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FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF KETOROLAC TROMETHAMINE

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ABSTRACT

Oral disintegrating tablets of Ketorolac tromethamine were developed by using different disintegrants to avert the problem of swallowing and to provide rapid onset of action, which improves patient compliance and quality of life. The results of this study concluded that super disintegrants addition technique was an interesting way of formulating oral disintegrating tablets using direct compression technique which is easy, inexpensive and does not require special production equipment. Oral disintegrating tablets were formulated by using various disintegrants like sodium starch glycolate, Croscarmellose sodium & Crospovidone. The disintegrants were taken in concentrations of 5%, 10%, 15% and microcrystalline cellulose was used as diluent. Formulations F6 & F9 which contains 15% of Croscarmellose sodium & Crospovidone respectively along with microcrystalline cellulose showed least *in- vitro* disintegration time i.e., below 30 seconds and more than 90% drug release within 8 minutes. So, for the above formulations even *in-vivo* disintegration time and palatability (mouth feel) studies were carried out on healthy human volunteers.

1. INTRODUCTION

In recent decades, a variety of pharmaceutical research has been conducted to develop novel dosage forms. Considering quality of life, most of the efforts have focused on ease of medication. Among the dosage forms developed to facilitate ease of medication, the orally disintegrating tablet (ODT) is one of them. Oral disintegrating tablets are also called as orodispersible tablets, mouth-dissolving tablet (MDT), quick-dissolve, fast-melt, and rapid disintegrating tablets and freeze-dried wafers, porous tablets and rapimelts.[1]

According to the US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines in the *Orange Book* an Orally disintegrating tablet as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

The European Pharmacopoeia however defines a similar term, *oro disperse*, as a tablet that can be placed in the mouth where it disperses rapidly before swallowing.[2]

The conventional dosage forms, which include tablets and capsules, are widely used. But, unlike the conventional dosage forms, the mouth dissolving tablets has some unique features.

Importance of orally disintegrating tablets

- As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, smaller packaging size, and easy to handle by patients.[3,4,5]
- No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water.
- Easy to administer for pediatric, geriatric, institutionalized patients (especially for mentally retarded and psychiatric patients).
- Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.[6]
- Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.
- Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased.[7,8,9]

Various processes employed in formulating ODTs include

- Lyophilization or Freeze Drying Technique.
- Tablet Molding Technique.
- Cotton Candy Process.
- Spray Drying Technique.
- Mass Extrusion Technique.
- Compaction.
- Direct compression.

Lyophilization or Freeze Drying Technique

Formation of porous product in freeze-drying process is exploited in formulating ODT. Lyophilization is a

process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug.

Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolves rapidly but also improves the bioavailability of several drugs such as spironolactone and tralendomycin.[7] Corveleyn and Remon studied various formulation and process parameters by using hydrochlorothiazide as a model drug on the basis of which US Patent 6.010719 was granted.[11] Tablets prepared by lyophilization are fragile and possess low mechanical strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions.

The ideal drug characteristics are relative water insolubility with fine particle size and good aqueous stability in the suspension. As the dose is increased, it becomes more difficult to achieve the optimum formulation. Drug loading for water insoluble drugs approaches 400mg. The upper limit for drug loading is much lower approximately 60mg for water insoluble drugs. The primary problems associated with water soluble drugs are the formation of eutectic mixtures, resulting in freezing point depression and the formation of a glassy solid on freezing which might collapse on drying because of loss of the supporting structure during the sublimation process.[3]

The addition of crystal-forming agents such as mannitol, which induce crystallinity and hence impart rigidity into the amorphous material, can be employed to prevent the collapse of the structure. The soluble drugs can be complexed with ion exchange resins to prevent the collapse of the structure, which is also useful in masking the bitter taste of the medicaments.[3] The sedimentation of larger drug particles may lead to the loss of the product. The appropriate particle size is less than 50 microns, although larger particle size drug material can be formulated by the use of suitable suspending agents, such as gelatin and flocculating agents such as xanthane gum.[3] Soluble drugs can also be incorporated into the formulation by their organic solvent-solution deposition onto preformed matrix, and subsequent removal of solvent by evaporation.

The matrix characteristics of the formulation are equally important in the product development. Typically, the matrix consists of polymers such as gelatin, dextran or alginates as glassy amorphous compounds providing structural strength, saccharides such as mannitol or sorbitol to provide crystalline, hardness and elegance and water as a manufacturing process media to induce the porous structure upon sublimation during the freeze drying step. The formulation can also contain taste masking agents such as sweeteners, flavors, pH-adjusting substances such as citric acid, and preservatives such as parabens to ensure aqueous drug suspension stability prior to the freeze-drying step. Finally, the freeze dried formulations are manufactured and packaged in PVC plastic packs or may be packed into Aclar laminates or aluminum foil preparations to protect the product from external moisture.[3]

The main advantage of this process is that pharmaceutical substances can be processed at non-elevated temperatures, thereby eliminating adverse thermal effects, and stored in a dry state with relatively few shelf-life stability problems. Freeze dried forms offer more rapid dissolution times than other available solid products.

Several technologies are patented involving lyophilization process. However, the ODTs formed by lyophilization have low mechanical strength, poor stability at higher temperature, and humidity. Along with above complications and its expensive equipment freeze-drying use is observed to be limited.[4]

Tablet molding technique

The major components of the molded tablets are water soluble ingredients. Molding process includes moistening, dissolving, or dispersing the drug with a solvent then molding the moist mixture into tablets (compression molding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution, or suspension at ambient pressure (no vacuum lyophilization), respectively.

The molded tablets formed by compression molding are air-dried. As the compression force employed is lower than conventional tablets, the molded tablet results in highly porous structure, which increases the disintegration and dissolution rate of the product. However, to further improve dissolution rate of the product powder mixture should be sieved through very fine screen.

As molding process is employed usually with soluble ingredients (saccharides) which offers improved mouth feel and disintegration of tablets. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the molding process are used. Tablets can be produced more simply by this technique. However, molded tablets have low mechanical strength, which results in erosion and breakage during handling. In order to overcome this problem, binding agent such as sucrose, acacia, poly vinyl pyrrolidone must be added to the solvent system, but then the rate of tablet solubility usually decreases.

ODTs having both adequate mechanical strength and good disintegration recently have been prepared by

molding techniques using nonconventional equipment or multistep processes. But nonconventional process is expensive. Compared with freeze drying, ODTs prepared by molding techniques can be produced more simply and efficiently at an industrial scale, although they cannot achieve disintegration times comparable with those of lyophilized forms.

Masaki described a process using an agar solution as a binding agent and a blister packaging well as a mold to prepare an intra-buccally oral disintegrating tablet. The process involved preparing a suspension containing an active ingredient, agar and sugars (e.g., lactose and mannitol) by filling the suspension into the well and solidifying the agar solution into the form of a jelly at room temperature and drying the jelly at 30°C under a pressure of 700 to 760 mm Hg. The hardness of the molded tablets was adequate, with crushing strengths >2Kg in most cases.

Cotton candy process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process (Meyers et al., 1995) involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT. This process can accommodate high doses of drug and offers improved mechanical strength. However, high-process temperature limits the use of this process.

Spray drying technique

Highly porous, fine powders are obtained by this method. Allen *et al*., prepared ODT by this process.[12] The ODT formulations consist of hydrolyzed or unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and sodium starch glycolate or Croscarmellose sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid (an acid) and sodium bicarbonate (an alkali). The formulation was spray dried to yield a porous powder. The ODT made from this method disintegrated in < 20 s.[13,14]

Mass extrusion technique

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking of bitter taste can be done.[15]

Compaction Melt granulation

In this technique ODT was prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate is a waxy material with a melting point of 33-37°C and a hydrophilic lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue.[16]

Super polystate was incorporated in the formulation of ODT by melt granulation method where granules are formed by the molten form of this material. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

Phase transition process

In this process the disintegration of tablets was due to phase transition of sugar alcohols using erythritol (m.p. 122°C), xylitol (m.p. 93-95°C), trehalose (97°C), and mannitol (166°C).[17] In this process any special apparatus is not required, tablets were produced by compressing a powder containing two sugar alcohols with high- and low-melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

Sublimation

Compressed tablets containing highly water soluble excipients as a tablet matrix often do not dissolve rapidly in water. This is because the low porosity of compressed tablets hinders water penetration into the matrix. Heinemann *et al*., and Roser *et al*., developed a technique to prepare porous tablets that dissolve or disintegrate quickly and simultaneously exhibit good mechanical strength.[17,18] Inert solid ingredients that volatize readily (e.g., urethane, urea, camphor, ammonium carbonate, benzoic acid, pthalic anhydride, hexamethlene tetramine and naphthalene) were added to other tabulating ingredients and the mixture was compressed into tablets. Volatile materials were then removed via sublimation, which generated a porous structure. Additionally, several solvents (e.g., cyclohexane, benzene, and tertiary butanol) were suggested for use as pore-forming agents.

Koizumi *et al*., developed ODT utilizing camphor; a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and

camphor.[20] Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.

Direct Compression

It is the simplest and most cost-effective tablet manufacturing method. The preparation of ODTs by this method involves same processing steps as that of conventional solid dosage forms such as weighing, screening, mixing and compression. Hence, most of the pharmaceutical companies adopt this method for preparing mouth dissolving tablets.

In this method tablets disintegration and solubilization are based on single or combined action of disintegrants, water soluble excipients and effervescent agents. The disintegration time is in general satisfactory although the disintegrating efficacy is strongly affected by tablet size and hardness. Large and hard tablets have a disintegration time greater than that usually required for ODTs. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of blister alveolus all result from insufficient physical resistance.

Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of the tablet can easily exceed that of other production methods. This technique can now be applied to mouth dissolving tablets because of the availability of improved tablet excipients, especially tablet disintegrants and sugar-based excipients.

Addition of disintegrants in ODTs, leads to quick disintegration of tablets and hence improves dissolution. In many ODT technologies based on direct compression the disintegrants basically affect the rate of disintegration and hence the dissolution. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegration concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxy propyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of ODTs.

Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug. The major drawback of effervescent excipients is their hygroscopicity (i.e., the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected by the overall cost of the product.[21]

Sugar-based excipients: Another approach to ODTs by direct compression is the use of sugar based excipients (e.g., dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose and xylitol) which display high aqueous solubility and sweetness and hence impart taste masking.

METHODOLOGY

6.1 Preparation of standard graph of Ketorolac tromethamine in pH 7.4 phosphate buffer

Accurately weighed amount (100mg) of the drug was dissolved in 100ml of pH 7.4 buffer in a 100ml volumetric flask. From this stock solution (1mg/ml) 10ml of solution was transferred into a 100ml volumetric flask and the volume was made up with pH 7.4 buffer. From this second stock solution (100µg/ml), different concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml were prepared and their corresponding absorbance values were measured at 320 nm in a UV/Visible spectrophotometer.

6.2 Preparation of the tablet formulation by direct compression Technique

Taste masking of the Ketorolac tromethamine tablets was done by using sweeteners. Tablets were prepared by direct compression technique. Accurately drug was weighed and to this other excipients were added (Drug, sodium starch glycolate, microcrystalline cellulose pH-102, mannitol, aspartame, Talc, magnesium stearate). All the ingredients were passed through sieve no 120.

Tablets were punched by using 6mm flat punches on sixteen station rotary tablet compression machine (Cadmach).

Table 3: General Composition of Formulations (F1 to F6) Prepared by Direct Compression Method.

Ingredients	F1	F2	F3	F4	F5	F6
Drug	10	10	10	10	10	10
Sodium starch glycolate	5	10	15	-	-	-
Cross carmellose sodium	-	-	-	5	10	15
Cross povidone	-	-	-	-	-	-
Microcrystalline cellulose 102	25	20	15	25	20	15
Di-basic calcium phosphate	-	-	-	-	-	-
Mannitol	50	50	50	50	50	50
Aspartame	4	4	4	4	4	4
Talc	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2
Total weight (mg)	100	100	100	100	100	100

Table 4: General Composition of Formulations (F7 to F12) Prepared by Direct Compression Method.

Ingredients	F7	F8	F9	F10	F11	F12
Drug	10	10	10	10	10	10
Sodium starch glycolate	-	-	-	15	-	-
Cross carmellose sodium	-	-	-	-	15	-
Cross povidone	5	10	15	-	-	15
Microcrystalline cellulose	25	20	15	-	-	-
Di-basic Calcium Phosphate				15	15	15
Mannitol	50	50	50	50	50	50
Aspartame	4	4	4	4	4	4
Talc	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2
Total weight (mg)	100	100	100	100	100	100

RESULTS AND DISCUSSION

The present study was carried out to prepare Ketorolac tromethamine oral disintegrating tablets by direct compression method. Preliminary trials were carried out to optimize the taste. Taste masking was done by using sweeteners. To develop the optimized formula, different super disintegrants like Sodium Starch Glycolate, Crospovidone and Croscarmellose sodium were used at different concentrations and diluents were changed in some formulations to know the diluent's effect.

7.1 Evaluation of Blend

Physical properties such as bulk density, tapped density, percent compressibility index, hausner ratio, angle of repose were determined (Tables 5 & 6) for the prepared tablet blend.

The tablet blend batches in which microcrystalline cellulose was used as diluent, the angle of repose is between 30° to 35°, this indicated the passable flowability. This property may be attributed due to the presence of microcrystalline cellulose having filamentous particles as diluent.

The tablet blend batches in which DCP was used, angle of repose values were found to be below 30°; this indicated good flow properties of the tablet blend. This property may be attributed due to the spherical shape of the particles.

The percent compressibility index and hausner ratio were within the limits.

Table 5: Tablet blend evaluation tests for formulations F1 to F6.

Formulations	Angle of Repose ± S.D.	Bulk Density ± S.D.	Tapped Density ± S.D.	Percent Compressibility Index ± S.D.	Hausner Ratio ± S.D.
F1	31.8 ± 0.08	0.30 ± 0.08	0.36 ± 0.15	16.6 ± 0.69	1.20 ± 0.22
F2	30.1 ± 0.12	0.25 ± 0.05	0.31 ± 0.09	19.3 ± 0.78	1.24 ± 0.57
F3	30.2 ± 0.08	0.21 ± 0.46	0.25 ± 0.2	16.0 ± 0.01	1.19 ± 0.63
F4	31.6±0.09	0.25 ± 0.18	0.30 ± 0.44	16.6 ± 0.71	1.20 ± 0.26
F5	32.5±0.04	0.33 ± 0.12	0.37 ± 0.11	10.8 ± 0.9	1.12 ± 0.81
F6	30.9±0.08	0.25 ± 0.75	0.30 ± 0.34	16.6 ± 0.51	1.21 ± 0.19

Table 6: Tablet blend evaluation tests for formulations F7 to F12.

Formulations	Angle of Repose ± S.D.	Bulk Density ± S.D.	Tapped Density ± S.D.	Percent Compressibility Index ± S.D.	Hausner Ratio ± S.D.
F7	31.2±0.04	0.37 ± 0.18	0.45 ± 0.3	17.7 ± 0.74	1.21 ± 0.64
F8	31.3±0.04	0.21 ± 0.66	0.25 ± 0.51	16.0 ± 0.18	1.19 ± 0.45
F9	32.6±0.02	0.20 ± 0.57	0.25 ± 0.31	20.0 ± 0.12	1.25 ± 0.58
F10	26.5 ± 0.14	0.21 ± 0.26	0.25 ± 0.77	16.0 ± 0.54	1.19 ± 0.29
F11	25.2 ± 0.08	0.25 ± 0.47	0.30 ± 0.91	16.6 ± 0.56	1.20 ± 0.53
F12	25.5 ± 0.04	0.25 ± 0.66	0.30 ± 0.69	16.6 ± 0.25	1.20 ± 0.39

Table 7: Standard graph of Ketorolac tromethamine

Concentration (µg/ml)	Absorbance in pH 7.4 buffer.
0	0
2	0.096
4	0.185
6	0.268
8	0.367
10	0.442
12	0.558
14	0.637
16	0.735
18	0.829
20	0.918
R^2	0.999

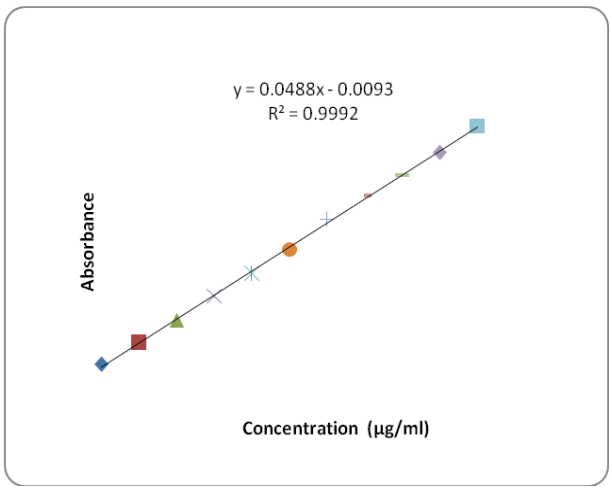

Figure 1: Plot of standard graph of Ketorolac tromethamine in pH 7.4 Buffer.

Standard graph of Ketorolac tromethamine (Table 7) has shown good linearity with R^2 value 0.999 in pH 7.4 buffer (Fig.1) , which suggests that it obeys the "Beer-Lambert's law".

7. 2 Evaluation tests for Ketorolac tromethamine ODT's.

The Ketorolac tromethamine orally disintegrating tablets were evaluated for hardness, friability, thickness, weight variation and content uniformity for all the batches and the results **(**Table 8 & 9**)** were found to be within the acceptable limits.

All the formulations were found to pass the weight variation test. Content of Ketorolac tromethamine from all the formulations was found to be in the range of 95% to 105%. The hardness was constantly maintained between 3-4 kg/cm^2 during compression. Friability for all the formulations was less than 0.9% which is in the acceptable limits indicated that formulations have good mechanical strength.

The *in-vitro* disintegration time, wetting time & water absorption ratio were determined for all the prepared formulations (Table 10 & 11). The wetting time for the optimized formulations was below one minute, which indicated quicker disintegration of the tablet. In the water absorption ratio test, F9 has loosened the shape because it absorbed large amount of water, when compared with other batches of formulations.

The *in-vitro* disintegration test was carried out for all the prepared formulations. Tablet disintegration was affected by the wicking and swelling nature of the disintegrants.[100] From the results the formulations in which Crospovidone was present showed less disintegration time when compared with other super disintegrants because it has excellent wicking nature, Crospovidone has a finer particle size distribution which improves mixing and minimizes changes in swelling properties on the tablet surface resulting from atmospheric humidity, so it swells only to a very less extent.

The mechanism involved in Croscarmellose sodium and sodium starch glycolate is when it comes in contact with water it swells to a large extent to disintegrate the tablet. Also it has fibrous nature that allows intra-particulate as well as extra-particulate wicking of water at low concentration levels.[101] The probable reason for delayed disintegration time of Croscarmellose sodium, and sodium starch glycolate might be due to their tendency to gel more than Crospovidone.

Table 8: Evaluation tests for Ketorolac tromethamine oral disintegrating tablets (F1 to F6)

Formulations	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Assay (Content uniformity) (%)
F1	100.15 ±1.83	3.5 ±0.02	0.52±0.04	3.00 ± 0.02	96 ± 0.08
F2	100.13±1.99	3.5±0.10	0.65±0.01	3.10±0.03	97±0.03
F3	100.3±1.13	3.2±0.02	0.54±0.01	2.98±0.02	95±0.68
F4	101.8±1.16	3.5±0.01	0.52±0.03	2.89±0.03	97±0.75
F5	98.8± 0.74	3.5±0.04	0.51±0.01	3.05±0.09	99±0.05
F6	99.3±0.33	3.4±0.00	0.51±0.02	3.11±0.06	98±0.88

Table 9: Evaluation tests for Ketorolac tromethamine oral disintegrating tablets (F7 to F12)

Formulations	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Assay (Content uniformity) (%)
F7	100.3±0.14	3.5±0.10	0.56±0.05	3.00±0.03	103±0.94
F8	100.7±0.28	3.5±0.06	0.62±0.03	3.12±0.03	98±0.03
F9	100.5±0.23	3.5±0.09	0.66±0.07	3.04±0.08	103±0.13
F10	100.1± 0.10	3.5 ± 0.02	0.85 ±0.07	3.21± 0.06	98±0.88
F11	98.2±0.14	3.5 ± 0.02	0.55 ±0.05	2.98 ± 0.03	95±0.61
F12	102.1±0.48	3.5 ± 0.01	0.72 ±0.03	3.16 ± 0.05	101±0.12

Table 10: Evaluation tests for Ketorolac tromethamine oral disintegrating tablets (F1 to F6).

Formulations	*In-vitro* disintegration time (sec)	Wetting time(Sec)	Water absorption ratio
F1	113 ± 1.34	122 ± 1.21	55.7 ± 0.56
F2	90 ± 1.24	98 ± 1.21	63.9 ± 0.45
F3	55 ±1.32	68 ± 1.24	75.6 ± 0.64
F4	52 ± 1.26	63 ± 0.95	78.9 ± 0.24
F5	37 ± 1.26	48 ± 1.24	84.7 ± 0.88
F6	28 ± 1.34	40 ± 0.92	90.6 ± 0.78

Table 11: Evaluation tests for Ketorolac tromethamine oral disintegrating tablets (F7 to F12).

Formulations	*In-vitro* disintegration time	Wetting time(Seconds)	Water absorption ratio
F7	42 ± 1.45	51 ± 0.95	76.9 ± 0.24
F8	31 ±1.24	38 ± 1.13	90.8 ± 0.45
F9	22 ± 0.98	29 ± 1.24	94.8 ± 0.65
F10	59 ± 0.54	69 ± 1.15	71.6 ± 0.58
F11	41 ± 1.14	55 ± 0.98	72.9 ± 0.54
F12	36 ± 0.68	48 ± 0.88	83.3 ± 0.45

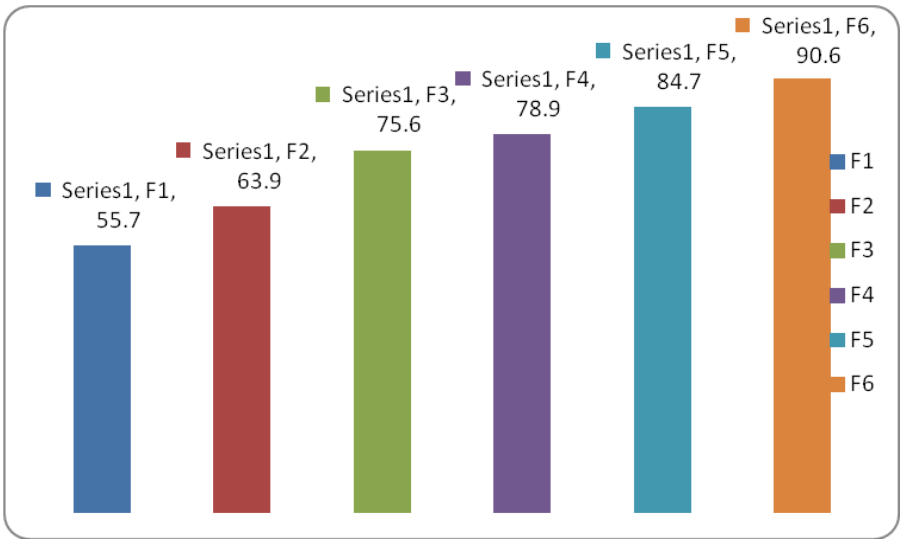

Figure 2: Water absorption ratio of Ketorolac tromethamine oral disintegrating tablets containing various disintegrants (F1 to F6).

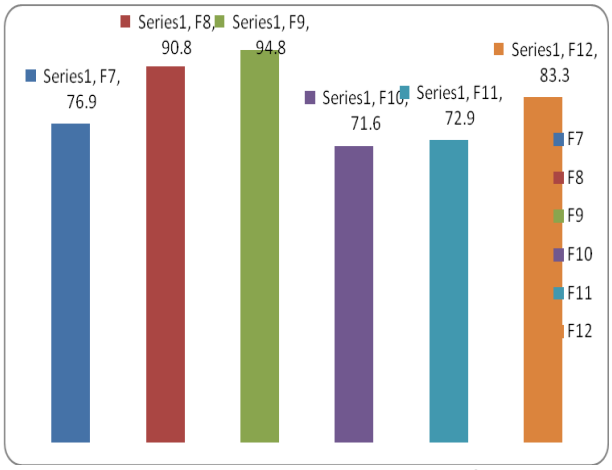

Figure 3: Water absorption ratio of Ketorolac tromethamine oral disintegrating tablets containing various disintegrants (F7 to F12).

Table 12: *In-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of sodium starch glycolate. Mean (±S.D.) cumulative percent of Ketorolac tromethamine released from formulations at specific time intervals.

Time (min)	F1	F2	F3
0	0	0	0
2	15.3 ± 0.33	28.3 ± 0.13	35.15 ± 0.46
4	34.4 ± 0.62	37.4 ± 0.32	42.85 ± 0.22
6	49.45 ± 0.43	54.45 ± 0.53	58.79 ± 0.06
8	56.6 ± 0.62	65.9 ± 0.79	69.6 ± 0.04
10	65.8 ± 0.58	74.1 ± 0.40	83.7 ± 0.29
15	75.1 ± 0.43	80.6 ± 0.89	91.6 ± 0.10
30	86.1 ± 0.23	88.7 ± 0.54	91.3 ± 0.34
45	90.2 ± 0.69	92.8 ± 0.72	91.6 ± 0.56

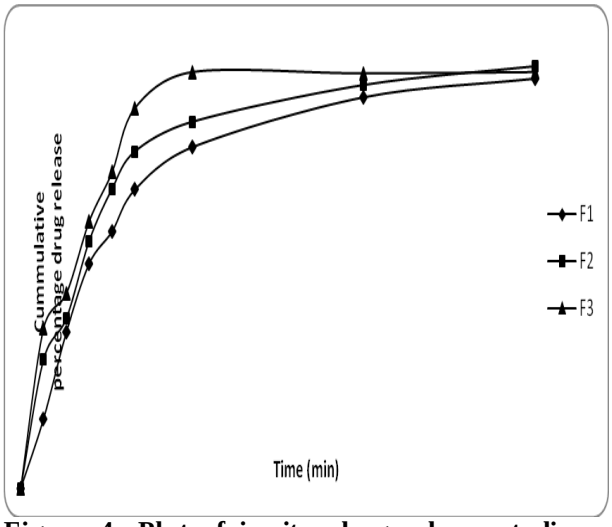

Figure 4: Plot of *in-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of sodium starch glycolate.

Table 13: *In-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of croscarmellose sodium.

Time (Min)	F4	F5	F6
0	0	0	0
2	29.14± 1.01	34.65± 0.19	37.3± 0.22
4	41.59± 1.91	47.83± 0.22	57.45± 0.54
6	54.37±0.89	65.73±0.62	82.5±0.45
8	62.02±0.35	79.33±0.66	91.34±0.53
10	75.35± 0.69	90.68± 0.46	93.5± 0.68
15	89.86± 1.26	92.02± 0.33	93.86± 0.34
30	91.5± 0.21	92.7± 0.62	94.97± 0.68
45	91.18± 0.84	95.7± 0.79	94.67± 0.23

Mean(±S.D.) cumulative percent of Ketorolac tromethamine released from formulations at specific time intervals.

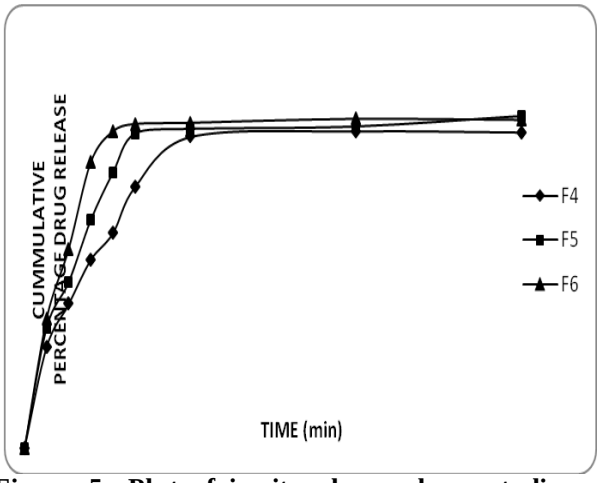

Figure 5: Plot of *in-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of croscarmellose sodium.

Table 14: *In-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of Crospovidone.

Time (Min)	F7	F8	F9
0	0	0	0
2	31.6± 0.62	37.8± 0.41	47.56± 0.84
4	62.8± 0.41	75.6± 0.35	75.84± 0.22
6	78.45±0.29	81.42±0.52	84.42±0.46
8	91.09±0.29	93.46± 0.33	96.56± 0.74
10	91.2± 0.54	93.04± 0.84	96.72± 0.45
15	93.46 ± 0.52	93.1± 0.39	96.9± 0.27
30	93.8± 0.45	95.5± 0.61	97.01± 0.64
45	97.8± 0.33	95.6± 0.12	96.09± 0.35

Mean (±S.D.) cumulative percent of Ketorolac tromethamine released from formulations at specific time intervals.

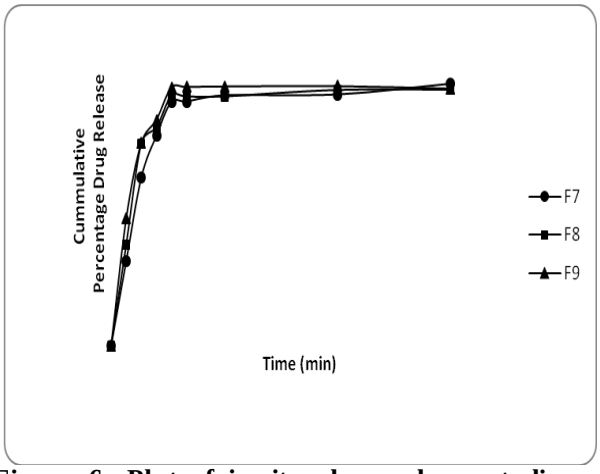

Figure 6: Plot of *in-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of Crospovidone.

Table 15: *In-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentration of Di-basic Calcium Phosphate.

Time (Min)	F10	F11	F12
0	0	0	0
2	27.51±0.72	29.28±0.02	35.83±0.74
4	35.03±0.27	47.51±0.72	45.61±0.46
6	44.61±0.46	59.36±0.25	67.39±0.84
8	58.16±0.22	74.03±0.27	79.64±0.14
10	70.03±0.27	88.27±0.54	89.03±0.62
15	82.64±0.14	93.04±0.41	92.58±0.84
30	92.16±0.22	92.47±0.62	95.74±0.27
45	95.47±0.33	92.33±0.74	95.68±0.35

Mean (±S.D.) cumulative percent of Ketorolac tromethamine released from formulations at specific time intervals.

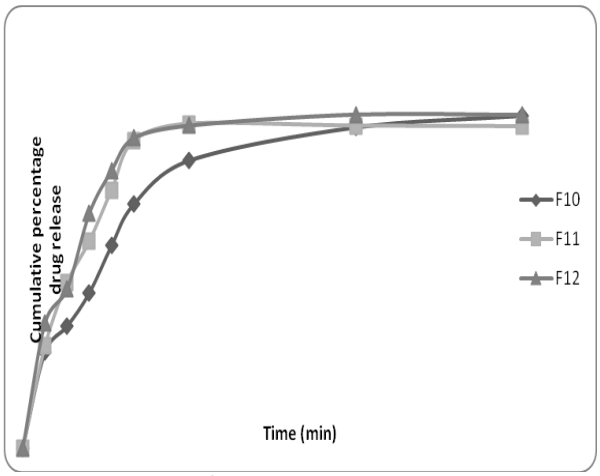

Figure 7: Plot of *in-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of Di-basic Calcium Phosphate.

Table 16: *In-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets, Comparison of F3, F6 and F9 Formulations.

Time (min)	F3	F6	F9
0	0	0	0
2	35.15±0.46	37.3± 0.22	47.56± 0.84
4	42.85±0.22	57.45± 0.54	75.84± 0.22
6	58.79±0.06	82.5±0.45	84.42±0.46
8	69.6±0.04	91.34±0.53	96.56± 0.74
10	83.7±0.29	93.5± 0.68	96.72± 0.45
15	91.6±0.10	93.86± 0.34	96.9± 0.27
30	91.3±0.34	94.97± 0.68	97.01± 0.64
45	91.6±0.56	94.67± 0.23	96.09± 0.35

Mean(±S.D.) cumulative percent of Ketorolac tromethamine released from formulations at specific time intervals

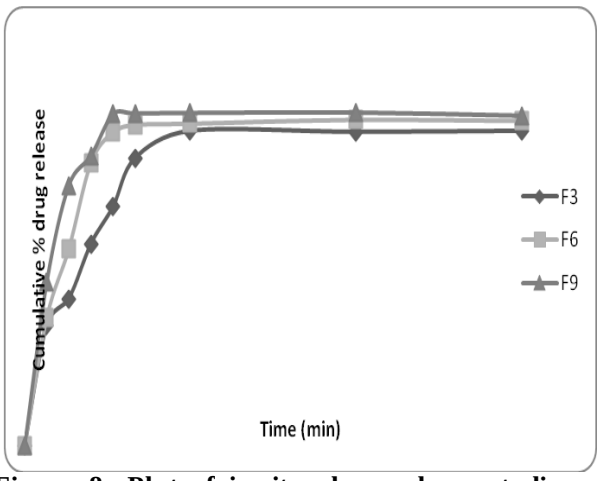

Figure 8: Plot of *in-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets, comparison of 3 different formulations.

***In-vitro* drug release studies of Ketorolac tromethamine oral disintegrating tablets containing different concentrations of super disintegrants are as follows**

The maximum drug release time for the formulations F1, F2 & F3 in which sodium starch glycolate was used were, at 45 min (90.2 ± 0.69), 45 min (92.8 ± 0.72) and 15 min (91.6 ± 0.10) respectively. By increasing the concentration of sodium starch glycolate, the drug release was increased (Table 12).

The maximum drug release time for the formulations F4, F5 & F6 in which Croscarmellose sodium was used were at 15 min (89.86 ± 1.26), 10 min (90.68 ± 0.46) and 8 min (91.34 ± 0.53) respectively (Table 13). From the above observations, 15% of superdisintegrant gave maximum drug release in 8 min.

The maximum drug release time for the formulations F7, F8 & F9 in which Crospovidone was used were at 8 min (91.09 ± 0.29), 8 min (93.46 ± 0.33) and 8 min (96.56± 0.74) respectively. From the above observations, all concentrations of Crospovidone gave better release in

very less time (8 min) and at higher concentration gave maximum drug release (Table 14).

In the formulations F10, F11 & F12 Di-basic calcium phosphate was used as diluent, instead of MCC pH-102. The maximum drug release time for these formulations was at 15min (82.64 ± 0.14), 15min (93.04 ± 0.41), and 15min (92.58 ± 0.84) respectively (Table 15).

The maximum drug release was shown by formulation F9 containing Crospovidone 15% (96.56% drug release in 8 min). When compared to other super disintegrants Crospovidone showed better drug release profile. The order followed is Crospovidone > Croscarmellose > Sodium starch glycolate (Table 16).

When the diluent was changed maximum drug release was within 15 min for Di-basic calcium phosphate (DCP) used formulations. In most of the formulations where microcrystalline cellulose pH 102 was used the maximum drug release was in 10 min.

In all the prepared formulations, formulations containing Crospovidone showed faster release than other super disintegrants used in the study. Crospovidone is a synthetic insoluble, but rapidly swellable, cross-linked polymer. This distinct morphology rapidly wicks solvents into the particle to speedup swelling and enhance disintegration and dissolution of tablets. The particle morphology of Crospovidone provides a highly compressible powder with good flow properties which result in hard & non friable tablets. In addition Crospovidone is non-ionic in nature so they do not form gel and do not retard the disintegration and dissolution processes.

Table 17: Regression coefficient values for Ketorolac tromethamine oral disintegrating tablets containing different disintegrants.

Formulations	First order (Regression coefficient)
F3	0.9633
F6	0.9815
F9	0.9635

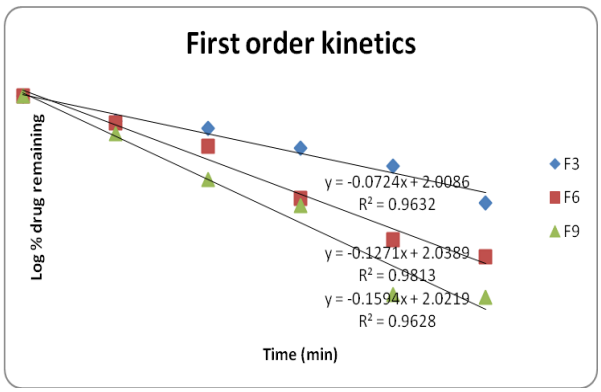

Figure 9: Graph showing first order kinetics for Ketorolac tromethamine oral disintegrating tablets, for formulations F3, F6 & F9.

From all the formulations the three formulations containing different disintegrants (F3, F6 and F9) which showed best drug release profile were chosen and the first order release rate kinetic data for F3, F6 and F9 formulations were calculated and the regression coefficients were determined (Table 17).

Table 18: *In-vivo* disintegration time evaluation test for Ketorolac tromethamine oral disintegrating tablets on human volunteers.

Formulations	*In-vivo* disintegration time (seconds)
F 6	46
F 9	36

Table 19: Evaluation of taste of Ketorolac tromethamine ODT on human volunteers.

Formulations	H1	H2	H3	H4	H5	H6
F6	+	++	++	+	+	+
F9	+	+	++	++	+	+

0 = Sweet, + = Acceptable, ++ = Less bitter taste, +++ = High bitter taste.

The *in-vivo* disintegration time and taste evaluation (palatability) studies were performed on human volunteers for formulations containing Croscarmellose and Crospovidone (F6 & F9). The *in-vivo* disintegration time for the above mentioned formulations was below 1min and were having acceptable taste (Table 18 & 19).The institute's human ethical committee approved the protocol for the study and the protocol number was BBCP/IHEC/2015-9/001.

7.3 : Drug-excipients compatibility studies

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000-400 cm^{-1}. In the optimized formulations, the presence of all the characteristic peaks of the Ketorolac tromethamine indicates lack of any strong interaction between the drug and the excipients which are indicated in figure 11 for formulation F9.

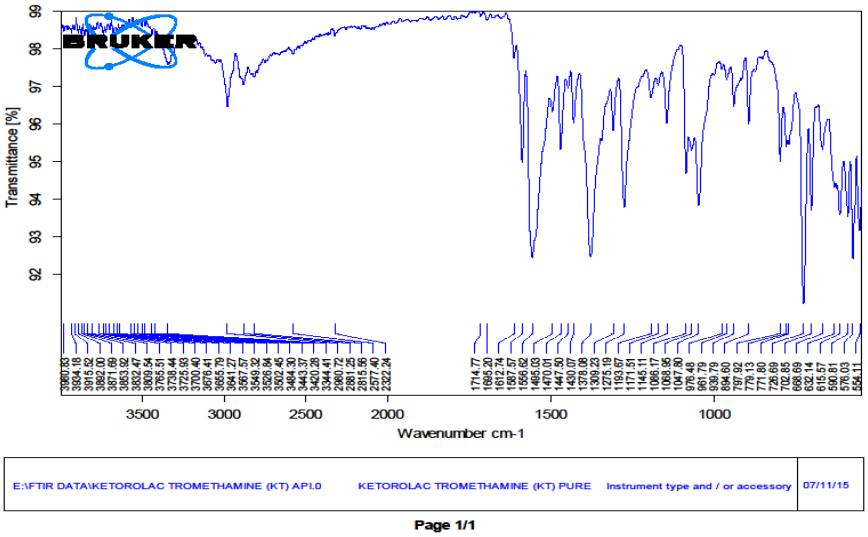

Figure 10: FTIR graph of pure drug Ketorolac tromethamine (KT).

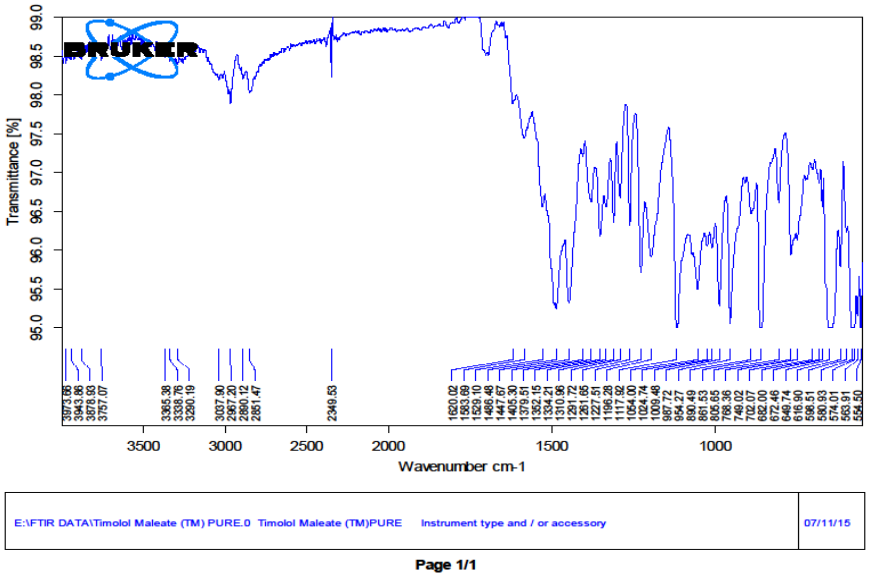

Figure 11: FTIR graph of KT + Crosspovidone.

8. SUMMARY AND CONCLUSION

The objective of present study was to develop oral disintegrating tablets (ODT) of Ketorolac tromethamine by using different disintegrants like sodium starch glycolate, Croscarmellose sodium, Crospovidone. A study on the influence of concentration of disintegrant, the effect of diluents like Microcrystalline cellulose and Di calcium phosphate on the disintegration time and drug release was conducted.

The development was initiated with standard calibration curve using UV spectrophotometric method as it is required for routine analysis of the drug. The UV spectrophotometric method was developed in 7.4 pH phosphate buffer at 320nm. The method showed good linearity in the concentration range of 2 to 20 µg/ml with a correlation coefficient of 0.999.

Oral disintegrating tablets were formulated by using various disintegrants like sodium starch glycolate, Croscarmellose sodium & Crospovidone. The disintegrants were taken in concentrations of 5%, 10%, 15% and microcrystalline cellulose was used as diluent.

The formulation blends showed good flow properties. The tablets were prepared by direct compression method by using 6mm flat punches. The formulated tablets complied with the pharmacopoeial specifications for hardness, friability, weight variation and drug content.

The wetting time & water absorption ratio was determined for all the prepared formulations. As the concentration of the disintegrants increased the wetting time decreased and water absorption ratio increased. The wetting time for F6 & F9 formulations was below one minute.

The *in-vitro* disintegration time was determined for all the formulations. The formulations formulated with 15% of Croscarmellose sodium & Crospovidone (F6 & F9) disintegrated the tablets in very less time.

The *in-vitro* drug release studies were performed on all the formulations. Better release in very less time was shown by all the formulations containing Crospovidone and at higher concentration release was maximum (96.56% in 8 minutes). The order followed is Crospovidone > Croscarmellose sodium > sodium starch glycolate.

For the optimized formulations the diluents were changed with Di calcium phosphate. When Di calcium phosphate was used the maximum drug release was at 15 minutes. In most of the formulations where microcrystalline cellulose pH 102 was used the maximum drug release was in 10 min.

Formulations F6 & F9 which contains 15% of Croscarmellose sodium & Crospovidone respectively along with microcrystalline cellulose showed least *in-vitro* disintegration time i.e., below 30 seconds and more than 90% drug release within 8 minutes. So, for the above formulations even *in-vivo* disintegration time and palatability (mouth feel) studies were carried out on healthy human volunteers. The *in-vivo* disintegration times for the above mentioned formulations was below one minute and were having acceptable taste. Thus F6 & F9 formulations can be stated as optimized formulations among all the prepared formulations in the entire study.

From all the formulations, the three formulations containg different disintegrants, which has given best drug release profile were chosen (F3, F6, F9).

Drug-excipients compatibility studies like FTIR was performed on formulations containing drug and crospovidone. The presence of all the characteristic peaks of the Ketorolac tromethamine in the FTIR graphs indicated lack of any strong interaction between the drug and the excipients. From this it can be interpreted that Ketorolac tromethamine was compatible with excipients used in the study.

Oral disintegrating tablets of Ketorolac tromethamine were developed by using different disintegrants to avert the problem of swallowing and to provide rapid onset of action, which improves patient compliance and quality of life. The results of this study concluded that super disintegrants addition technique was an interesting way of formulating oral disintegrating tablets using direct compression technique which is easy, inexpensive and does not require special production equipment.

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