	82	84	81	79	88	80	72	70
Aerosol	1	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1
Aspartame	20	20	20	20	20	20	20	20	20	20

3. RESULTS AND DISCUSSION

3.1 Pre-formulation studies

Table no 2 Pre-formulation studies of Ketorolac trimethamine

S. No	Parameters	Observations
1	Solubility	Free soluble in water
2	Bulk density	0.42 gm/ml
3	Tapped density	0.51 gm/ml
4	Melting point	132-135^{0}c
5	% compressibility	17.64%

3.2 Drug-Excipient compatibility studies: Ketorolac and excipients were subjected to FT – IR spectral analysis. The drug was compatible with excipients since no changes were observed in intensity and position of the peaks in the IR spectra's (Abdelbary G, 2005) (Bartified JM, 1994) (Rooks WH, 1985).

3.3 Evaluation of the Blend: The blend was evaluated for Tapped Density, Bulk Density and Hausner's ratio. The results are shown in the Table.3

Table no 3 Evaluation of the Blend

Formulation Code	Bulk Density	Tapped Density	Powder Flow properties	Hausners ratio
F-1	0.46	0.55	16.36	1.01
F-2	0.45	0.54	16.66	1.2
F-3	0.46	0.55	16.52	1.19
F-4	0.32	0.38	14.73	1.18
F-5	0.45	0.52	18.75	1.15
F-6	0.48	0.57	15.32	1.18
F-7	0.47	0.57	17.42	1.21
F-8	0.47	0.56	16.07	1.19
F-9	0.45	0.54	16.14	1.2
F-10	0.45	0.56	19.08	1.24

3.4 Evaluation of Fast Dissolving Tablets: The formulated tablets were evaluated for Physical Characterization, Weight Variation, Hardness, Friability, Disintegration test, Dissolution test, wetting time.

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Table no 4 Evaluation of the physical parameters of fast dissolving tablet of Ketorolac trimethamine

Formulation code	Weight Variation	Hardness Kg/cm^2	Friability %	Disintegration Time (sec)	Wetting Time (sec)
F-1	passes	3.7	0.56	29	52
F-2	passes	3.6	0.47	28	49
F-3	passes	3.6	0.51	34	61
F-4	passes	3.5	0.64	39	55
F-5	passes	3.8	0.45	47	59
F-6	passes	3.6	0.40	52	55
F-7	passes	3.5	0.51	30	36
F-8	passes	3.5	0.44	32	27
F-9	passes	3.5	0.39	18	20
F-10	passes	3.6	0.38	12	18

3.5 *In-vitro* Disintegration test: The disintegration time obtained for formulation F-1 to F-10 was shown in Table 5 and figure 1.

Table no 5 *In-vitro* Disintegration test of FDT of Ketorolac trimethamine

S.No	Formulation No.	Disintegration time (sec)
1	F-1	29
2	F-2	28
3	F-3	34
4	F-4	39
5	F-5	47
6	F-6	52
7	F-7	30
8	F-8	32
9	F-9	18
10	F-10	12

3.6 *In-vitro* Dissolution Studies: All the 10 formulations and pure drug were subjected to in vitro dissolution studies by using water. The results obtained were shown in Table.6. The following are the results of the dissolution studies (% of drug release) of the formulated tablets and pure drug. Ten prototype formulations were prepared and evaluated for tablet properties (Disintegration time, Wetting time& Dissolution studies). Dissolution data shows that formulations F-9, F-10 showed improved dissolution rate when compared to other formulations. Hence, F-10 was selected for further (stability) studies. Dissolution study of pure drug and batch F1 to F10 were carried out and results are represented in table no 6. It was concluded that batch F10 containing both Ac-Dil-Sol (HPMC brand name) and camphor showed the improved dissolution as compared to other formulations.

3.7 Stability studies: There was no significant change in physical and chemical properties of the tablets (F10) after one month. Parameters quantified at various time intervals were shown in Table.7 and 8.

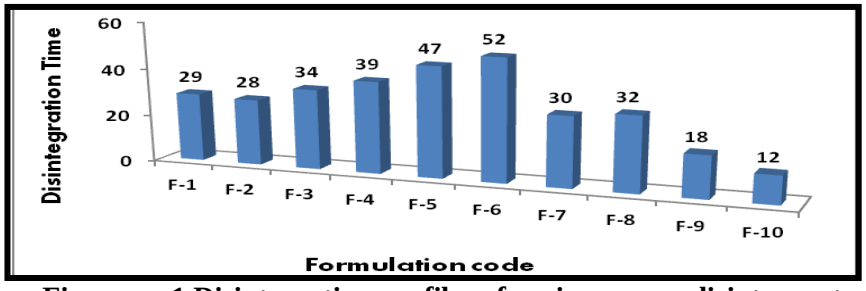

Figure no 1 Disintegration profiles of various super disintegrants

Table no 6 Dissolution studies of ketorolac trimethamine in water:

S.No	Time (min)	PERCENTAGE OF DRUG RELEASE									
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
1	0	0	0	0	0	0	0	0	0	0	0
2	5	66.81	67.50	61.38	65.65	64.60	65.93	64.95	68.70	72.56	75.01
3	10	68.32	69.33	62.64	75.13	69.13	70.68	74.05	75.11	80.43	81.76
4	15	76.20	77.06	77.60	79.13	72.58	75.02	79.36	79.03	88.30	88.75
5	20	83.08	85.70	81.06	86.03	77.13	79.73	83.61	86.16	91.03	94.08
6	30	90.30	93.11	89.05	97.46	80.81	82.10	88.05	89.18	-	-
7	45	-	-	87.41	91.06	85.15	90.02	91.34	92.42	-	-
8	60	-	-	-	-	-	-	-	-	-	-
9	120	-	-	-	-	-	-	-	-	-	-

Table no 7 Evaluation of the fast dissolving tablets (selected formulation) at various time interval for the studies at 30^0C/ 65 % RH

Batch details	Parameters	0 days	10 days	20 days	30 days
F-10	% Drug release	95.85	96.23	94.91	94.42
	Disintegration time (sec)	44	45.3	46.5	48

Table no 8 Evaluation of the fast dissolving tablets (selected formulation) at various time interval for the studies at 40^0C/ 75 % RH

Batch details	Parameters	0days	10days	20days	30days
F-10	% Drug release	97.14	97.10	95.43	96.00
	Disintegration time (sec)	44.1	45.2.	46.3	47.60

4. CONCLUSION

Fast dissolving tablets dissolves in saliva within few seconds. Among the ten formulations, F10 showed better results than other formulations. All formulations showed disintegration time of within 60 seconds. Fast dissolving tablets by using a combined approach of subliming agent and super-disintegrant solved the problems encountered in the administration of drug by oral route. The results showed low weight variation, good hardness and acceptable friability. The release profile revealed that optimized formulation (F10) showed greater release than the commercial ketorolac.

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