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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF NON-STEROIDAL ANTI- INFLAMMATORY DRUG

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ABSTRACT
Objectives: The aim of the present work was to formulate and evaluate fast dissolving tablets of non-steroidal anti-inflammatory drug (KT) by super disintegration and sublimation approach. Along with this a comparison between natural and synthetic super disintegrants was also done on the basis of disintegration time and drug release.
Methodology: Tablets were prepared using direct compression method with camphor, ammonium bicarbonate and benzoic acid as subliming agent and sodium starch glycolate (SSG) and Plantago ovata mucilage as superdisintegrants.
Results: All the pre-compression and post-compression parameters were determined and disintegration time (DT) and % drug release were also calculated to find the best formulation.
Conclusion: Fast dissolving tablets of ketorolac tromethamine were prepared and formulation F1out of all containing camphor and SSG was found to be best formulation because of its best drug release rate in less time.

KEYWORDS: Super disintegration, disintegration time, drug release, Anti-inflammatory.

INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance. FDTs are intended and designed to disintegrate and dissolve in saliva and then easily swallowed without need of water, which is a major benefit over conventional dosage form. In the present era, NSAIDs are the most widely preferred drugs which are very effective in the treatment of treating pain, fever and inflammation. Many of these side effects may be prevented by careful considerations of patient risk factors and have subsequent preventive strategies.

- Ketorolac a non-steroidal anti-inflammatory drug (NSAIDs) used for treating inflammation and pain. Apart from Ibuprofen and naproxen, Ketorolac is more effective NSAID in reducing pain from both inflammatory and non-inflammatory causes.
- It is widely used for short-term management (up to 5 days) of moderately severe acute pain. Its shows its effect by inhibition of prostaglandin synthesis.

It is a BCS class – I drug with high solubility and high permeability many of the existing fast disintegrating formulations were prepared or formulated using synthetic disintegrates available at higher cost. Ketorolac tromethamine being an analgesic drug should produce instant effect after administration. IV or IM

administration of drug shows quick response but oral dosage form are the most convenient and acceptable form. Convectional tablets administration produce severe gastric side effect. The need for dosage form which shows quick response, thattoo is convenient in administration with minimum side effect bring about FDT of Ketrolac tromethamine is hence chosen to study for quick onset of action with minimum side effect.

MATERIALS AND METHODS

Ketorolac tromethamine, Sodium starch glycolate, Plantago ovate mucilage, Aerosil, Sodium saccharine, Camphor, Ammonium bicarbonate, Benzoic acid, microcrystalline cellulose, Mannitol, Magnesium stearate, Talc.

Preparation of plantago ovata mucilage

Seeds of Plantago ovate were soaked in distilled water for 48 hours and then boiled for 1hour for complete release of mucilage into water. The material was filtered by squeezing in a muslin cloth to remove marc. Then equal volume of acetone was added to filtrate to precipitate the mucilage. The mucilage was separated and dried in oven at a temperature of less than 60^0C, powdered using #22 mesh, weighed and stored for further use.

Formulation of Ketorolac tromethamine tablet blend

All the ingredients were weighed and sieved through mesh#22 accurately. Drug and superdisintegrants were mixed at first, and then all other excipients were mixed except magnesium stearate and talc. At last magnesium stearate and talc were passed through mesh#60 and mixed to blend.

Table 1: Formulation of different batches of ketorolac tromethamine ODT's

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Ketorolac tromethamine	10	10	10	10	10	10
Camphor	20	-	-	20	-	-
Ammonium Bicarbonate	-	20	-	-	20	-
Benzoic acid	-	-	20	-	-	20
Sodium starch Glycolate	8	8	8	-	-	-
Plantagoovata Mucilage	-	-	-	8	8	8
Aerosil	2	2	2	2	2	2
Sodium Saccharine	1.5	1.5	1.5	1.5	1.5	1.5
Microcrystalline cellulose	30	30	30	30	30	30
Mannitol	25.5	25.5	25.5	25.5	25.5	25.5
Magnesium Stearate	1	1	1	1	1	1
Talc	2	2	2	2	2	2

EVALUATION OF PRE-COMPRESSION PARAMETERS

Pre-compression parameters study gives the information needed to define the nature of drug substance and

provide framework for the drug combination with pharmaceutical excipients in the dosage form.

Bulk density: Apparent bulk density was determined by pouring pre sieved drug- mixture blend into a graduated cylinder and measuring the weight and volume as it is. It is measured ingm/ml unit and given as

$$D_b = M/V_b$$

Where, M is mass of powder. V_b is bulk volume of powder.

Tapped density: It was determined by placing a known mass of drug- excipient blend into a graduating cylinder on mechanical bulk density apparatus until constant volume obtained. The tapped density is expressed in gm/ml and is given by

$$D_t = M/V_t$$

Where, M is mass of powder blend. $V_t$is tapped volume of the powder.

Carr's compressibility index: It is expressed in percentage and given by

$$I = D_t - D_b/D_t$$

Where, D_b is bulk density of powder. D_t is tapped density of powder.

Hausner's ratio: It is an indirect index of ease of powder flow. It is calculated by the given formula.

$$H = D_t/D_b$$

Lower hausner's ratio (<1.25) indicates better flow property than higher ones (>1.25). It can measure the frictional forces of loose powder and indicates flow properties of powder. It is defined as the maximum angle possible the surface of pile of powder and the horizontal plane.

$$\text{Tan } \theta = h/r \quad \theta = \tan^{-1} h/r$$

Where, θ is angle of repose

h is height in cm

r is radius in cm

In this, the powder mixture could flow through funnel fixed at a definite height. Angle of repose was calculated by measuring the height and diameter of a heap of powder made by keeping the height of funnel2cm. Care was taken to note that the particles of powder slip and rolls over each other through sides of funnel.

Table 2: Powder flow properties

Flow property	Angle of repose(θ)	Compressibility Index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Extremely poor	>65	>38	>1.60

Method of Preparation of ODT's

The blend was compressed by direct compression method using rotary punching machine with round punches of diameter 8 mm. Tablets of 100mg was prepared by adjusting hardness and volume screw of compression machine properly.

EVALUATION OF POST COMPRESSION PARAMETERS OF ODTS

General appearance: The general appearance of tablet was visually identified, it is essential for consumer's acceptance. Tablet's size, shape, colour, odour, texture, physical flaws and consistency were identified.

Hardness and friability: Hardness was measured using the Monsanto hardness tester. The friability of 65 tablets was measured using Roche friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25rpm for 4 minutes. The tablets were then de-dusted, reweighed and percentage weight loss was calculated. Compress tablet that lose less than 0.1-0.8 % of tablet weight are considered acceptable.

% friability = Initial weight – final weight ÷ initial weight × 100

Average weight and % weight variation:
Twenty tablets were selected randomly from each formulation and weighed individually and average weight and percentage weight variation was calculated.

Thickness and diameter: Ten tablets were taken and their thickness and diameter was recorded using vernier callipers and micrometer.

Drug content: Ten tablets were crushed in mortar and powder equivalent to 10 mg KT was dissolved in sufficient quantity of distilled water and make up volume in 100 ml volumetric flask. The solution was filtered through whatmann filter paper (0.45 micron), suitably diluted with distilled water, and analyzed at .....nm, using a UV-Visible double beam spectrophotometer. Each sample was analyzed in triplicate.

Wetting time: Apiece of tissue paper(12cm×10.75cm) folded twice was placed in a small petridish (ID=10cm)containing 6ml of p^H 6.8 phosphate buffer, a tablet was put on the amaranth powder containing paper the time required for upper surface of tablet to form pink colour was measured.

Disintegration time: Disintegration time for fast disintegrating tablet was determined using USP tablet disintegration apparatus with water as a medium. The temperature was maintained at 37±2ºC.The time in minutes taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

In-vitro drug release study: In-vitro drug release rate of KT was carried out using USP dissolution type-2 testing apparatus. The dissolution test was carried out using 900mlofphosphate buffer p^H 6.8, at 37±0.5ºCandstirredat50rpm.5mlofalliquoteswerewithdrawnatdifferenttime intervals (2, 4, 6, 8, 10, and 12 till 24) and an equivalent volume of medium (pre-warmed at 37ºC) was added to maintain constant volume. Withdrawn sample were analyzed spectrophotometrically at 322 nm using UV spectrophotometer.

RESULTS

Table 3: Evaluation of pre-compression parameters

S No.	F Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (gm/ml)	Carr's compressibility index(gm/ml)	Hausner's ratio (gm/ml)	Flow properties
1	F1	0.471±0.006	0.562±0.012	17.31±0.12	16.91±0.01	1.19±0.002	Excellent
2	F2	0.482±0.001	0.581±0.009	19.60±0.23	20.53±0.03	1.20±0.007	Excellent
3	F3	0.461±0.004	0.570±0.002	19.31±0.21	23.41±0.01	1.23±0.002	Good
4	F4	0.447±0.009	0.561±0.003	20.11±0.04	20.32±0.04	1.25±0.001	Good
5	F5	0.454±0.002	0.557±0.001	22.17±0.03	18.49±0.08	1.22±0.005	Good
6	F6	0.471±0.001	0.581±0.007	25.09±0.07	18.93±0.02	1.23±0.003	Good

Table 4: Evaluation of Average weight, thickness, hardness and friability of ODT's

S No.	Formulation code	Average weight	thickness	Hardness	friability
1	F1	100.02±0.21	2.56±0.58	2.45	0.51
2	F2	99.97±0.21	2.44±0.27	2.47	0.49
3	F3	99.12±0.21	3.13±0.41	2.42	0.62
4	F4	100.20±0.21	2.91±0.21	2.31	0.65
5	F5	99.34±0.21	3.04±0.57	2.59	0.60
6	F6	100.24±0.21	3.17±0.12	2.94	0.52

Table 5: Evaluation of wetting time, disintegration time and drug content of ODT's

S No.	ɔrmulation code	′etting ne (sec)	Disintegration time (sec)	′ug content (%)
1	F1	25±0.318	35	99.07±0.41
2	F2	32±0.120	40	99.85±0.54
3	F3	34±0.88	42	99.79±0.70
4	F4	28±0.256	38	98.90±0.47
5	F5	36±0.946	54	99.63±0.22
6	F6	39±0.557	59	99.27±0.12

Table 6: Cumulative % drug release for formulations (F1-F6)

F code	Time (min)						
	2	4	6	8	10	12	24
F1	4.22±0.232	17.56±0.348	32.97±0.648	49.23±0.639	68.14±0.312	84.25±0.637	98.12±0.396
F2	3.45±0.412	15.14±0.674	31.56±0.632	48.55±0.463	64.88±0.982	80.63±0.625	94.44±0.414
F3	2.26±0.564	12.74±0.376	29.58±0.795	45.94±0.582	60.64±0.584	79.15±0.385	93.59±0.654
F4	6.25±0.112	14.46±0.812	31.31±0.154	47.22±0.417	65.45±0.324	83.98±0.365	97.42±0.873
F5	4.54±0.546	13.64±0.698	27.14±0.432	45.55±0.632	67.24±0.312	80.37±0.116	96.58±0.997
F6	5.32±0.324	11.23±0.342	26.11±0.825	42.32±0.365	61.82±0.852	79.99±0.471	93.54±0.632

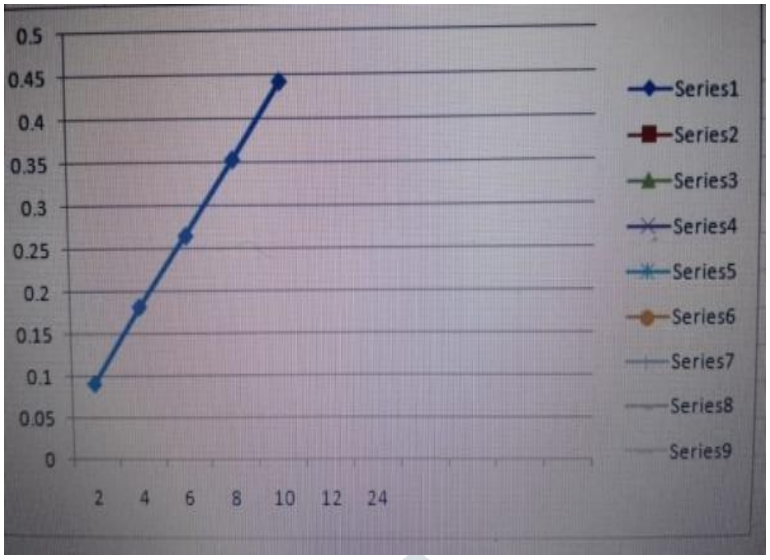

Figure 1: Calibration curve of KT in phosphate buffer pH 6.8

Table 7: Concentration and corresponding absorbance of KT in phosphate buffer pH 6.8

Sr. No.	Concentration (Microgram per ml)	Absorbance
1	0	0
2	2	0.091±0.006
3	4	0.182±0.032
4	6	0.245±0.214
5	8	0.330±0.316
6	10	0.402±0.122

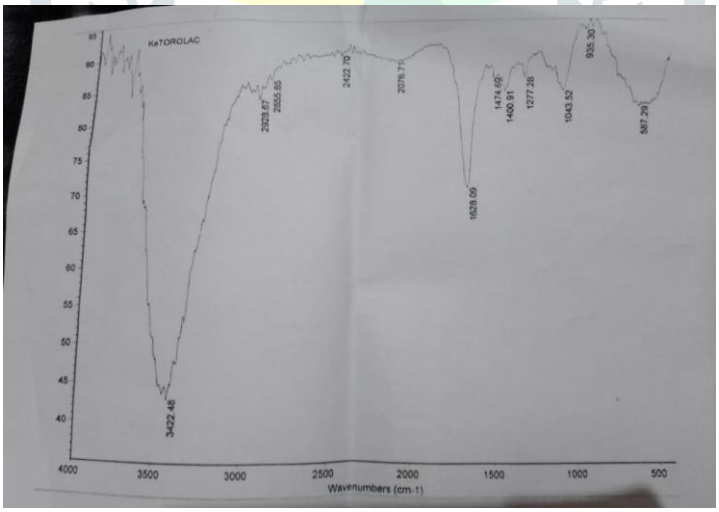

Figure 2: FT-IR of KT

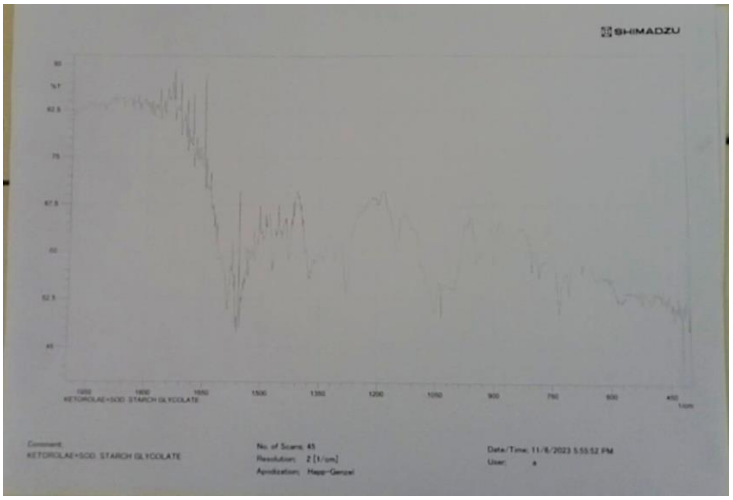

Figure 3: FT-IR of KT+SSG

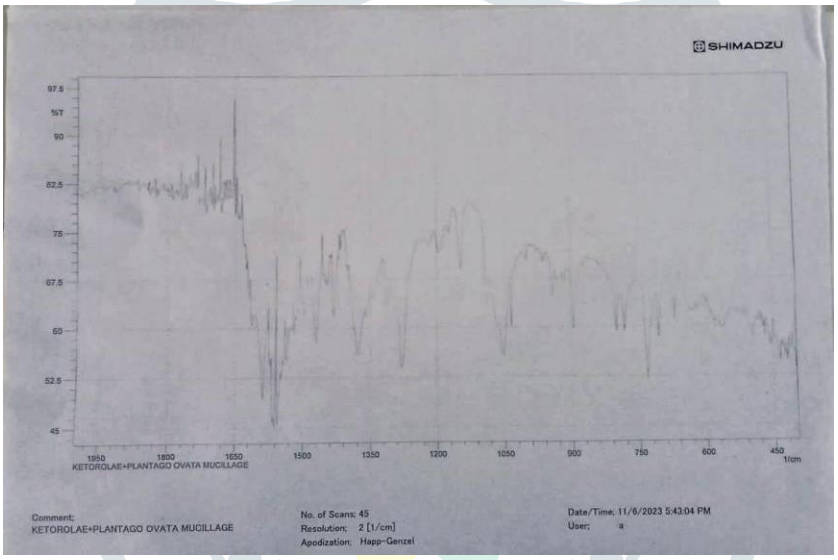

Figure 4: FT-IR of KT + Plantago ovate mucilage

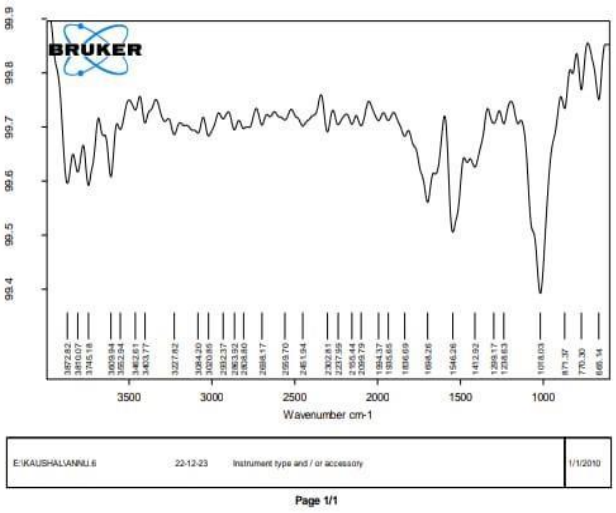

Figure 5: Physical mixture

Table No.8: Interpretation of FTIR spectra

S No.	Functional group	Characteristic peak (cm^{-1})	Observed peaks(cm^{-1}) Pure drug	Ketorolac +SSG	Ketorolac + Plantago mucilage	Physical mixture
1	O-H	3200-3600	3422.48	-	-	3403.77
2	C=O	1670-1820	1628.09	1680	1680	1698.26
3	C-N	1080-1360	1277.28	1260	1290	1238.63
4	C=C	1400-1600	1474.69	1590	1560	1546.26

CONCLUSION

Fast disintegrating tablets offer a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic with increased bioavailability.

It may be concluded that direct compression method with sublimation approach showed better disintegration and drug release. The prepared tablet disintegrates within few seconds, thereby enhancing the absorption leading to its increased bioavailability.

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