

Research Article

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Formulation and Pharmacokinetics of Ketorolac Tromethamine Floating Compression Coated Mini-Tablets

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Abstract

Present research is intended to develop the Ketorolac Tromethamine (KTM) effervescent floating mini-tablets using compression coating method. Mini-tablets have the advantages of both tablets and multiparticulate formulations such as pellets. The main principle of floating mini-tablets can be applied to decrease the irritant effect of KTM on the stomach by avoiding the direct contact with the gastric mucosa and obtaining a low dosage for prolonged periods. KTM mini-tablets were prepared using 4 mm round flat punches and compression coated with hydroxypropyl methylcellulose and effervescent mixture. The prepared tablets were evaluated for weight variation, thickness, friability, hardness, drug content, *in vitro* buoyancy and *in vitro* release and the best formulation was subjected to further *in vivo* examination. The prepared mini-tablets exhibited satisfactory physicochemical characteristics. Formulation F3 offered the best controlled drug release (99.46 ± 0.93% in 12 h and T80%=9.4 h) along with floating lag time <30 s and total floating time >12 h. Pharmacokinetic studies of F3 formulation in male albino rabbits showed 2.25-fold higher bioavailability and 1.35-fold higher C_{max} compared to immediate release core mini-tablets. Hence development of KTM effervescent compression-coated floating mini-tablets is the best way to give through oral route to maximize the therapy.

Keywords: Bioavailability; Compression-coating; Floating lag time; Floating mini-tablets; Pharmacokinetic studies

Introduction

Control and prolongation of gastric residence time is one of the key strategies to improve the absorption and bioavailability for dosage forms which remain in the stomach for a longer period of time. Gastroretentive drug delivery systems are such dosage forms that can reside in the gastric region for several hours. Extended gastric retention enhances bioavailability and improves solubility for drugs that are less soluble in high pH environment [1]. One of the simplest approaches to achieve the gastro retention is formulation of Floating Drug Delivery Systems (FDDS). FDDS are low density systems that include different effervescent components for floatation and some cellulose derivatives for controlled/sustained release. When FDDS come in contact with gastric content, carbon dioxide is released and is entrapped in the hydrocolloids which make the dosage forms to float and the drug is released slowly [2].

Multiple-unit systems (pellets or mini-tablets) act as prominent floating systems that avoid all or nothing emptying, less chance of localized mucosal damage. They also offer high predictable drug release kinetics and able to administrate as different release profile layers [3,4]. Development of mini-tablets is a significant alternative to pellets and other multiple-unit systems that show the following advantages like ease of manufacturing, packaging, storage and minimum scalability problems. Mini-tablets also exhibits equal dimensions and weight with smooth regular surface in a reproducible and continuous way unlike pellets [5]. Some of the research examples on mini-tablets of various delivery systems are flurbiprofen [6], ketorolac tromethamine [5], levofloxacin [7], theophylline [8], furosemide [9], ibuprofen [10] and diclofenac sodium [11].

Ketorolac Tromethamine (KTM) is a potent non-steroidal antiinflammatory drug with short biological half-life (4-6 h) and it is mainly absorbed in the proximal part of the small intestine [12]. KTM is 800 times more potent than aspirin and produces strongly analgesic and moderate anti-inflammatory activity [13]. The main principle of floating beads can be applied to decrease the irritant effect of KTM on the stomach by avoiding the direct contact with the gastric mucosa and obtaining a low dosage for prolonged periods [14,15]. The aim of the present work is to prepare KTM floating mini-tablets using hydroxypropyl methylcellulose (HPMC K15M) to control the drug release and sodium bicarbonate as a gas forming agent.

Materials and Methods

Materials

KTM was obtained from KP labs, Hyderabad, India. HPMC K15M belongs to Finar Chemicals Ltd, India. All other materials and solvents used were of analytical grade, purchased from SD Fine Chemicals India. Preparation of floating compression coated mini-tablets KTM core mini-tablets were prepared using wet granulation method. Accurately weighed amount of KTM and excipients other than glidant and lubricant passed through 60# sieve and mixed in a poly bag for 5-10 min. The obtained uniform blend was converted in to granules using 10% starch paste, lubricated after drying and sieving and compressed into tablets on 8 station rotary tabletting machine using 4 mm round flat punches at 10 rpm speed at 3000 kg compression force. Each minitablet contains 20 mg drug and final weight was adjusted to 60 mg (Table 1). Then the core tablets were compression coated with different compositions of coats given in using the procedure given in Veerareddy

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and Vemula, 2012 with 8 mm round, flat and plain punches at 5000 kg compression force [16].

Determination of tabletting parameters

To certify the tablet uniformity and mechanical integrity, the prepared tablets were evaluated for weight variation, hardness, friability and drug content. Using the standard procedures, the above parameters were determined [17]. Drug content uniformity was assessed by estimation of drug content in randomly picked ten tablets (drug powder equivalent to 100 mg in 100 ml of 0.1 N HCl buffer) at λ_{max} of 322 nm using UV-Visible spectrophotometry. Floating lag time and total floating time were determined using the procedure described by Rosa et al. [18]. The tablets were also evaluated for the swelling behaviour by calculating the percentage swelling index using the standard procedure described by Tadros [19].

In vitro dissolution studies

In vitro dissolution studies were conducted using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L) in 0.1 N HCl solution at 50 rpm speed and $37 \pm 0.5^{\circ}$ C temperature. 2 ml samples were collected (n=6) and restored the same level of fresh pre- warmed media at scheduled time intervals for 24 h, filtered through 0.45 µm membranes (Millipore, USA) and analyzed by HPLC method [12,17]. Then the dissolution data was interpreted to zero order, first order and Higuchi models and Koresmeyer–Peppas model [20] to elucidate the drug release mechanism. Also calculated the mean dissolution time, dissolution efficiency [21], T50% and T80% (time in hours to take 50% and 80% drug release) from above data to explain the drug release pattern.

Stability studies

Stability studies were conducted for F3 floating tablets using ICH guidelines i.e., stored at $40 \pm 2^{\circ}$ C and $75 \pm 5\%$ RH in the humidity chamber for six months [22]. Then the collected samples were determined for assay and *in vitro* dissolution rate and statistically analysed using paired t-test at 0.05 significance level [23]. Then the similarity factor (f2) was calculated between dissolution rates of F3 tablets before and after storage Similarity factor is calculated to show the similarity between best formulation dissolution profile before and

Ingredients	Quantity (mg)		
КТМ	20		
Avicel PH 102	35.2		
Crosspovidone	3		
Starch paste (10%)	Q.S [•]		
Talc	1.2		
Magnesium stearate	0.6		
Core weight	60		

^{*}Q.S: Quantity Sufficient

Table 1: Composition of KTM core mini-tablets.

after storage. If similarity factor value will be above 50, it indicates the similarity and if less than 50 they are non-similar.

F2= 50 × log {[1 + (1/n) Σ t=1n (R_t-T_t)2]-0.5 × 100}

In vivo pharmacokinetics-study design

In vivo pharmacokinetics studies were conducted in albino male rabbits weighing 2 kg after obtaining approval from the Institutional Animal Ethical Committee (IAEC/VCP/2015/6/2). The present study was designed to compare the KTM compression coated floating tablets with immediate release core mini-tablets using a two-way crossover design with 2 weeks of washout period. Male albino rabbits were divided into two groups (n=6), in which group I animals were treated with immediate release core mini-tablets (20 mg dose) and group II with compression coated floating mini-tablets of same dose in the first phase whereas vice versa in second phase of study. Blood samples (0.5 ml) were collected from marginal ear vein at 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 h post oral dose in EDTA coated Eppendorf tubes. Plasma was separated by centrifuging at 4000 rpm for 15 min and stored at -20° C until analysis.

HPLC analysis of KTM in plasma

Plasma concentrations of KTM from above samples were determined by HPLC method adopted from Vemula et al. [12,17] with slight modifications. To 1 ml of plasma sample 1 ml of acetonitrile was added and centrifuged for 10 min at 3000 rpm and the supernatant liquid was separated and filtered through 0.2 m filter and 20 ml was injected in to the system. The analysis was carried out using Shimadzu HPLC (Shimadzu Corporation, Japan) equipped with C18 column and UV detector. The mobile phase consisted of acetonitrile and water (1:1). The eluents were examined at wavelength of 319 nm at a flow rate of 0.8 ml/min.

Pharmacokinetic analysis

Required pharmacokinetic parameters were calculated using Kinetica software (Kinetica 2000 version 3.0, InnaPhase Corporation, 2000). Peak plasma concentration (C_{max}) and the time to reach peak plasma levels (T_{max}) were attained directly from the time versus plasma concentration graph, the area under the curve (AUC) and the Area under First Moment Curve (AUMC) were estimated by trapezoidal rule and calculated the Mean Residence Time (MRT) and relative bioavailability [24]. Above pharmacokinetic parameters of both immediate release and floating tablets were subjected to statistical analyses using Analysis of Variance (ANOVA) and the difference less than the probability level 0.05 was considered statistically significant. *In vitro* cumulative percent of drug release of F3 tablets was compared against the cumulative AUC values of the same to demonstrate the *in vitro-in vivo* correlation (IVIVC) (Table 2).

Formulation code*	Core tablet (mg)	HPMC K15M (mg)	Sodium bicarbonate (mg)	Citric acid (mg)	Total tab weight (mg)	
F1	60	15	30	15	180	
F2	60	30	30	15	180	
F3	60	45	30	15	180	
F4	60	60	30	15	180	
F5	60	75	30	15	180	

Core tablet thickness=1.72 ± 0.01 mm; Tablet thickness after compression coating=2.51 ± 0.02 mm; Total coating thickness on core tablet is 0.79 mm (2.51-1.72=0.79)

Each compression coat formulation contains 1% Magnesium stearate, 2% Talc and Avicel PH 102 to make up the compression coat weight **Table 2:** Composition of KTM floating compression coated mini-tablets. Citation: Vemula SK, Venisetty RK, Veerareddy PR (2017) Formulation and Pharmacokinetics of Ketorolac Tromethamine Floating Compression Coated Mini-Tablets. J Bioequiv Availab 9: 493-498. doi: 10.4172/jbb.1000351

Results

Evaluation of floating compression coated mini-tablets

Table 3 showed all the evaluated physical parameters of prepared floating tablets. All the tablets were found to be uniform in the weight variation and drug content. The hardness and friability of tablets were found to be around 5 kg/cm² and below 0.5% respectively. The prepared floating tablets demonstrated adequate buoyancy ability and floated for more than 12 h in the dissolution medium. The floating lag time is found to be 26-37 sec, which is influenced by amount of effervescent mixture and the concentration of HPMC. From the swelling studies, the percentage water uptake of the floating tablets was found in the range of 78-116% (Table 4). F5 tablets have shown maximum swelling index due to high concentration of HPMC K15M.

In vitro dissolution studies

In the preliminary studies, the ratio of effervescent mixture was optimized to give floating ability to tablets within 1 min and for more than 12 h (not shown in the manuscript). Among the different viscosity grades of HPMC, K15M was selected as sustained release polymer and the concentrations were selected in a way to avoid the adverse effect on floating ability. Figure 1 explains the drug release pattern from F1 to F5 formulations and Figure 2 shows the comparison between F3 floating compression coated mini-tablets and immediate release core mini-tablets. Among the all formulations, F3 formulation was selected as the best formulation based on the drug release and floating property and used for further *in vivo* studies. By applying various release order kinetics to dissolution data, all the tablet formulations were shown zero order release with non-fickian diffusion, super case-II. Other model independent parameters derived from dissolution data, such as DE, MDT, T50% and T80% values were calculated and they revealed that the drug release was in a sustained manner (Table 5).

Stability studies

Stability studies results of F3 floating compression coated minitablets were given in Table 6. These studies revealed that the *in vitro* dissolution profile and drug assay have not shown any significant difference (P<0.05) between before and after storage of the same formulation. The similarity factor (f2) was found to be 85.54 between dissolution profiles of F3 tablets before and after storage of 6 months.

Formulation	Weight variation ^{**} (mg)	Hardness [*] (kg/cm ²)	Friability (%)	Drug content [*] (%)
F1	180.32 ± 2.45	5.1 ± 0.56	0.42	99.92 ± 1.26
F2	181.04 ± 2.78	4.9 ± 0.48	0.52	99.43 ± 1.41
F3	180.32 ± 2.92	5.0 ± 0.71	0.46	100.01 ± 1.32
F4	179.95 ± 2.81	4.9 ± 0.64	0.49	99.71 ± 1.64
F5	181.12 ± 2.74	5.1 ± 0.82	0.44	100.38 ± 1.57

*Data represents mean ± SD (n=3); **Data represents mean ± SD (n=20)

Table 3: Tabletting parameters of KTM floating compression coated mini-tablets.

Formulation	Floating lag time (s)	Total floating time (h)	Swelling index
F1	26	17.4	78
F2	29	16.3	82
F3	28	13.9	96
F4	34	12.1	109
F5	37	11.2	116

Table 4: Evaluation of KTM floating compression coated mini-tablets.





Formulation Code	Zero order (R ²)	First order (R ²)	Higuchi (R ²)	Koresmeyer & Peppas (R ²)	Peppas (n)	MDT (h)	DE (%)	T50% (h)	T80% (h)
F1	0.982	0.832	0.968	0.927	0.62	1.44	63.12	1.1	2.6
F2	0.987	0.851	0.963	0.936	0.67	3.19	59.15	2.8	5.8
F3	0.989	0.834	0.972	0.931	0.71	4.70	60.48	4.4	7.8
F4	0.971	0.853	0.968	0.921	0.64	4.85	53.47	5.2	9.4
F5	0.982	0.812	0.970	0.924	0.69	6.10	36.56	7.7	12.6

R²: Correlation coefficient; n: Diffusional exponent; MDT: Mean Dissolution Time; DE: Dissolution Efficiency; T50%: Time to release 50% drug release; T80%: Time to release 80% drug release





Figure 3: Time versus mean plasma concentration profiles of KTM following the oral administration of floating compression coated mini-tablets F3 and immediate release core mini-tablets (n=12).

Time (h)	Before storage	After 6 months	<i>t</i> -test at 0.05 LS	Similarity Factor (f ₂)
0	0.00 ± 0.00	0.00 ± 0.00	Not Significant	85.54
0.5	7.82 ± 0.42	7.14 ± 0.51]	
1	17.15 ± 0.67	16.43 ± 0.32		
2	31.54 ± 0.98	30.26 ± 0.48]	
4	46.39 ± 0.45	44.92 ± 0.56]	
6	62.98 ± 0.86	61.54 ± 0.87		
8	81.34 ± 0.82	79.81 ± 0.91]	
12	99.46 ± 0.93	98.06 ± 0.78		
% Assay	100.01 ± 1.32	99.61 ± 1.53	Not Significant	-

Table 6: Stability studies of KTM floating compression coated mini-tablets F3.

Pharmacokinetics in healthy volunteers

All the useful and possible pharmacokinetic parameters were determined for F3 floating tablets in comparison to immediate release core mini-tablets. KTM plasma concentrations comparison between immediate release and floating tablets were shown in Figure 3. All the calculated mean pharmacokinetic parameters were given in Table 7.

In vitro-in vivo correlation (IVIVC)

IVIVC was carried out for F3 floating tablets using *in vitro* cumulative percent drug release (X-axis) and cumulative AUC obtained after oral administration (Y-axis). From the obtained graph, correlation coefficient (r2) was found to be 0.9302 that indicates the good correlation between the *in vitro* and *in vivo* parameters (Figure 4).

Parameters	F3 Floating tablets	Immediate release tablets	P<0.05	
C max (ng/ml)	4566.23 ± 28.17	3396.47 ± 25.83	0.05	
T max (h)	8.00 ± 0.01	2.00 ± 0.01	0.05	
AUC _{0-*} (ng-h/ml)	43028.91 ± 71.58	19194.07 ± 62.34	0.05	
MRT (h)	8.83 ± 0.02	4.86 ± 0.02	0.05	
Relative bioavailability: AUC of F3 tab/AUC of Conventional tab=2.242				

 Table 7: Pharmacokinetics of KTM floating compression coated mini-tablets and immediate release core mini-tablets.



Discussion

Formulation of floating tablets with acceptable tabletting properties and desired prolonged release without adverse effect on floating ability is a big challenge to the formulation scientists. In the present study, an attempt was made to solve this problem by compression coating of mini-tablets. The prepared floating mini-tablets were characterized for different physical properties such as weight variation, hardness friability and drug content to check the compliance with pharmacopoeial standards and they were found to be uniform. Evaluation of weight variation and drug content indicates the uniformity in drug dose and total tablet weight and determination of hardness and friability denotes the tablets strength and mechanical integrity.

Besides the above tabletting parameters, the floating tablets were also evaluated for floating lag time, total floating time and % swelling index. Floating lag time and total floating time depend highly on the amount of effervescent mixture incorporated in the tablet. 30 mg of sodium bicarbonate is optimized to give make the tablets float in less than 40 sec. It was clearly observed that the increase in the concentration of HPMC K15M, the floating lag time was increased. Similar type of results in floating behaviour was observed in clarithromycin floating tablets using various grades of HPMC [25]. Among the all formulations, F5 formulation was shown maximum swelling index due to high concentration of HPMC K15M. Similar type of results in swelling index was observed in a study developed by Pawar et al. [26].

From the preliminary studies, the suitable HPMC grade for compression coating was selected. Different formulations were prepared and evaluated for drug release using various grades of HPMC and from the dissolution studies, HPMC K15M was selected as the compression coating polymer to provide the desirable prolonged drug release. The swelling index of HPMC K15M was showed higher value than lower grades but less than K100M. Among the different HPMC viscosity grades, HPMC K15M was superior in the swelling, compressibility and mechanical integrity. Similar type or results were observed with ketorolac tromethamine colon targeted compression coated tablets developed by Vemula and Veerareddy [17].

After the *in vitro* dissolution studies and floating studies of preliminary formulations, final ratio of core mini-tablets and sodium bicarbonate was set to 2:1. This set of composition was shown not only optimized floatation but also the desired sustained drug release that depends on HPMC concentration. From the *in vitro* dissolution studies of F1 to F5 formulations, as the HPMC K15M increased, the more sustained release was observed due to increase in swelling index. In the present study, the F3 formulation is incorporated with 30 mg of HPMC K15M was able to produce 99.46 \pm 0.93 % drug release in 12 h with significant floating capacity. Hence F3 formulation was considered as the best formulation and used for further evaluations in this study.

The results of different kinetic models revealed that they followed zero order release as it was shown high correlation coefficient values. The n values from Peppas model indicated supercase-II transport. Results of DE, MDT, T50% and T80% were revealed that the drug release was in a sustained manner as the HPMC K15M concentration was increased. From the stability studies, after storage of six months, F3 tablets were shown no significant difference in drug release behaviour before and after storage. The similarity factor (f2) was found to be 85.54 between dissolution profiles of F3 tablets before and after storage.

Possible pharmacokinetic parameters were estimated for F3 floating compression coated mini-tablets and compared with immediate release core mini-tablets. Above results were shown in Table 7 and when observed those results, it is clear indication that the change in C_{max} and shift in T_{max} are the evidence of sustained drug release of F3 tablets. This may be due to fast disintegration, dissolution and absorption of KTM from core mini-tablets, but due to presence of HPMC K15M, F3 floating tablets were shown prolonged drug release. The AUC value of F3 floating tablets was the indication of 2.25-fold increase in bioavailability when compared to immediate release core mini-tablets. MRT value indicating long resident time of floating compression coated tablets. Applying of statistical analysis to above pharmacokinetic parameters was revealed that there was a significant difference in the C_{max}, T_{max}, AUC and MRT. IVIVC results signified the good correlation between in vitro and in vivo parameters. Hence, development of floating compression coated mini-tablets is a suitable approach to enhance the bioavailability and reduce the irritant effect on stomach of KTM (Supplementary Files 1 and 2).

Conclusion

This research was planned to design and develop the floating tablets using compression coating of HPMC K 15M and effervescent mixture on the KTM core mini-tablets. Incorporation of 30 mg of sodium bicarbonate was able to float the prepared compression coated mini-tablets for 12 h. From the various evaluation tests, F3 formulation was considered as the best formulation to give the desired prolonged drug release. Calculated pharmacokinetic parameters were proved the increase in bioavailability of F3 tablets in comparison to core mini-tablets.

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