ORIGINAL ARTICLE

Design, Formulation, and Optimization of Novel Mouth Dissolving Tablet of Drug Ketorolac Using Special Super Disintegrate

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Abstract

Background: Due to its versatility and convenience, the orally disintegrating tablet is the most advanced type of oral solid dosage form. Compared to traditional tablets, it dissolves in the oral cavity within 1 min of contact with saliva, increasing the effectiveness of the active pharmaceutical ingredient without chewing, and without the need for water for administration. **Materials and Methods:** Oral soluble ketorolac tromethamine tablets have been prepared by direct compression using various superdegradants such as crospovidone, croscarmellose sodium, and sodium starch glycolate at different concentrations. The manufactured tablets are evaluated for hardness, crushability, weight change, breakdown time, wetting time, and drug release *in vitro*. **Results and Conclusion:** Study results before compression and after compression for all formulations are within standard limits. All batches of tablets were found to release more than 80% of the drug within 5 min. The desired quality of the tablets disintegrates in the mouth and contributes to a faster absorption of the drug and a rapid onset of the therapeutic effect.

Key words: Ketorolac tromethamine, Mouth dissolving tablets, Sodium starch glycolate, superdisintegrant, Tablet

INTRODUCTION

Tablets are defined as solid pharmaceutical dosage forms with or without the appropriate diluent and are manufactured by either a compression or molding process. The oral route of drug administration is a popular, convenient, and widely accepted method of drug administration. Over the past two decades, there has been a growing demand for more patient-acceptable dosage forms. As a result, the demand for technology has tripled each year.[1] The oral route of drug administration is widely accepted up to 50–60% of the total dosage form. This study was attempted to prescribe a taste-masked orally disintegrating tablet used in acute disorders such as hypertension and heart failure for the benefit of delivery system. Lisinopril taste masked by complex formation with beta-cyclodextrin using the slurry method.[2-5]

Recently, much research has been done in the field of geriatrics, from the physiology of aging to the design of drugs and medicines, daily care, and support. According to Silver Scientific Research conducted by the Ministry of Health and Welfare of Japan, "Study on Design of New Drugs and Packaging Containers Optimal for Administration to the Elderly" (Masayasu Sugihara, Tokyo Women's Medical University, etc.)

As such novel preparations, (a) cheek dissolving preparation, (b) paste-like preparation, and (c) jelly-like

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preparation will be described as examples. In particular, it is said that the orally dissolved type preparation[6] and the paste-like preparation are easy to take for the elderly and have excellent stability. The main aim of proposed project is to develop mouth dissolving tablet for taste masking of ketorolac tromethamine.[7]

The proposed concept based on oral administration of ketorolac tromethamine has emerged with the aim of improving bioavailability and patient compliance. Recommended dosage rapidly breaks down and/or dissolves to releases drug as early as family to in contact with saliva, an attribute that makes them very attractive to pediatric and geriatric patients. It will also improve the formulation characteristic's.[8-10]

MATERIALS AND METHODS

Formulation of fast-disintegrating sublingual tablet was done in three steps.

Step 1: All excipients and active pharmaceutical ingredient-weighed accurately as per given order [Table 1]

Ketorolac tromethamine, spray-dried mannitol, lactose monohydrate, Kyron T-134 saccharin, flavors, croscarmellose sodium, passed through 60# sieve while Aerosil, magnesium pass through 80#seive.

Step 2: Mix ketorolac tromethamine and Kyron T-134 mix properly for 5 min

Table 1: Ingredients present in the tablet

Ingredients	Quantity (in mg) present in each tablet														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35
Crosspovidone	4	-	-	8	-	-	4	4	-	4	4	-	8	8	-
Carboxymethylcellose calcium	-	4	-	-	8	-	4	-	4	8	-	4	4	-	8
Indion 234s	-	-	4	-	-	8	-	4	4	-	8	8	-	4	4
Microcrystalline cellose pH(102)	121	121	121	117	117	117	117	117	117	113	113	113	113	113	113
Mannitol	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Talc	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Papermint	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 2: Evaluation of tablets prepared by different superdisintegrants

Formulations	Thickness (mm)±SD	Hardness (kg/cm^2)±SD	Friability (%)±SD	Weight Variation (mg)±SD
F1	2.82±0.4	3.10±0.1	0.132	180.8±0.56
F2	2.83±0.6	3.10±0.3	0.134	180.9±0.83
F3	2.83±0.4	3.20±0.5	0.200	180.6±1.57
F4	3.00±0.3	3.10±0.1	0.0.95	180.4±1.38
F5	2.88±0.2	3.00±0.2	0.510	181.3±1.56
F6	2.81±0.7	3.30±0.9	0.71	180.4±1.04
F7	2.82±0.5	3.30±0.5	0.09	179.6±0.90
F8	2.87±0.3	3.20±0.4	0.18	187.3±1.85
F9	2.86±0.3	3.40±1.0	0.20	180.4±0.75
F10	2.85±0.4	3.20±0.5	0.50	182.1±0.56
F11	2.86±0.2	3.15±0.2	0.57	181.2±0.70
F12	2.83±0.8	3.40±0.3	0.69	181.3±0.50
F13	2.84±0.4	3.30±0.2	0.16	180.4±1.60
F14	2.86±0.2	3.10±0.5	0.134	180.9±0.83
F15	2.83±0.9	3.20±0.4	0.06	181.5±1.20

Table 3: Formulae for trial batches including the optimized batch

Ingredients (mg)	Trial batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketorolac tromethamine	10	10	10	10	10	10	10	10	10
MCC 102	71				20		55	60	
PVK-30									10
Spray-dried mannitol		53	57	52		53			50
Lactose monohydrate		20		12	43	20	12	12	16
Kyron T-134	0.5	4	4	4	4	4	4	4	4
Sodium stearyl fumarate	1		01	06			06		06
L-HPC	10		10	10					
Flavors	0.5	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
AC-Di-Sol (CCS)		02			06	06		06	
Talc					05				
Aerosil	2	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium stearate		1	1	1	1	1	1	1	1
Saccharin	5	08	12		10		11	10	
Aspartame			4	4		5			4
Total weight (mg)	100	100	100	100	100	100	100	100	100

Table 4: Evaluation of tablets prepared by different superdisintegrants

Formulations	Wetting time	Water absorption ratio	Disintegrating time	Drug content (%)
F1	16	40.91±2.1	21	98.89
F2	18	43.30±1.9	23	98.42
F3	15	51.23±1.4	19	97.82
F4	12	72.35±1.7	9	99.22
F5	24	58.11±1.2	11	98.77
F6	22	49.89±1.4	15	100.83
F7	19	42.92±1.9	13	101.65
F8	22	44.47±2.2	15	99.01
F9	14	59.73±2.4	13	100.04
F10	18	58.60±1.8	16	97.75
F11	17	65.12±2.9	19	93.67
F12	17	45.91±2.4	17	97.14
F13	16	54.75±1.3	13	95.32
F14	14	73.70±1.1	7	99.85
F15	18	66.75±2.5	14	98.86
Marketed tablet	20	59.23	55	98.56

Step 2.1 Mix spray-dried mannitol, lactose monohydrate, saccharin, croscarmellose sodium, flavor, properly for 5 min with above blend of step 2

Step 2.2 Mix Aerosil for 7 min with above blend of step of 2.1

Step 2.3 Mix magnesium stearate, properly for 3 min with above blend of 2.2

Step 3: The tablets were prepared by direct compression method [Table 2].

Super solvers (Ac-Di-Sol, sodium starch glycolate, and crospovidone) at different concentrations (1–5%) were used to develop the tablets. All ingredients have been presented in the table and passed through a numerical sieve 60 and cofounded in the glass pestle motor. These mixtures have been evaluated for mass-volume relationships and flow characteristics. The mixed excipients were compressed using a single tablet press (Cadmach, Ahmedabad) to produce convex tablets weighing 100 mg/round. All chemicals including starting materials, reagents, and solvents were purchased from commercial suppliers.

Table 5: *In vitro* release data of ketorolac tromethamine marketed tablet zero-order and first-order release (comparision of release with marketed tablets)

Time (min)	Cumulative drug release (%)	Log release
0	0	2
5	5.607±1.332	1.974±0.024
10	12.405±0.933	1.942±0.16
15	18.519±2.323	1.911±0.013
20	23.178±2.544	1.885±0.014
30	33.140±1.743	1.825±0.011
40	39.954±3.534	1.778±0.012
50	43.692±0.743	1.750±0.011
60	44.562±1.212	1.743±0.009

Data are expressed as mean±S.D (*n*=3)

The tablets were prepared using superdisintegrants in different concentrations without active ingredient. The step was done for the selection of superdisintegrants for further preparation of rapidly disintegrating sublingual tablet. From this study, it was concluded that the tablet formulation F14 produces rapid disintegration of the tablet.

RESULTS AND DISCUSSION

Many patients, especially children and the elderly, have difficulty swallowing tablets and capsules and, therefore, do not follow prescriptions and have a high incidence of non-compliance. Fast-dissolving tablets are one such example for rapid dissolution or when using saliva. The importance of this drug delivery system includes water-free administration, dosing accuracy, portability, and alternatives to liquid dosage forms, ideal for pediatric and elderly patients, and the onset of rapid action. It is a target.

Ketorolac tromethamine is a potent nonsteroidal anti-inflammatory drug agent with moderate bioavailability with highly bitter in taste. We have found that mean dissolution time (MDT) technology will be better to improve bioavailability and taste masking of the selected drug. MDT tablet will releases their contents rapidly for immediate onset of action, to prevent its first pass metabolism, and to improve bioavailability. It also leads to reduction of dose and drug toxicity, which lead to improve patient compliance.

Solubility of ketorolac tromethamine was measured with various solvent systems and buffers. Physical changes and absorption maxima were also evaluated. When developing fast-dissolving tablets, it was essential to consider the compatibility of the drugs and polymers used in the system.

It is, therefore, necessary to conform that drug is not interacting with polymer under experimental conditions (40 ± 50°C and 75 ± 5% RH) for 4 weeks. The infrared absorption spectra of pure polymer and physical mixture of polymer and drug were run and between 4000 cm^{-1} and 500 cm^{-1}.

Figure 1: Mouth dissolving tablet before sublimation

Figure 2: Mouth dissolving tablet after sublimation

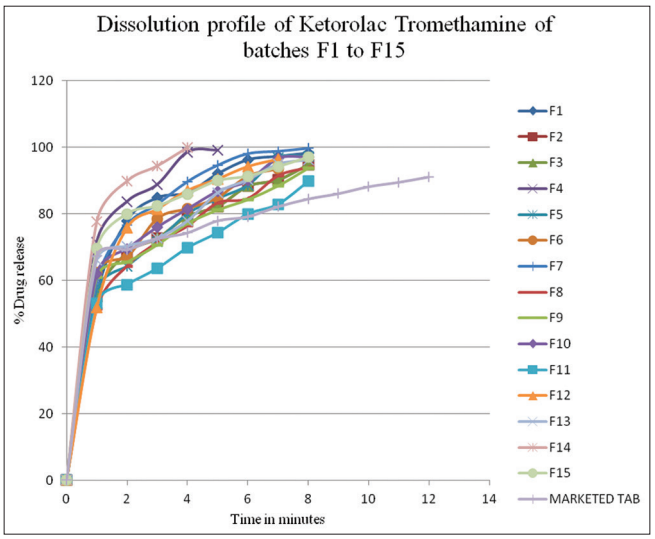

Figure 3: Dissolution profile of ketorolac tromethamine of batches F1–F15

Table 6: Dissolution profile of all batches

Batches	Time in minutes							
	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)
F1	55.80	77.84	84.77	86.26	91.99	96.20	97.23	98.20
F2	52.70	67.20	78.58	84.56	88.98	92.13	94.64	97.13
F3	55.12	68.25	72.64	79.23	82.25	88.34	90,23	94.80
F4	71.47	83.65	88.74	98.50	99.10	_	_	_
F5	56.96	64.21	71.67	79.98	84.56	88.61	96.79	97.12
F6	62.28	66.87	78.52	81.49	84.86	91.24	93.44	98.07
F7	59.37	76.57	82.85	89.64	94.56	98.03	98.76	99.67
F8	51.45	64.28	71.31	76.29	83.28	84.56	91.42	93.89
F9	61.02	65.46	70.67	77.09	81.15	84.29	88.45	93.76
F10	62.00	69.45	75.98	81.44	86.76	89.90	96.65	97.00
F11	53.14	58.75	63.57	69.75	74.31	79.89	82.88	89.74
F12	51.81	75.73	81.35	86.97	90.41	94.17	96.34	_
F13	66.17	70.16	72.65	77.85	86.29	90.21	94.87	96.12
F14	77.56	89.71	94.29	99.80	_	_	_	_
F15	69.49	79.91	82.34	85.96	89.91	91.26	94.12	96.95
Marketed tablet	67.23	74.53	79.12	83.23	87.86	89.09	92.06	94.565

Table 7: Stability parameters of F14 batch stored at room temperature

Parameters	Initial	After 15 days	After 1 month
Drug content (%)	98.23	98.20	97.95
In vitro disintegration time (in seconds)	7	Hn, j 7um hjknmm	8
Wetting time in seconds	14	15	15
Drug release (%)	99.80	99.48	99.05

Table 8: Stability parameters of F14 batch stored at 40°C for 75% RH

Parameters	Initial	After 15 days	After 1 month
Drug content (%)	98.23	97.85	97
In vitro disintegration time (in seconds)	7	8	9
Wetting time (in seconds)	14	15	16
Drug release (%)	99.80	99.20	98.50

Ketorolac tromethamine mouth dissolving tablet melting point-166.6 between 165 and 170 with decomposition and contain protein binding 99.2%. For the determination of partition coefficient of human insulin, n-octanol was used as oil phase and phosphate buffer pH 7.4 was used as aqueous phase.

Phosphate buffer saline pH 7.4 and n-octanol=0.64.

The absorption maxima (λmax) of ketorolac tromethamine (5 μg/ml) in solution was found to be 372 nm which is concordant with the Indian Pharmacopoeia (1996). Tablets with mouth dissolving drug delivery were prepared and evaluated with aim to obtain fast-disintegrating sublingual tablet for immediate onset of action and to prevent its first pass metabolism, improve bioavailability, it also leads to reduction of dose and drug toxicity, which lead to improve patient compliance. Before the formulation, pre-formulation study was carried out on drug and excipients, in the present work, formulation part divided into four steps. In the first step, preparation of dummy tablets was done using[11] different superdisintegrate such as lactose monohydrate, mannitol, microcrystalline cellulose, and its combination in different ratio.

The dummy lock was also evaluated for various physical parameters [Figures 1 and 2] such as thickness, hardness, crushability, weight variation, and disintegration. Powder blends have been evaluated for angle of repose, bulk density, tap density, compressibility, Hausner ratio, and more. Note that the tablet parameters are shown in tabular form [Table 3]. The combination of these matrices of lactose and microcrystalline cellulose was selected for further tablet formulations.

In the second stage, the tablets were made using different hyperdisintegrants and their different ratios. The detailed configuration is shown in Table 4. Tablets were evaluated with various parameters such as thickness, hardness, brittleness, weight variation, and disintegration. Powder blends have been evaluated for angle of repose, bulk density, tap density, compressibility, Hausner ratio, and more. It was

found that the effect of the super-degrading agent is shown in the table. From this study, crospovidone, which is 5% of the total weight of tablets, was selected as the superdisintegrant for additional tablet formulations.[12]

In the third step, tablets were made using different permeation enhancers and different ratios. The detailed configuration is shown in the table. Tablets were evaluated for various physical parameters such as thickness, hardness, brittleness, weight variation, disintegration, wetting time, water absorption, drug permeability, drug content uniformity, and *in vitro* dissolution studies. The powder mixture was evaluated for angle of repose, bulk density, tap density, compressibility%, Hausner ratio, etc [Table 5].

Pre-compression

The values of pre-compression parameters (angle of repose, Carr's index, tap density, bulk density, and Hausner's ratio) evaluated were within the prescribed limits and indicated good free flowing property.

Post-compression

The data obtained from post-compression parameters such as weight variation, hardness and friability, wetting time, drug content, disintegration, and *in vitro* dissolution are as follows:

Hardness

In all the formulations, hardness test indicated good mechanical strength; hardness of the tablets was within the range of 2–3.1 kg/cm^2. From the result, it has been observed that the hardness of the tablets of F2 batch is more than F1 batch followed by F3 >F5–F9 batch.

Disintegration time

The formulations prepared with different superdisintegrant (natural and synthetic) showed disintegration time between the ranges of 10 and 18 s.[13] It was clear that the disintegration time of the tablets of F1 batch was less than F2 batch followed by F3 >F5–F9 batch. Hence, sodium stearyl fumarate is the best superdisintegrant of these nine, as explained in Table 4.

Friability

The friability of the all formulations was found to be <1%, indicated that tablets had a good mechanical resistance.

Drug content

Drug content was found to be uniform in all the tablet formulations within 93.67–101.65% [Table 4].

In vitro dissolution

In vitro dissolution studies showed that more than 70% of the drug released from all the formulations within 5 min. The F9 formulation containing sodium stearyl fumarate showed minimum dissolution. The results are shown in Table 6 and Figure 3.

Stability study

The stability study of optimized batch was carried out at 40°C and 75% RH for 6 month. The tablets were found to be stable at such condition and other parameters were found to be unaffected [Tables 7 and 8].

From the result, it has been observed that the natural superdisintegrant (sodium stearyl fumarate) showing better performance in wetting time, disintegration, and drug release comparison of other superdisintegrant.[14,15]

CONCLUSION

Nowadays, there is a need of developing unique delivery system for immediate release of drugs due to recent advances in technology. In the present study, fast-dissolving tablet of ketorolac tromethamine was designed, prepared, and evaluated. These tablets can disintegrate or dissolve rapidly once placed into the oral cavity. These tablets may helpful for geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which lead to poor patient compliance.

From the above experimental finding, it can be concluded that fast-dissolving tablet of ketorolac tromethamine would be an effective alternative approach for the management of Type II diabetes. Superdisintegrant Ac-Di-Sol in 4% w/w concentration is promising for rapid release of ketorolac tromethamine. Incorporation of effervescent agent in 3% w/w with Ac-Di-Sol 1% w/w concentration enhanced released rate of ketorolac tromethamine. The prepared tablets were maintained rapid and constant drug level in the blood and avoid excess drug loading into the body. This present approach is more effective to deliver ketorolac tromethamine to the patient. It was concluded that the bitter taste of ketorolac tromethamine can be masked by forming direct compression with Kyron T-134. Mouth dissolving tablets of ketorolac tromethamine having rapid disintegration and good mechanical strength can be prepared using a novel combination of crospovidone and Ac-Di-Sol.

CONFLICTS OF INTEREST

None.

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None.

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