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Original Research

Formulation, Development and Evaluation of Colon-specific Ketorolac Tromethamine Compression Coated Tablets

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Abstract

The major intention to formulate and develop colon targeted tablets is to improve the therapeutic efficacy by increasing therapeutic drug concentrations in colon. The present study was aimed to develop guar gum compression coated tablets ketorolac tromethamine to achieve the colon-specific drug release. In this study, both core and compression coated tablets were prepared by direct compression method. The prepared colon targeted tablets were characterized for different pre-compression and post-compression evaluations. *In vitro* drug release studies were performed by using USP XXIV Type II dissolution apparatus in simulated gastrointestinal fluids. From the *in vitro* dissolution studies, the formulation F4 showed 4.72±0.76% drug release in 5 h and it was progressively increased to 99.12±0.42% in 24 h that indicates retardation of drug release in stomach and small intestine and significant amount of drug release was observed in colonic environment. The accelerated stability studies proved the stability of guar gum compression coated tablets. From the above results, achievement of colon specific drug release might be due to substantial integrity of the compression coated guar gum in the upper gastrointestinal tract, but microbial degradation in the colon. In conclusion, development of microbial degradation compression coated tablets was suitable to target the ketorolac tromethamine to colon. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies.

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INTRODUCTION

Progressive development of new formulations of previously marketed drugs using current formulation technologies is the latest trend in pharmaceutical industries to overcome high expenses and longer duration requirement in the new drug development (Vemula and Veerareddy, 2013). Formulation of colon-targeted/colon-specific tablets is one of the examples for above that enhance the therapeutic efficacy by rising colonic drug concentrations (Vincent and Suman, 2002). Development of colon-specific medication is useful to treat local disorders of colon as well as to improve the delivery of proteins and peptides (Vemula *et al*., 2014a). Colon targeting can achieve by employing the principles like prodrug approach, pH-sensitive drug delivery, time-dependent delivery systems, and microbial degradation methods (Vemula and Veerareddy, 2009). Among the above, microbial degradation system is the most widespread and successful strategy to design the colon targeted formulations, which is fit to retard the drug release in initial lag period (stomach and small intestine) and gives complete drug release in sustained manner within the colon (Sinha and Kumaria, 2002).

Ketorolac Tromethamine (KTM), classified as non steroidal anti-inflammatory drug (NSAID) used to treat colonic inflammation and pain, but leads to gastric ulceration due to frequent intake KTM (Brahmankar *et al*., 1996). As a result the, development of colonic delivery of KTM is to overcome its adverse symptoms and to achieve high local drug concentration in the colon. Hence it is decided to develop a microbial degraded guar gum compression coated tablets of KTM for colon specific delivery in the present study, not only to retard the release of the drug in the upper gastro intestinal tract (GIT) and also to give slow and complete drug release in colon. Some of the recent research examples reported in literature on KTM colon-specific tablets are Formulation and pharmacokinetics of colon-specific double-compression coated pulsatile mini-tablets of ketorolac tromethamine (Vemula, 2015a), Colon-specific double-compression coated pulsatile tablets of ketorolac tromethamine (Vemula and Katkum 2015a), time-dependent ketorolac tromethamine-sodium alginate compression coated tablets (Vemula *et al*., 2014), time-dependent ketorolac tromethamine compression coated tablets using HPMC (Vemula and Veerareddy, 2013),

eudragit coated ketorolac tromethamine-hydroxypropyl methylcellulose pH and time-dependent matrix tablets (Vemula and Veerareddy, 2012) etc.

Guar gum (GG), a natural polymer classified as galactomannan polysaccharide form *Cyamopsis tetragonolobus* (Sinha and Kumaria, 2001). GG is widely used polymer to develop the colon-specific drug delivery systems and some of the research examples for GG colon targeted formulations are ketorolac tromethamine (Vemula and Katkum 2015b), flurbiprofen (Vemula and Bontha, 2013), tamoxifen (Randhawa *et al*., 2012), 5-amino-salicylic acid (Ji *et al*., 2008; Krishnaiah *et al*., 1998), trimetazidine dihydrochloride (Krishnaiah *et al*., 2002) and mebendazole (Krishnaiah *et al*., 2001). The objective of the study was to formulate KTM-GG colon targeted compression coated tablets.

MATERIALS AND METHODS

Materials

Ketorolac Tromethamine was gift sample from Bright Labs, Hyderabad, India. Guar gum and HPMC K4M were gift samples from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Preparation of Core and Compression Coated Tablets

Direct compression method was employed to prepare the KTM core and compression coated tablets using Avicel PH 102 as diluent (Vemula, 2015b). Accurately weighed quantity of KTM and excipients other than glidant and lubricant passed through 60 mesh sieve and mixed in a poly sack for 5-10 min. Then the obtained blend was lubricated with talc and magnesium stearate for 5 min and compressed into tablets with 6 mm round flat punches using 8 station rotary tabletting machine. The amount of KTM present in each tablet was 20 mg and the final weight was acclimated to 80 mg (Table 1). Then the core tablets were compression coated with different compositions of coats given in Table 2 using the procedure given in Veerareddy & Vemula, 2012 with 8 mm round, flat and plain punches.

Table 1: Composition and characterization of KTM core tablets

Ingredients	Quantity (mg)
Ketorolac tromethamine	20
Avicel PH 102	53
Crosspovidone	4
Talc	1
Magnesium stearate	2
Core weight	80

Table 2: Composition of KTM colon specific compression coated tablets

Formulation Code*	KTM Core Tablet (mg)	Guar Gum (mg)	Total tablet weight (mg)
F1	80	25	280
F2	80	50	280
F3	80	75	280
F4	80	100	280
F5	80	120	280

***** Each compression coat formulation contains 1% Magnesium stearate, 2% Talc and Avicel PH 102 to make up the compression coat weight to 200 mg.

Estimation of Tablet Physical Parameters

The prepared tablets were assessed for weight variation, hardness, friability and for drug content. To compute the weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (Shimadzu, Japan) and determined the average weight and deviation. The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was calculated on ten tablets in a Roche friabilator (Electrolab, India). Drug content uniformity was estimated by randomly picked ten tablets and taken the drug powder equivalent to 100 mg by crushing the selected tablets to prepare the drug solution and finally analyzed for at 322 nm (Vemula, 2015c).

In vitro dissolution study

In vitro dissolution study was conducted using USP XXIV Type I dissolution apparatus (Electro lab, TDT-08L) at 50 rpm rotation speed and 37±0.5°C temperature. To mimic the gastrointestinal environment, dissolution test was performed in different dissolution media. Initially, the drug release was carried out for 2 h in simulated gastric fluid (SGF, pH 1.2), then in enzyme-free simulated intestinal fluid (SIF, pH 6.8) for 3 h, the average small intestinal transit time and finally in simulated colonic fluid (SCF) i.e., pH 6.8 phosphate buffer containing 4% w/v of rat caecal contents up to 24 h to simulate colonic environment. At pre-determined time intervals, 5 ml samples were withdrawn, filtered and analyzed at 322 nm using UV-Visible spectrophotometer. Then using the above dissolution data, calculated the mean dissolution time (MDT), T10% and T80% (time in hours to take 10% and 80% drug release) to explain the colon-specific drug release from prepared KTM-GG compression-coated tablets (Talukder and Fassihi, 2008; Vemula and Veerareddy, 2013).

Stability studies

Stability studies were designed to assess the stability of KTM in compression coated tablets using ICH guidelines. Three replicates of formulation F4 tablets were sealed in aluminum coated inside with polyethylene pack and stored at 40±2 ^{o}C and 75±5% RH in the humidity chamber for six months (Chaudhary *et al*., 2011). Collected samples after six months of storage were evaluated for the drug content and *in vitro* dissolution rate (Mathews, 1999). Then similarity factor was calculated between dissolution rates of optimized tablets before and after storage. At this point, the data was statistically analyzed using paired *t*-test to test the significance of difference at level of significance 0.05 (Vemula and Katkum, 2014).

RESULTS AND DISCUSSION

Estimation of Tablet Physical Parameters

Various physical parameters of prepared tablets were determined. In these, the weight variation of the tablets was found in the range of 279.25±2.96 - 281.34±3.18 mg and all the formulation tablets were fell within the pharmacopoeial limit i.e., average weight±5%. The thickness (2.97±0.04 mm) and diameter (8.03±0.02 mm) of the tablets were found to be uniform in all formulations. The hardness of the tablets was found as 5.93±0.28 - 6.04±0.13 kg/cm^2. The percentage friability for all formulations was underneath 1% i.e. 0.24% - 0.36%, demonstrating that the friability is inside as far as possible. The tablets were found to contain 100.14±1.56 - 98.25±1.38% of the labeled amount indicating uniformity

of drug content. All the tablet formulations were complied with pharmacopoeial standards, so all the tablets were with worthy physical attributes. In weight variation test, the pharmacopoeial limit for tablets is not more than 5% of the average weight. The average percentage deviation of all tablet formulations was discovered to be inside as far as possible and henceforth all formulations passed the uniformity of weight as per the official requirements of Indian Pharmacopoeia, (1996). From the physical characterization, all the tablet formulations were uniform in hardness, friability and drug content uniformity.

***In vitro* Dissolution Study**

Figure 1 demonstrated the release profiles of KTM from the compression coated tablets containing different levels of GG (F1-F5) and it was found to vary from 4.61±0.12 to 98.72±0.36% after 5 h of testing in simulated gastric and intestinal fluids and the percent drug release was progressively improved after 5 h and it was found to be 78.56±0.21 to 99.12±0.42% in 24 h testing in simulated colonic fluid. From the consequences of *in vitro* drug release studies thinks about, the cumulative mean percent of KTM discharged from compression coated tablets containing shifting measures of GG (25 mg, 50 mg, 75 mg, 100 mg & 125 mg), joining of 100 mg of polymer in the aggregate tablet weight (F4) was discovered to be satisfactory to define a tablet with great respectability and acceptable *in vitro* drug release i.e., 4.72±0.76% drug release in 5 h and it was continuously expanded to 99.92±0.42% in 24 h.

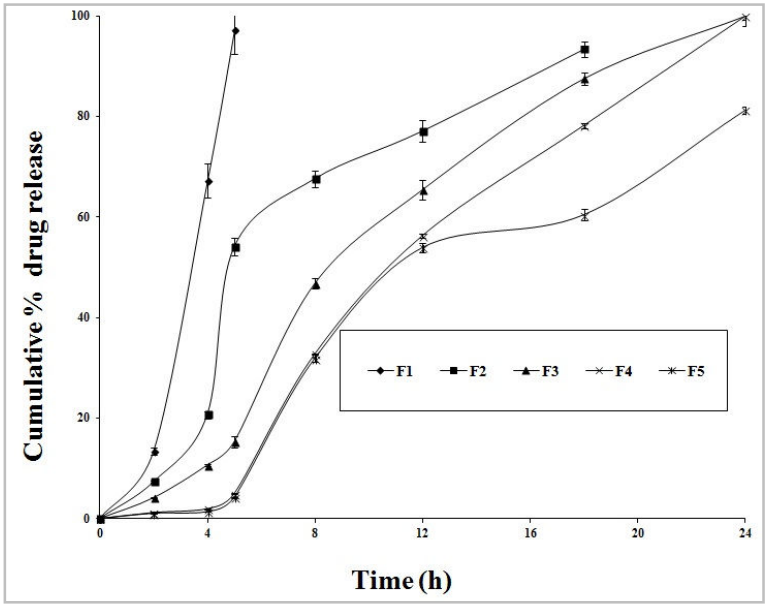

Figure 1: Release profile of KTM from GG compression coated tablets (n=3)

Optimization of compression coat weight was done to gain the significant protection in upper GIT and suitable dissolution profiles in colon by formulating the compression coated tablets with distinctive GG coat weights. By comparing the drug release profiles of above formulations, 200 mg coat weight was found as the suitable compression coat weight. Then drug release studies were carried out for F1-F5 formulations containing distinctive GG weight, and the results demonstrated that 100 mg of GG in 200 mg of compression coat was proved as best among others. Similar type of results was observed in flurbiprofen guar gum compression coated tablets conducted by Vemula and Bontha, (2013) that signifies the potential utility of GG as colon-specific polymer. But in comparison to other reported study by Krishnaiah *et al*. (1998), 125 mg of GG in the coat weight of 175 mg for indomethacine was showed similar type of results.

In the present study, dissolution studies of F1-F5 formulations demonstrate the impact of GG amount on KTM release from the prepared compression coated tablets and this study showed negligible drug release (5%) in the upper GIT environment and dynamic drug release was observed in the colon environment with 100 mg of GG (F4 formulation). From these results, the formulation F4 considered as the best formulation that demonstrated 4.72±0.76% drug release in the initial lag period (5 h) followed by 99.92±0.42% drug release for 24 h in a slow manner. Formulations with higher than 100 mg of GG gave minimum drug release in the initial lag time, but failed to complete the drug release in 24 h. By giving importance to mechanical strength of tablets, 5% HPMC K4M was incorporated in compression coat to magnify the mechanical strength because GG alone failed to give sufficient mechanical strength due to its low compressibility. Comparable kind of perceptions was seen in piroxicam guar gum compression coated tablets formulated by Veerareddy and Manthri, (2010).

The MDT values were found to be 2.41-13.92 h. The T10% and T80% values of optimized formulation (F4) was found to be 5.8 h and 17.9 h respectively (Figure 2). From the dissolution data, the computed mean dissolution time was increased as increasing the concentration of GG demonstrate the sustained release capacity of polymer and the time in hours to take 10% and 80% drug release (T10% and T80%) were able to illustrate the capability of GG as colon specific polymer. The above calculated parameters demonstrated that the F4 formulation compression coated tablets gave not only 5 h lag time to reach colon but also gave the complete drug release in colon in slow manner in contrast to other formulations.

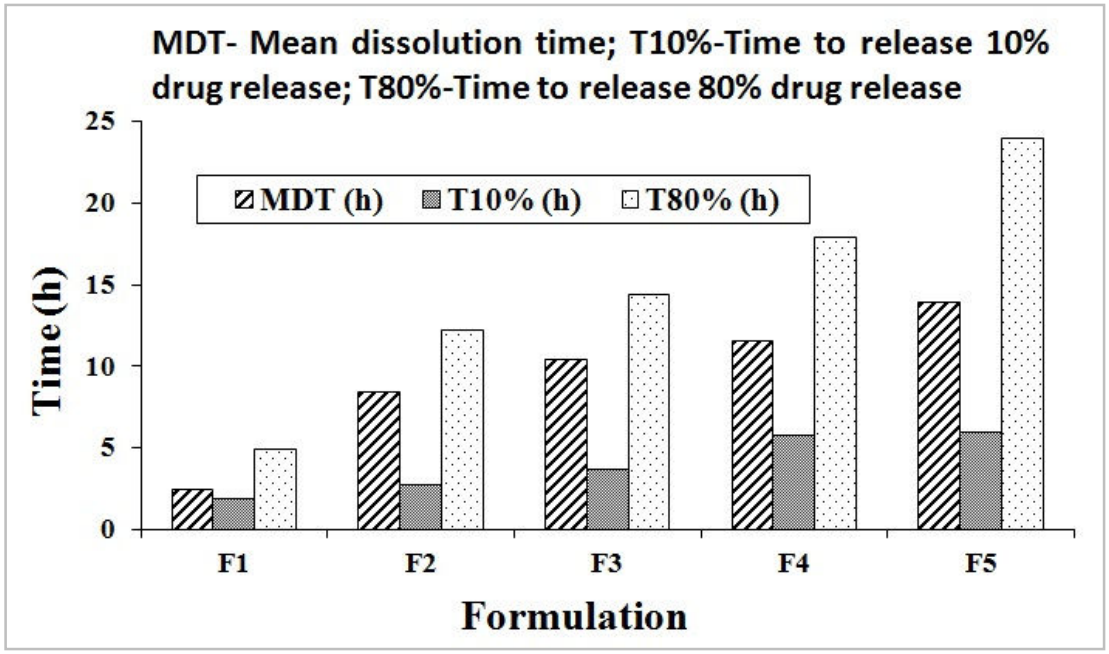

Figure 2: Drug release parameters of KTM-GG compression coated tablets

Stability Studies

Stability studies were performed at 40±2°C and 75±5% RH for six months for selected F4 tablets. After storage of six months, the tablets were evaluated to assay and dissolution studies (Figure 3). The stability studies data of F4 formulation revealed that there was no significant change in drug content and dissolution rate of tablets before and after storage. The similarity index value was found as 83.42, which is more than 50 indicates similarity between the dissolution profile before and after storage. From the statistical analysis there was no significant difference between before and after storage (p<0.05).

From the above results, F4 formulation was considered as the best formulation that gave less than 5% drug release in 5 h and it was progressively increased to 100 % in 24 h, which demonstrates just a little measure of medication was discharged in stomach and small intestine, and a measurable quantity of drug was released in colonic environment with the help of microbial degradation of GG. From all these perceptions it was inferred that the colon targeted GG compression coated tablets were indicated immaterial KTM release in stomach and small intestine, yet released promisingly in colon.

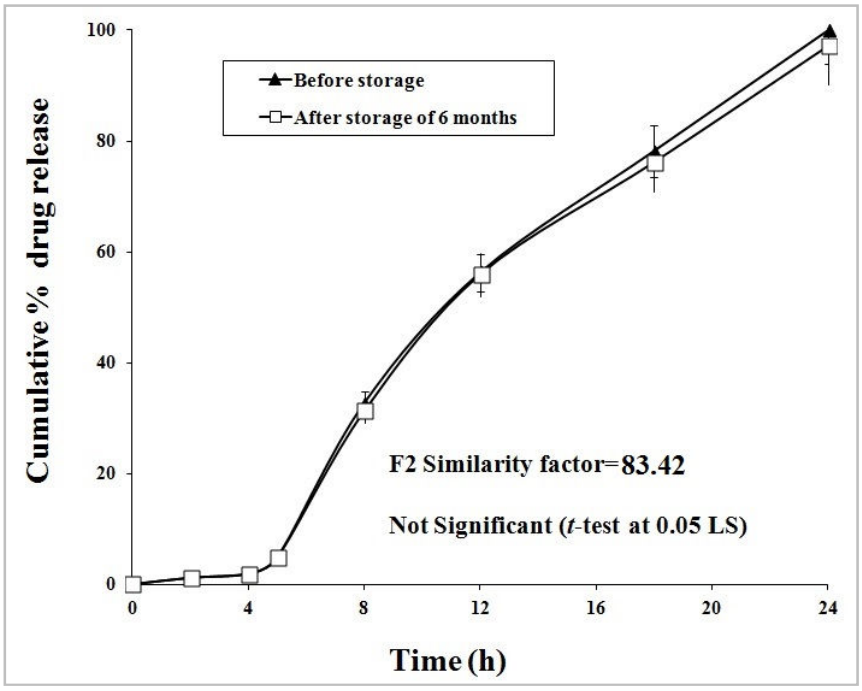

Figure 3: Effect of stability studies on the release profile of KTM from GG colon targeted compression coated tablet F4 (n=3)

CONCLUSION

In the present study, considerable effort was put to formulate and develop the successful colon-specific system of KTM using guar gum compression coated tablets to generate the colon specific drug release without loss in the stomach and small intestine. From the *in vitro* drug release studies, F4 formulation showed significant amount of drug release in the colon with minimum release in lag period of 5h with proved stability of drug in GG compression coat. The stability studies data of F4 formulation revealed that there was no significant change in drug content and dissolution rate of tablets before and after storage. The similarity index value was found as 83.42, which is more than 50 indicates similarity between the dissolution profile before and after storage. In conclusion, development of GG compression coated tablets using microbial dependent strategy is an appropriate approach for colon targeting of KTM.

Conflict of Interest

Conflict of interest none declared.

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