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Formulation and Evaluation of Mouth Dissolving Tablet of Ketorolac Tromethamine for Pain Management by Using Superdisintegrants

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Abstracts: Mouth dissolving tablet is the fast growing and highly accepted drug delivery system. This study was aimed at development of Ketorolac Tromethamine mouth dissolving tablet, which can disintegrate or dissolve rapidly once placed in the oral cavity. Conventional Ketorolac tromethamine tablet require water to swallow it and have disadvantages like low disintegration rate, low solubility etc.Ketorolac Tromethamine mouth dissolving tables (formulation) consists of super-disintegrate like Ac-Di-Sol, Polyplasdone XL, and Explotab. Fillermicrocrystalline cellulose (MCC), sweetener aspartame, strawberry flavor and menthol for good mouth feel. Tablets of batch F1 (formulation without disintegrants) was compared with batches F2 to F4 (formulation with disintegrants) and comparison between the three superdisintegrants has shown remarkable results.
Key words: Mouth dissolving tablet, Ketorolac tromethamine, Disintegration Time, Wetting Time.

1. Introduction

Mouth dissolving tablets are gaining importance as a potential drug delivery system. This dosage form dissolves and disintegrates in the oral cavity within minutes without need of water or chewing. This formulation is useful in administration of drug in pediatric, geriatric patients[1]. Several approaches have been employed to formulate mouth dissolving tablet which include freeze drying, sublimation, spray drying, addition of disintegrants, and use of sugar base excipients [2]. Most of the marketed mouth dissolving tablets consists of nonsteroidal anti inflammatory drugs e.g. Rofecoxib, Ketotifen, antihypertensive drugs e.g. Atenolol, Metoprolol, antiemetic drugs e.g. Ondansetron, Granisetron.Disintegrants can help to facilitate drug dissolution and subsequently improve bioavailability. A number of disintegrants, known as superdisintegrants like cross linked carboxy methyl cellulose (Ac-Di-Sol), sodium starch glycolate (Explotab), crosspovidone (Polyplasdone XL) markedly improve tablet disintegrantion by swelling and or capillary action, cause tablet to break into fragments. The efficacy of these superdisintegrants in any fast dissolving dosage forms depend on its selection, concentration, method of incorporation, steps used for preparation[3].Ketorolac tromethamine is an effective anti-inflammatory agent that has been extensively used for the prevention of pain and inflammation associated with a wide variety of reasons[4]. It does not require water to swallow and suitable when patient have the uneasy feeling due to pain.

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2. Material and methods

2.1 Materials:

Ketorolac Tromethamine (< 150 µm) was obtained as gift sample from Cadila Pharma, Gujarat. Ac-Di-Sol (NMT 2 % retained # 200, NMT 10 % retained # 325) and Polyplasdone XL (< 400 µm) were obtained from Wockhardt Research Center, Aurangabad. Explotab (46 µm) was obtained as gift sample from JRS Pharma,

USA, Magnesium Stearate and Colloidal silicon dioxide were obtained from S.D. Fine Chemicals, Mumbai.

2.2 Methods:

Characterization of Disintegrate Powder:

Angle of Repose:

The angle of repose [5] was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder heap was measured and angle of repose was calculated using following equation:

$\tan(\theta) = h/r$

Where h and r indicate the height and radius of the powder heap.

Moisture sorption study:

Moisture sorption study[5] was performed using Programmable environmental test chamber (Remi labs, Mumbai).

One gram of disintegrant was taken in a petridish and spread uniformly. Then it was kept in programmable environmental test chamber at 37 ± 1 ^{0}C and 75% and 85% relative humidity for two days. Then calculated moisture sorption by recording weight difference of the sample before and after exposure to programmable environmental test chamber.

Swelling capacity:

Disintegrant (1g) was taken in the measuring cylinder. Then distilled water (10 ml) was poured in it. The measuring cylinder was shacked vigorously for 10 minutes and allowed to stand for 24 hrs at 37 ± 1 ^{0}C. Swelling capacity[5] was expressed as percentage and calculated using following equation,

Swelling capacity = (Xv/Xi) 100

Where Xv: Final volume occupied by swollen material after 24 hrs.

Xi: Initial volume occupied by powder in measuring cylinder.

Hydration Capacity (H. C.):

Disintegrant (1g) was taken in the 15 ml tarred centrifuge tube. Then 10 ml of distilled water was added to it and allowed to centrifuge for 10 minutes. After the centrifugation process the tarred centrifuge tube was taken out and inverted to remove the supernent. The decanted tube then weighed on digital balance (Shimadzu) and the hydration capacity [5] was calculated using following equation,

H. C. = weight of hydrate sample/ weight of dry sample

Density:

The loose bulk density (LBD) [6] and tapped bulk density (TBD) of disintegrant were determined. Disintegrant (2g) was poured into calibrated measuring cylinder (10 ml) then noted initial volume. Then the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5 cm at 2 seconds intervals. The tapping was the continued no further change in volume was noted. LBD and TBD were calculated using following equation,

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility:

The compressibility index (Carr's Index) [6] was determined by using following equation,

Carr's Index (%) = [(TBD- LBD) × 100] / TBD

2.3 Preparation of tablets:

Ketorolac tromethamine, microcrystalline carboxymethyl cellulose (MCC) and Aspartame were mixed with disintegrant for 15 minutes in porcelain mortar then passed through sieve # 60. This blend then mixed with Strawberry flavour, Menthol, colloidal silicon dioxide and magnesium stearate for 5 minutes. Then directly compressed by using 7 mm round flat faced punch of rotary tablet machine (Karnavati, India). Compressed force was kept constant for all formulations. The magnesium stearate level was fixed at 1% w/w for all formulation. Disintegrants were used at 4% w/w in tablets.

2.4 Evaluation of tablet characteristics:

Weight Variation, Drug Content, Friability, Hardness and Thickness:

Tablet weight variation, thickness, and friability were measured using the USP methods and criteria. Drug content was analyzed using a UV spectrophotometer (Shimadzu, UV-1700) at λ_{max} 322 nm in methanol and tablet friability was measured using the friability tester (Roche friabilator). Thickness was measured using the vernier caliper. Hardness was measured using the Monsanto hardness tester. Weight, drug content, hardness and thickness of tablets were represented as mean ± SD.

Disintegration test:

Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in distilled water using USP disintegration apparatus. The mean ± SD of 6 tablets were calculated.

Dissolution test:

Dissolution test of Ketorolac Tromethamine tablets was performed using distilled water with USP dissolution apparatus II at 50 rpm and 37 ± 1 ^{0}C temperature. Test sample (5 ml) was withdrawn at particular time interval (1, 2, 5, 10, 15, 29, 30 minutes) and replaced with fresh dissolution medium (distilled water) maintained at 37 ± 1 ^{0}C. The samples then filtered (membrane filter, 0.45μm) and analyzed using a UV spectrophotometer at λ_{max} 322 nm. This test was performed on 3 tablets and mean ± SD calculated.

Wetting time:
The double folded absorbent paper was kept in a petridish and thoroughly wetted with distilled water. The excess distilled water was drained out of the petridish. Then tablet was placed at the center of the wet paper. The time required for the distilled water to diffuse from the absorbent paper throughout entire tablet was recorded using a stopwatch. This test was performed in triplicate and mean ± SD calculated (n = 3).

Maximal water uptake capacity:
Modified method and apparatus used for the water uptake study [8]. The apparatus consists of a sample holder and a liquid holding vessel (petridish) that is set on the electronic digital balance (Shimadzu). When tablet was placed onto sample holder, distilled water was then passively withdrawn in to the tablet. The loss of the weight from the liquid holder was read from the digital balance. All result was reported as mean ± SD (n = 3).

3. Result and discussion

Particle size is one of the factors that affect disintegration activity. A larger particle size and hence increased porosity leads to a faster wicking and swelling of disintegrants [9]. Larger particle size probably yielded greater pore size and altered the shape of the pore. Larger particles of disintegrants swelled more rapidly and to a greater extent than the smaller particles. As Ac-Di-Sol has spherical particle shape and larger size it has taken less time for disintegration of the tablet than other superdisintegrants containing tablet.
Polyplasdone XL has smaller particle size than Ac-Di-Sol so have less disintegration efficiency than Ac-Di-Sol. Explotab have the smaller particle size than Ac-Di-Sol as well as higher hydration capacity, which decreases its disintegration efficiency. Powder properties like compressibility index, angle of repose, loss on drying, LBD, TBD, and moisture absorption capacity represented in Table I. LBD of disintegrate was found to be Polyplasdone XL> Ac-Di-Sol > Explotab indicates more porous structure of Polyplasdone XL thus have faster wicking action. Swelling and hydration capacity of disintegrate are the important parameters for comparing disintegration efficiency represented in Table III. Higher swelling and hydration capacity of Ac-Di-Sol leads to faster disintegration of batch F2 (10.5±0.3 seconds). Higher swelling and hydration capacity of Explotab did not lead to faster disintegration than Ac-Di-Sol as Explotab consist of starch which for gel consistency on hydration. Ac-Di-Sol has less swelling capacity than other two but found to be faster disintegrating because the capillary action of Ac-Di-Sol is responsible for its fast tablet disintegration. All tablet properties shown in Table V. Using distilled water showed that Ac-Di-Sol was found to be best among all disintegrants used performed disintegration and dissolution test of all batches. Cumulative percent drug release verses time plot of all batches shown in Fig. 3. Wetting time of all batches shown in Table V. Faster wetting occur for tablets in batch F3 containing Polyplasdone XL due to capillary action. Wetting time of tablets was found in decreasing order as Ac-Di-Sol > Polyplasdone XL> Explotab. The wetting time study of tablets shown in Fig.4 and Fig. 5. Maximal water uptake of all batches shown in Table V. Higher water uptake leads to faster disintegration and dissolution of tablets. Drug release of tablets containing Ac-Di-Sol is faster (F2, F3, and F4) than tablets containing Polyplasdone XL (F5, F6, F7) and Explotab (F8, F9, F10). Explotab forms gel after hydration so prolong complete drug release time. Increased quantity of MCC (from F2 to F10) decreases disintegration process due to decreased swelling capacity and porosity.

4. Conclusion

Mouth dissolving tablets from batch F2 showed best result compare to other formulations. It showed complete drug release in two minutes. This indicates that this formulation is ideal for quick drug delivery and onset of action in painful conditions. Ac-Di-Sol was found to be more effective super-disintegrates among all used in formulation development. It is due to its high swelling capacity and hydration capacity. The comparative efficiency of used super-disintegrates can be shown in decreasing order as Ac-Di-Sol > Polyplasdone XL> Explotab. Ac-Di-Sol is superior to other used super-disintegrates in all aspects. Increased quantity of MCC decreases disintegration process due to decreased swelling capacity and porosity.

Table 1: Particle Size Distribution of super disintegrate

Size (mesh)	Ac-Di-Sol	Polyplasdone XL	Explotab
	Weight (%)		
20/40	0	0	0
40/60	1.3	1.2	0.6
60/100	6.4	4.6	1.6
100 pass	92.3	94.2	98.4

Table 2: Super-Disintegrates Powder Properties

Disintegrants	Angle of repose (^{o})	LBD (g/ml)	TBD (g/ml)	Compressibility Index (%)	Loss On drying (%)	Moisture absorption uptake at 75%RH (%)	Moisture absorption uptake at 85%RH (%)
Ac-Di-Sol	41.8	0.528	0.817	35.37	8.8	0. 085	0.12
Polyplasdone XL	28.65	0.212	0.272	22.05	4.6	0.026	0.098
Explotab	20.67	0.755	0.945	20.10	6.1	0.223	1.09

Table 3: Super-Disintegrates Powder Properties

Disintegrants	Swelling capacity (%)	Hydration capacity (g water/g polymer)
Ac-Di-Sol	702.38± 8.2	9.12 ± 0.05
Polyplasdone XL	214.67± 10.5	5.45± 0.02
Explotab	615.13± 15.4	8.95± 0.3

* **All values are Mean ± SD (n=3)**

Table 4: Composition of the Ketorolac Tromethamine single tablet

Ingredient (mg)	Formulation Batches									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ketorolac Tromethamine	10	10	10	10	10	10	10	10	10	10
Ac-Di-Sol	-	5	5	5	-	-	-	-	-	-
Polyplasdone XL	-	-	-	-	5	5	5	-	-	-
Explotab	-	-	-	-	-	-	-	5	5	5
MCC (Avicel PH 102)	80	72	82	92	72	82	92	72	82	92
Aspartame	20	20	20	20	20	20	20	20	20	20
Strawberry flavor	1	1	1	1	1	1	1	1	1	1
Menthol	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	113	110	120	130	110	120	130	110	120	130

Table 5: Tablet Properties

Batch	Weight* (mg)	Thick-ness* (mm)	Hard ness* (Kg/cm^2)	D.T.* (sec)	Friability (%)	Drug content* (%)	Wetting time* (sec)	Max.water uptake * (mg/tablet)
F1	112.6 ±0.4	3.0±0.7	3±0	460.9±0.8	0.0945	101.2± 1.3	70.1±0.7	190±0.76
F2	109.8 ±0.3	3.0±0.4	2±0	10.5±0.3	0.8422	101.1± 2.6	47.6±0.8	295.1±0.5
F3	118.9 ±0.9	3.1±0.4	3±0	19.7±0.5	0.721	101.4± 1.4	54.4±0.6	313±0.67
F4	129.3 ±0.6	3.2±0.9	3±0	26.4±0.4	0.705	99.4± 1.5	65.5±0.9	321±0.65
F5	110.2 ±0.14	3.0±0.4	2±0	20.8±0.8	0.6653	99.3± 0.7	52.7±0.57	236.7±0.7
F6	118.7 ±0.7	3.1±0.3	3±0	28.8±0.6	0.5612	99.9± 0.5	61±0.64	241±0.6
F7	130.3 ±0.12	3.2±0.7	3±0	39.3±0.3	0.3879	101.2± 1.3	69±0.41	259±0.2
F8	110.2 ±0.4	3.0±0.1	2±0	40.7±0.6	0.3745	101.1± 2.6	57.3±0.6	239±0.61
F9	119.5 ±0.41	3.1±0.4	3±0	48.9±0.7	0.1940	101.4± 1.4	65±0.40	242.9±0.5
F10	129.6 ±0.5	3.2±0.1	3±0	57.5±0.8	0.0845	99.4± 1.5	69±0.77	256±0.66

* **All values are Mean ± SD (n=10)**

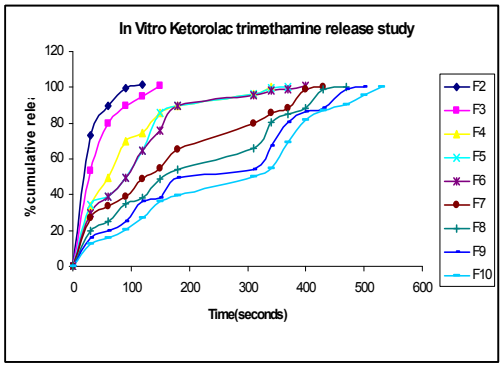

Fig.1

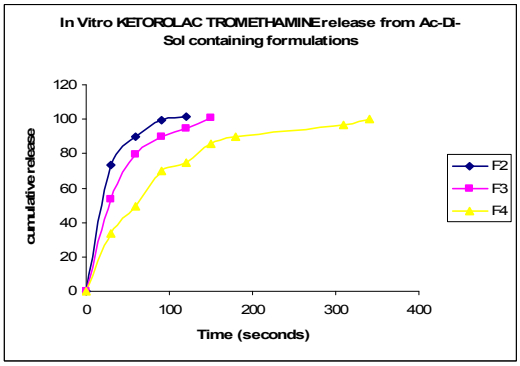

Fig.2

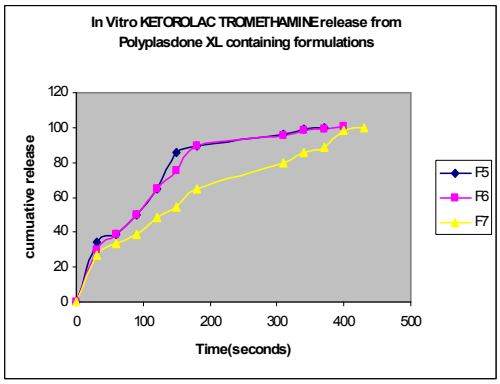

Fig.3

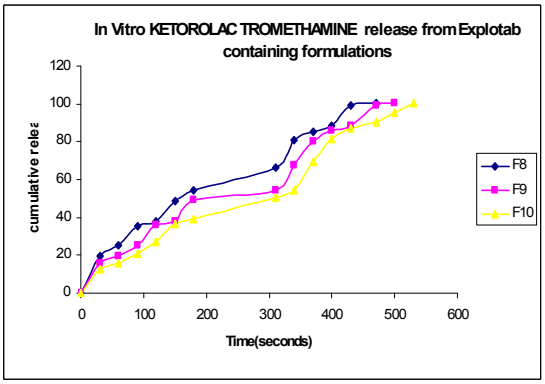

Fig.4

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