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DESIGN AND EVALUATION OF ORODISPERSIBLE TABLETS OF KETOROLAC TROMETHAMINE

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Abstract:
The orodispersible tablets of ketorolac tromethamine were prepared by direct compression method using super disintegrants with varying ratios of croscarmellose sodium, sodium starch glycolate, and crospovidone. The developed tablets were evaluated for pre-compression and post-compression parameters. The results of all formulations were found within the pharmacopeia limits. The optimized formulation (F9) with crospovidone (15%) showed the maximum percentage of drug release for 5 min was 75.42% and for 45 min was 96.58%, which is the desired aspect of fabricated orodispersible tablets that helps in faster absorption of the drug and quick onset of pharmacological action. The disintegration time, drug content, wetting time, and water absorption studies were evaluated for all the formulations.

Keywords: *Ketorolac tromethamine, orodispersible tablets, super disintegrants, and taste masking*

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INTRODUCTION:

Patient acceptability and compliance are important in the design of novel approach one such drug delivery system are orodispersible tablets (ODT) which have gained acceptance and popularity in recent times [(1)]. The prime factor for the commercial success of ODT is its significant impact on patient compliance of all age groups [(2)]. The purpose of the present study was to formulate and evaluate taste-masked orodispersible tablets to avert the problem of swallowing and to provide a rapid onset of action [(3)]. Ketorolac tromethamine (KRT) belongs to the category of nonsteroidal anti-inflammatory drugs (NSAIDs) that showed more pronounced analgesic activity [(4)]. It inhibits the cyclooxygenase enzyme (COX) and hence prostaglandin synthesis [(5)]. The present study was focused on the design and evaluation of orodispersible tablets of Ketorolac tromethamine and thus relieving pain immediately.

2. MATERIALS AND METHODS:

2.1. Materials

Ketorolac tromethamine was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad. Croscarmellose sodium, Crospovidone, Sodium starch glycolate, and Avicel PH 101 were purchased from Hiranya Cellulose Products, Hyderabad. Mannitol and Aspartame were received from Green Pharma, Hyderabad. Talc and Magnesium stearate was from Neutron Drugs and Pharmaceuticals Pvt Ltd, Hyderabad. All other chemicals and reagents are analytical grade were used in the study.

2.2. Methods

2.1. Preparation of the tablet formulation by direct compression method

The orodispersible tablets of ketorolac tromethamine were prepared by direct compression technique. Accurately drug was weighed and to this adds super disintegrants like crospovidone/sodium starch glycolate/cross carmellose sodium and other excipients such as avicel PH 101, mannitol, aspartame, and talc and magnesium stearate were added. All the ingredients were passed through sieve no 120. The taste is masked by using aspartame as a sweetening agent. Tablets were compressed by using 6mm flat punches on sixteen stations rotary tablet compression machine [(6)]. The compositions of formulations are listed in Table 1.

Table 1: Composition of ketorolac tromethamine formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketorolac tromethamine	10	10	10	10	10	10	10	10	10
Cross carmellose sodium	5	10	15	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	5	10	15	-	-	-
Cross povidone	-	-	-	-	-	-	5	10	15
Avicel PH 101	25	20	15	15	25	20	25	20	15
Mannitol	40	40	40	40	40	40	40	40	40
Aspartame	3	3	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	12	12	12	12	12	12	12	12	12
Total weight (mg)	100	100	100	100	100	100	100	100	100

2.2. Characterization of oral disintegrating tablets

2.2.1. Evaluation of pre-compression parameters

Angle of repose

The angle of repose was determined by using the funnel method. The powder was poured from a funnel that can be raised vertically until a maximum cone height (h) was obtained. The diameter of the heap (D) was measured.

Bulk density

Apparent bulk density was determined by pouring the pre-sieved drug excipient blend into a graduated cylinder and measuring the volume and weight as it is.

Tapped density

It was determined by placing a graduated cylinder containing a known mass of drug, excipient blend on mechanical tapping apparatus, which was operated for a fixed number of taps until the powder bed volume has reached a minimum. Using the weight of a blend in a cylinder and with the minimum volume occupied, the tapped density was computed [(7)].

Percent compressibility and Hausner ratio

These were calculated by using the following equation. % Compressibility = $\{(\rho_t - \rho_b)/\rho_t\} \times 100$ and Hausner ratio = ρ_t/ρ_b.

2.2.2. Evaluation of post-compression tablets

Weight variation

Twenty (20) tablets were weighed randomly using an electronic balance and the average weight was determined. The individual tablets were weighed and compared with the average weight [(8)].

Hardness

The hardness of tablets was determined by using a Monsanto tablet hardness tester [(9)].

Friability

The Friability of ten tablets from each formulation was determined using the Roche friabilator. This device subjects the number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed [(10)].

Assay

Ten tablets were finely powdered; quantities of the powder equivalent to 10 mg of ketorolac tromethamine were accurately weighed, and transferred to a 100 ml volumetric flask containing 50 ml of pH 7.4 phosphate buffer and allowed to stand for 5 hrs with intermittent shaking to ensure complete solubility of the drug. The mixture was made up to volume with buffer. The solution was suitably diluted and the absorption was determined by a UV-Visible spectrophotometer at 320 nm. The drug concentration was calculated from the calibration curve [(11)].

Wetting time and water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was taken and weighed [(12)].

Thickness

Ten (10) tablets were taken randomly from each formulation and their thickness was measured using Vernier calipers [(13)].

Disintegration studies

In-vitro disintegration time for ODTs was determined using USP disintegration apparatus with pH 7.4 buffer as the disintegration medium [(14)].

Dissolution study

The dissolution rate was studied by using USP type II apparatus at 50 rpm, pH 7.4 phosphate buffer, 900 ml was used as dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5°c. An aliquot of dissolution medium was withdrawn at a specific time interval and it was filtered. The absorbance of the filtered solution was checked by UV spectroscopy at 332 nm wavelength and drug content was determined from the standard calibration curve. The dissolution rate was studied for all designed formulations [(15)].

3. Results and Discussion

3.1. Evaluation of pre-compression studies

The pre-compression studies like bulk density, tapped density, percent compressibility index, Hausner ratio, and angle of repose were determined for the prepared powder blend. The results are shown in Table 2.

Table 2: Results of pre-compression parameters (Mean ± SD)

Formulation codes	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner ratio
F1	29.1 ± 0.14	0.28 ± 0.08	0.32 ± 0.11	17.2 ± 0.28	1.18 ± 0.13
F2	26.7 ± 0.15	0.24 ± 0.05	0.29 ± 0.14	20.8 ± 0.42	1.32 ± 0.26
F3	28.2 ± 0.09	0.29 ± 0.12	0.30 ± 0.06	18.6 ± 0.13	1.16 ± 0.41
F4	23.4 ± 0.05	0.26 ± 0.09	0.27 ± 0.15	21.3 ± 0.35	1.23 ± 0.23
F5	27.6 ± 0.12	0.32 ± 0.14	0.31 ± 0.08	15.9 ± 0.27	1.19 ± 0.64
F6	29.8 ± 0.18	0.28 ± 0.06	0.33 ± 0.24	18.2 ± 0.36	1.16 ± 0.28
F7	24.6 ± 0.13	0.23 ± 0.13	0.37 ± 0.29	15.1 ± 0.26	1.20 ± 0.41
F8	26.8 ± 0.17	0.24 ± 0.15	0.26 ± 0.23	18.1 ± 0.49	1.15 ± 0.36
F9	23.2 ± 0.08	0.21 ± 0.10	0.24 ± 0.19	19.6 ± 0.51	1.21 ± 0.24

The powder blend evaluated for pre-compression studies' angle of repose was found in the range of 23.2° to 29.8°, this exhibits good flow properties. The results of the Carr's index and Hausner ratio were found within the limits. Among these formulations (F9) exhibits a good flow pattern.

3.2. Evaluation of post-compression studies

The developed orodispersible tablets of KRT were evaluated for post-compression studies such as hardness, friability, thickness, weight variation, and content uniformity for all the formulations. The results were found to be within the acceptable limits. The disintegration time, wetting time, and water absorption ratio was determined for all the developed formulations. The results are presented in Table 3.

Table 3: Results of post-compression studies (Mean ± SD)

Formulation codes	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Assay (%)
F1	112.15 ± 2.12	4.2 ± 0.09	0.72 ± 0.02	3.15 ± 0.08	97.38 ± 2.18
F2	106.24 ± 2.46	3.7 ± 0.12	0.63 ± 0.04	3.12 ± 0.12	98.67 ± 2.36
F3	103.17 ± 3.12	4.2 ± 0.08	0.54 ± 0.07	2.86 ± 0.05	96.74 ± 1.65
F4	99.63 ± 2.51	4.0 ± 0.05	0.62 ± 0.05	3.07 ± 0.11	98.91 ± 2.45
F5	97.82 ± 1.95	4.3 ± 0.15	0.71 ± 0.08	2.92 ± 0.15	99.12 ± 3.01
F6	104.31 ± 2.78	4.2 ± 0.13	0.82 ± 0.06	3.17 ± 0.09	98.81 ± 2.81
F7	101.45 ± 3.11	3.8 ± 0.11	0.59 ± 0.03	3.09 ± 0.07	105.46 ± 1.78
F8	100.68 ± 2.93	4.1 ± 0.17	0.67 ± 0.01	2.90 ± 0.10	98.39 ± 2.16

F9	100.21 ± 2.14	3.9 ± 0.10	0.64 ± 0.05	3.02 ± 0.04	102.84 ± 3.11

The results of the post-compression studies are within the limits. Friability studies of all formulations showed less than 0.8% which indicates the tablets are having good mechanical strength. The results of the hardness of tablets were found to be 3.7 to 4.3 kg/cm^2. The assay results were found between 96.74 to 105.46%.

3.3. Evaluation of disintegration, wetting time, and water absorption studies

The disintegration time, wetting time & water absorption ratio of developed formulations was determined. The results are shown in Table 4.

Table 4: Results of evaluation parameters (Mean ± SD)

Formulation codes	Disintegration time (sec)	Wetting time (Sec)	Water absorption ratio
F1	103 ± 2.61	116 ± 3.16	62.9 ± 2.67
F2	108 ± 3.17	95 ± 2.35	71.6 ± 2.79
F3	89 ± 2.34	81 ± 2.69	58.9 ± 3.12
F4	76 ± 2.06	68 ± 3.14	67.1 ± 2.03
F5	48 ± 1.97	51 ± 2.61	79.5 ± 2.81
F6	51 ± 2.81	59 ± 2.93	84.2 ± 3.18
F7	34 ± 2.69	45 ± 1.98	74.8 ± 2.04
F8	30 ± 1.54	38 ± 1.53	89.6 ± 2.13
F9	24 ± 1.83	32 ± 2.06	91.3 ± 2.57

The fabricated formulations were studied for wetting and disintegration time times were found to be below 103 sec and 116 sec, which exhibits faster disintegration of the orodispersible tablets. In the case, of the water absorption ratio experiment, formulation (F9) loosened the shape because it absorbed more amount of water when compared with other formulations. So, based on the above results F9 formulation is considered an optimized formulation.

3.4. *In vitro* drug release studies

The formulations F1 to F3 were prepared by using croscarmellose sodium, the release was found to be 81.49%, 86.15%, and 89.32% in 45 min respectively. Formulations F4 to F6 were made by sodium starch glycolate and release was found to be 88.02%, 90.63%, and 91.05%. Formulations F7 to F9 were utilizing crospovidone and the percentage of drug release was found to be 92.18%, 94.11%, and 96.58%. Increasing the concentration level of super disintegrant, the drug release was increased gradually. Based on studies, 15% of crospovidone-containing formulation (F9) showed the maximum amount of drug release of 96.58% in 45 min. The results were represented in Figure 1.

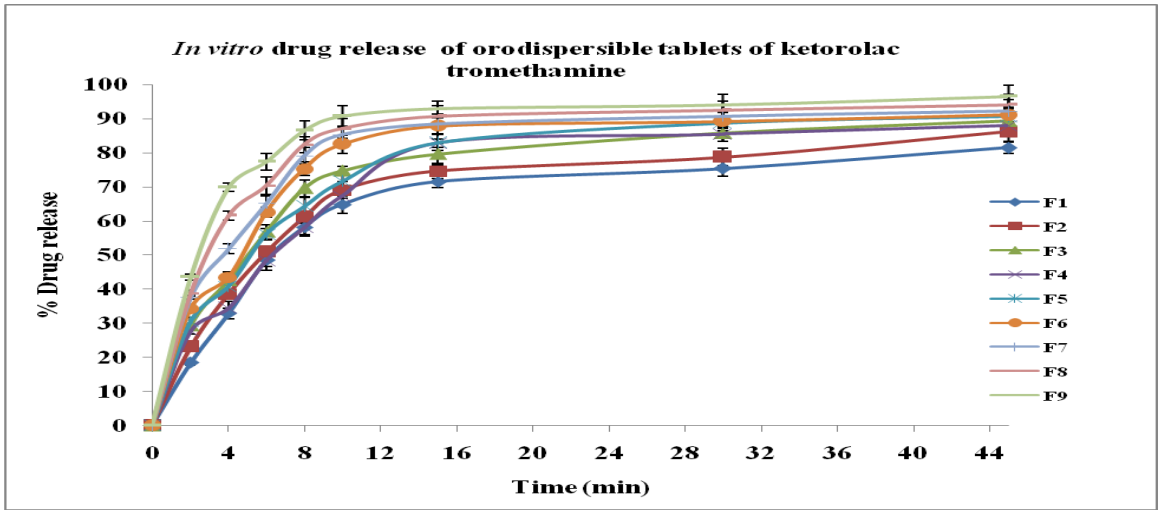

Figure 1: *In vitro* release studies of orodispersible tablets of ketorolac tromethamine

Crospovidone-containing formulations (F7 to F9) showed faster release than other super disintegrants used in the present work. It is synthetic water insoluble and non-ionic, but rapidly swellable, cross-linked polymer properties. This rapidly wicks solvents into the particle to increase swelling and enhance the disintegration and dissolution of tablets.

3.5. Drug-excipients compatibility studies

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug, and the optimized formulation (F9) were recorded in the range of 4000-400 cm^{-1}. The results are shown in Figure 2.

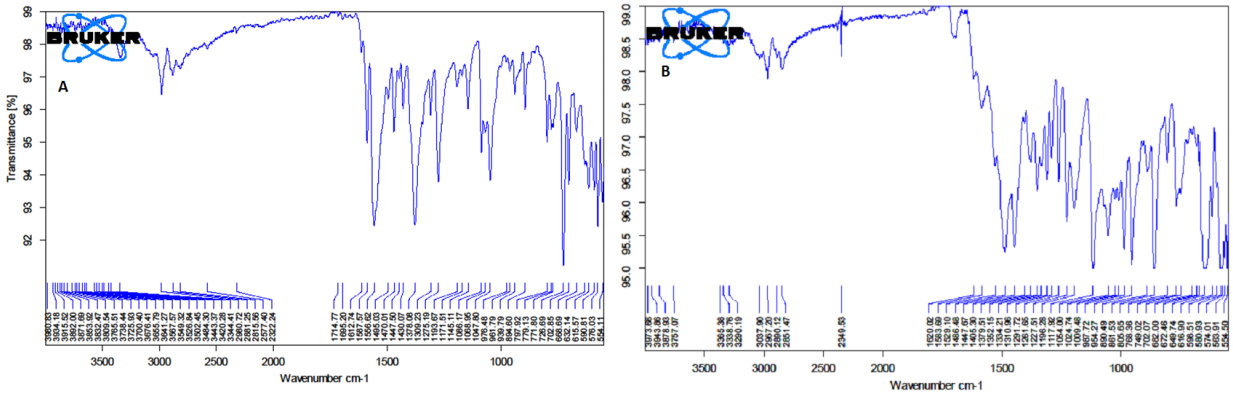

Figure 2: FTIR spectra of A) Pure drug; B) Optimized formulation (F9)

4. CONCLUSION:

The present work was to develop oral disintegrating tablets of ketorolac tromethamine by using different super disintegrants such as croscarmellose sodium, sodium starch glycolate, and crospovidone with various concentrations (5%, 10%, and 15%) on the disintegration time and drug release studies. The tablets were prepared by direct compression technique. The developed formulations evaluated and met the pharmacopoeial specifications for hardness, friability, weight variation, and drug content. The optimized formulation (F9) containing 15% of crospovidone showed the maximum amount of drug release of 96.58% in 45 min. The disintegration time was found to be 24 sec. The wetting time and water absorption ratio were evaluated for all the developed formulations. As the concentration of the super disintegrants increased; the wetting time (32 sec) decreased and the water absorption ratio (91.3 sec) increased. The wetting time for the F9 formulation was below one minute.

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