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FORMULATION AND EVALUATION OF ETODOLAC MOUTH DISSOLVING TABLETS

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ABSTRACT

Etodolac has been shown to have potent analgesic and anti-inflammatory activities similar to indomethacin and diclofenac and due to its preferential Cox-2 blockade; it has a better safety than conventional Non steroidal anti-inflammatory drug (NSAIDs) with respect to adverse effect on gastrointestinal and cardiovascular systems. Etodolac is superior to other NSAIDs as it has selectivity for Cox-2, a beneficial Cox inhibitor is well tolerated, has better Gastrointestinal (GI) tolerability and improved cardiovascular safety when compared with other selective Cox-2 inhibitor. To provide the patient with the most convenient mode of administration, there is need to develop a fast-disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without water, anywhere, any time. Such tablets are also called as "melt in mouth tablet." Direct compression, freeze drying, sublimation, spray drying, tablet molding, disintegrant addition and use of sugar-based excipients are technologies available for mouth-dissolving tablet. Mouth-dissolving tablets of Etodolac were prepared with direct compression, in which different formulations were prepared with varying concentration of excipients. These tablets were evaluated for their friability, hardness, wetting time and disintegration time; the drug release profile was studied in buffer Phosphate Saline. F6 batch with crosprovidone with mannitol showed more release than other formulations and better results. The F6 batch of mouth dissolving tablets was found to be 98% drug release in 30 minutes. The F6 was the best of all nine formulations of mouth dissolving tablets of etodolac. Bioavailability of etodolac can be increased by formulating it as a mouth dissolving tablets.

Key words: Etodolac, Crospovidone, Sodium Starch Glycolate, Cross Carmellose Sodium, Mannitol, Mouth dissolving tablets.

INTRODUCTION

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with the prescription which results in noncompliance and ineffective therapy. Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration to achieve better patient compliance. Rapidly disintegrating tablet are appreciated by significant segment of the population, particularly pediatric, geriatric, unconscious, and bed-ridden patients who have difficulty swallowing conventional tablet and capsule [1,2]. To overcome this, dispersible tablets and fast-disintegrating tablets have been developed. Most commonly used methods to prepare these tablets are freeze drying/lyophilization, tablet moulding and direct compression methods. Lyophilized tablets show a porous structure, which causes very quick penetration of saliva into the pores when placed in oral cavity, but it has disadvantage of high cost production process.

Conventional etodolac tablet available in the market are not suitable for acute pain and inflammatory conditions where quick onset of action of drug is required. This is because of poor patient compliance, particularly by the geriatric and pediatrics patient who experience difficulty in swallowing and by those who are bed ridden or who are traveling and do not have an easy access to water. Etodolac is superior than other NSAIDs as it has selectivity for Cox-2, a beneficial Cox inhibitor, well-tolerated, better GI tolerability and improved cardiovascular safety to other selective Cox-2 inhibitors. It also shows increased matrix component synthesis and protection of chondrocytes against apoptosis. Etodolac has a faster and more potent effect than the other NSAIDs. Etodolac has a faster and more potent effect than the other

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NSAIDs. It efficiently interferes with neutrophils adhesion to endothelium and this effect may represent an additional relevant mechanism in its anti-inflammatory activity. Etodolac has an outstanding anti-inflammatory profile, involving a classical inhibition of prostaglandins E_2, a decrease in the expression of several cytokines including interleukin and tumor necrosis factor. It also inhibits activated oxygen species production and influences cell adhesion. It is mainly used for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, dental pain, postoperative pain, post-traumatic pain, low back pain and gynecological pain. Thus, it can be concluded that Etodolac may be a better option for the management of pain [3,4].

The rapidly disintegrating tablets in oral cavity can be swallowed with a small amount of water or saliva. The tablet manufactured by any of the above mention methods are composed of drug and other excipients which disintegrate in small amount of water or saliva in the oral cavity within seconds. Hence, an attempt was made to improve the dissolution of Etodolac through the formulation of mouth-dissolving tablets with appropriate mechanical strength, which would disintegrate in oral cavity and would provide an immediate relief from pain due to its faster dissolution in gastrointestinal tract.

MATERIALS AND METHODS

Etodolac, mannitol, avicel ph101, sodium starch glycolate, cross povidone, croscarmellose sodium, talc, magnesium stearate

Preparation and Evaluation of Tablets

Nine formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) of Etodolac fast dissolving tablets are prepared at varying concentrations of superdisintegrants are formulated. Sodium starch glycolate, Crospovidone and Croscarmellose sodium are choose as superdisintegrants. Direct compression method is choosing for formulation.

Etodolac, microcrystalline cellulose, Mannitol are taken in the mortar and mixed thoroughly. After mixing pass all the ingredients into 40#.Other excipients aspartame, magnesium stearte were added and mix for 10 minutes than sifted through #40 mesh. Tablets are prepared by fixing the tablet machine and compress the granules using Rotary press tablet compression machine as per the SOP. Prepared tablets were evaluated [5-7].

Evaluation of Tablets

Compressed tablets were then evaluated for hardness, wetting time, disintegration, friability, and drug content. Hardness was measured by Monsanto type hardness tester. One tablet was placed in each tube of disintegration apparatus (model DT-2D scientific), and the test was carried out using distilled water as a disintegrating media at 37±2°C. Friability was determined in friabilator (Roche friabilator) by taking ten tablets [8,9]. For drug content analysis, a tablet contained 100 mg of aceclofenac, was pulverized and taken into a 100 ml volumetric flask, and dissolved in 100 ml of methanol. One milliliter of the filtrate was diluted to obtain the concentration of solution 50 mg/ml, and assayed for drug content using a double-beam UV/Vis spectrophotometer (Shimadzu 1700) at 276 nm. All the dispersions contained 95±5% of the drug.

In-Vitro Dissolution Study

The dissolution study of tablet was conducted using USP dissolution apparatus II in 900 ml of PBS pH 7.4 maintained at 37 ± 0.5°C at a speed of 50 rpm.[10] One milliliter of samples was withdrawn at time intervals of 5, 10, 15, 20, 30, 60, and 90 minutes, filtered through a 0.45µ membrane filter, diluted, and assayed at 276 nm, using a UV/Vis double-beam spectrophotometer. The volume of dissolution fluid was adjusted to 900 ml by replacing each 1 ml aliquot withdrawn with 1 ml of PBS pH 7.4. The cumulative % release of etodolac in tablet sample was determined by using standard curve [10,11].

RESULTS AND DISCUSSION

In the preformulation study, Etodolac was characterized for bulk, tapped density and angle of repose. Results of the compressibility index, Hauser's ratio and angle of repose show that the all material has sufficient compressibility and flow properties.

Table 1. Precompression Properties

F	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's Ratio	Carr's index	Angle of repose (^{0})
F_1	0.312± 0.14	0.400± 0.14	1.28± 0.11	22 ± 2.32	29º.06'±0.04
F_2	0.326± 0.11	0.442± 0.33	1.35 ±0.63	18± 0.11	27º.67'± 0.11
F_3	0.322 ± 0.63	0.450± 0.04	1.39±0.36	28±0.36	26º.85'± 0.24
F_4	0.294± 0.33	0.312± 0.11	1.06± 0.14	5± 0.04	27º.78' ±0.63
F_5	0.303 ± 2.32	0.322±0.36	1.06± 0.33	5.9± 0.33	26º.08'±'0.36
F_6	0.310± 0.04	0.333 ± 2.32	1.07 ±0.63	6± 0.24	25º.08'± 0.14
F_7	0.290 ± 0.63	0.320± 0.11	1.10± 0.14	9± 0.14	28º.67'± 0.11
F_8	0.285± 0.11	0.326 ± 0.63	1.0 ± 2.32	12.5±0.24	27º.55' ±0.63
F_9	0.306±0.36	0.357± 0.14	1.16± 0.11	14.2±0.63	27º.08±'0.36

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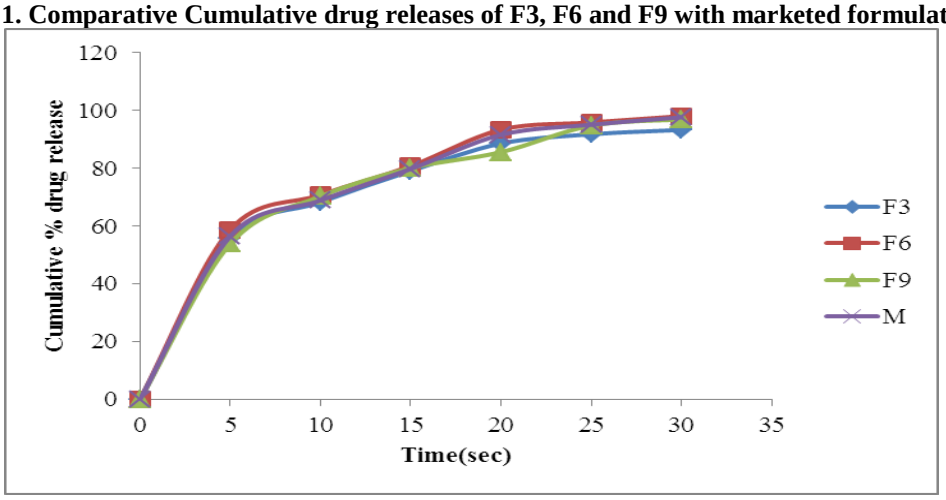
Table 2. Post Compression Studies

F	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)
F_1	249.1 ± 0.12	2.65±0.02	3.3± 0.12	0.61± 0.06	65± 0.54
F_2	248.8 ±1.12	2.78±0.01	3.4± 0.21	0.58± 0.12	58 ± 0.02
F_3	247.3 ± 0.54	2.74±0.01	3.7± 0.23	0.52± 0.11	37± 0.14
F_4	248.2 ± 0.63	2.68±0.02	3.1± 0.08	0.45± 0.04	34± 0.25
F_5	247.6 ± 0.87	2.72±0.01	4.1± 0.14	0.59± 0.12	39± 0.14
F_6	247.2 ± 0.36	2.73±0.02	3.5± 0.18	0.68± 0.02	25 ± 0.01
F7	247.6 ± 0.74	2.72±0.03	4.3± 0.22	0.42± 0.04	50 ± 0.36
F8	248.3 ± 0.52	2.73±0.01	3.1± 0.18	0.54± 0.08	45 ± 0.14
F9	248.5 ± 0.14	2.71±0.01	2.7± 0.16	0.63± 0.12	37 ± 0.14

Fig 1. Comparative Cumulative drug releases of F3, F6 and F9 with marketed formulation



All the formulated (F1 to F9) tablets were passed weight variation test as the % weight variation was within the IP limits of ±7.5% of the weight. The average thickness of the all formulation was found to be 2.71mm. The hardness of the tablet was found to be 3.1 to 4.3 Kg/cm^2. The maximum drug content for the all formulation was found to be 100.51% and minimum % drug content from the all formulation was found to be 97.14%. The results were within the limit specified by the IP.

In vitro Disintegration time was found to be in the range 25 to 65 sec. From all formulations, F6 (10 % CP) has minimum disintegration time. Formulations containing sodium starch glycolate has taken more time for disintegration because of its gelling properties. All the 9 formulations were subjected to in vitro dissolution studies by using 6.8 phosphate buffers. Dissolution data shows that formulation F6 shows improved dissolution as compared to other formulations.

CONCLUSION

The study and results revealed that the method of preparation of formulation significantly affect the disintegration time, percentage friability and release of drug. Present study underlines the importance of process variables. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

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