



Statistical design and optimization of ketorolac tromethamine gastroretentive multiparticulate delivery system

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ABSTRACT

The aim of the present research is to design and optimize floating multiparticulate drug delivery system of Ketorolac tromethamine (KT) so as to reduce its irritant effect on the gastric mucosa. Extrusion and spheronization process were used to prepare a drug-containing core pellets. A 3 level 2 experimental factor design was used to examine the effect of the amount of Eudragit RS 100, effervescent agent (NaHCO₃: HPMC K4M) on floating lag time and drug release in 6 h. Fourier Transform Infra-Red (FTIR) spectrum, physical characterization, particle size distribution analysis, scanning electron microscopy, floating studies and in vitro drug release studies of prepared floating pellets were evaluated. The study reveals the significant effect of the amount of Eudragit RS 100 and NaHCO₃: HPMC K4M on floating lag time and drug release. The optimized batch showed floating lag time of 3.2 min and 95.15% average drug release in 6 hours. 80–95% of pellets remained floating for up to 6 h. All the batches showed excellent flow properties having an angle of repose in the range 29.85±0.2° to 21.60±0.5°, Carr's index and Hausner's ratio in the range of 14.49±0.26% to 7.54±0.32% and 1.08±0.04 to 1.16±0.7 respectively. The sustained release gastroretentive floating pellets of Ketorolac tromethamine were obtained and could be effectively used in the delivery of drug with less irritant effect on the gastric mucosa.



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INTRODUCTION

The gastro-retentive dosage form can prolong and control the gastric residence time by allowing the drugs to reside in the gastric region for several hours. Various approaches have been reported to retain the formulation in the upper part of gas-

tro intestinal tract (GIT) such as swelling systems, high-density systems, magnetic systems, mucoadhesive systems and floating systems (Aj, 1993). Among all the gastroretentive systems, due to minimum affect on GIT motility, floating drug delivery systems (FDDS) are considered suitable and preferable (Kotreka and Adeyeye, 2011; Reddy and Murthy, 2002; Strusi et al., 2008). These systems are particularly useful for drugs having absorption in upper GIT, drugs which are unstable in the intestine and exhibits poor solubility in intestinal pH (Singh, 2000). FDDS are a low-density system, which allows them to remain buoyant over gastric content for a prolonged period of time (Badve et al., 2007). Based upon the mechanism of buoyancy effervescent systems are the widely employed technique used in the development of FDDS. In the effervescent systems, carbon dioxide gas liberation occurs upon contact with gastric fluid due to neutralization reac-

tion which lowers the density and allows the system to remain buoyant (Ichikawa *et al.*, 1991). A wide range of single-unit and multiparticulate FDDS were designed and developed, the multiparticulate FDDS were preferred over single-unit system due to minimum inter and intra subject variabilities in drug absorption and lower possibility of dose dumping (Bulgarelli *et al.*, 2000; Iannuccelli *et al.*, 1998; Streubel *et al.*, 2003).

Ketorolac tromethamine (KT) an pyrrolizine carboxylic acid derivative is a non-Steroidal anti-inflammatory drug (Etman *et al.*, 2008). KT is used for the short-term management of moderate acute severe pain and post-operative pain. It is having short plasma half-life 2.5 h with multiple dosing in a day (Sinha *et al.*, 2009). However, it suffers with the drawback of producing an irritant effect to the stomach mucous membrane. In addition, due to its weak acidic nature, it gets preferentially absorbed from the upper portion of the GIT. Hence, the concept of floating pellets could be employed to reduce the irritant effect of KT on the stomach by avoiding its direct contact with the gastric mucosa. In addition, the formulation of floating KT pellets would allow sustained drug release into the upper part of the GIT and reduces the need of multiple dosing.

Hence, the objective of present research work is to design and optimize floating multiparticulate drug delivery system of KT based on effervescent technique so as to reduce its irritant effect on gastric mucosa and to obtain sustain drug release. The drug-containing core pellets were prepared by extrusion and spheronization process. The sustained release floating pellets was prepared using Eudragit RS 100 as release retardant, sodium bicarbonate (NaHCO₃) and hydroxylpropyl methyl cellulose K4M (HPMC K4M) as gas former and matrix polymer respectively. The effect of the amount of effervescent agent and polymer coating level on floating and drug release behaviour were studied and optimized using, a 3-level, 2-factor, factorial design.

MATERIALS AND METHODS

Materials

Ketorolac Tromethamine obtained as a gift sample from Wockhardt Limited, Aurangabad India. Eudragit RS100 was provided by Evonik, Mumbai, India. The other chemicals were used are of analytical grade.

Method of Preparation of Ketorolac-Tromethamine Pellets

Extrusion and spheronization

The KT core pellets were prepared by extrusion

and spheronization process using wet granulation method. Microcrystalline cellulose used as spheronizing aid, polyvinylpyrrolidone K30 (PVP K30) as a binder, NaHCO₃ and HPMC K4M as gas former and matrix polymer respectively. Powder mixture of KT, microcrystalline cellulose, NaHCO₃ and HPMC K4M was mixed in mortar for 20 min. This was followed by the addition of binding liquid consisting of 10% PVP K30 in water. The obtained wet mass was passed through BSS sieve no.16 to get the extrudates. The prepared extrudates were transferred to spheronizer (Shakti Pharmatech, Ahmedabad, India) and spheronized at 950 rpm for 15 min to form pellets. The prepared core pellets are dried overnight at room temperature.

Coating of Ketorolac Tromethamine pellets

The Ketorolac tromethamine pellets further coated with Eudragit RS100 using fluidized bed processor (ACG, Miniquest-F, Mumbai, India), to obtain weight gain of 5% w/w, 10% w/w and 15% w/w. The coating solution was obtained by dissolving the required amount of Eudragit RS100 in isopropyl alcohol and stirred to form a clear solution. The coating process parameters were: batch size, 10 g; inlet temperature, 45 °C; product temperature, 38 °C; air flow, 0.8–1.0 bar; spray pressure, 0.5–0.9 bar; spray rate, 0.130 g/min and final drying at 40 °C for 10 min.

Experimental Design

A 3² factorial design was employed to optimize the level of variables in the KT floating pellets preparation. The ratio of NaHCO₃: HPMC K4M (X1), Eudragit RS 100 (X2) were selected as independent variables and floating lag time (Y1) and drug release in 6 h. were the dependent variables (Y2). Shown in (Table 1). The statistical analysis and optimization was carried out by Design-expert[®] software 11. The formulation batches prepared was indicated in (Table 2).

Evaluation of Ketorolac tromethamine Floating Pellets

Spectroscopic Studies

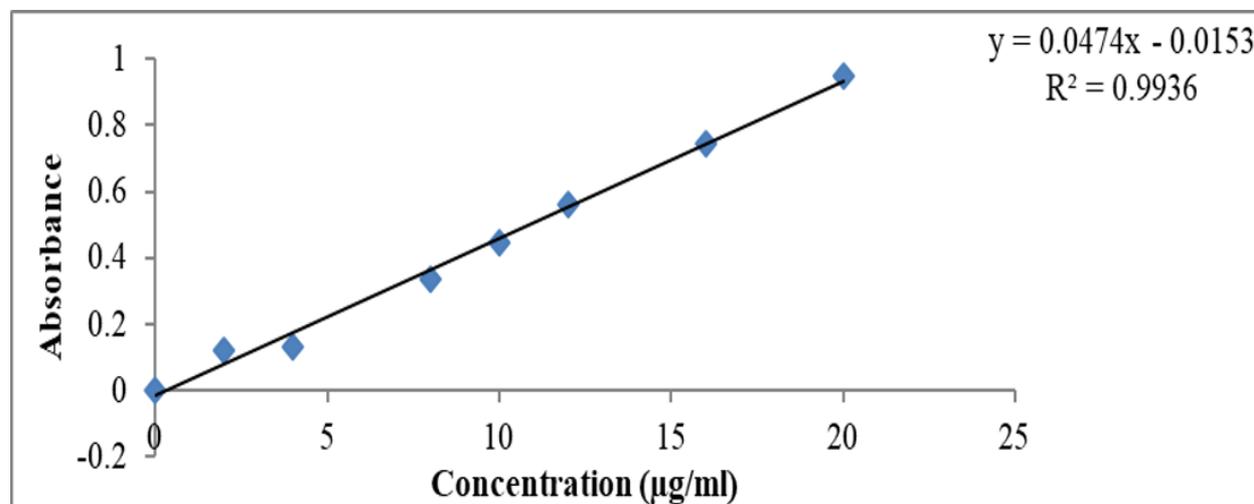
Calibration curve of Ketorolac tromethamine in 0.1N HCl

10mg of Ketorolac tromethamine was accurately taken and dissolved in 100 ml of 0.1 N HCl to get 100 µg/ml stock solution. The stock solution was further diluted to get solutions in a concentration range of 1 to 10 µg/ml with 0.1 N HCl. The absorbance of these solutions were determined spectrophotometrically (Shimadzu 1700, Japan) at 322 nm (Etman *et al.* 2008).

Fourier Transform Infra-Red (FTIR) spectrum

Table 1: Experimental design parameters

| Factors | Levels used (coded value) | | | Actual value (%) | | |
|---------------------------------|---------------------------|--------|------|------------------|--------|------|
| | Low | Medium | High | Low | Medium | High |
| NaHCO ₃ : HPMC K4M | -1 | 0 | +1 | 1:2 | 1:1 | 2:1 |
| Eudragit RS 100 (% Weight gain) | -1 | 0 | +1 | 5 | 10 | 15 |

**Figure 1: Calibration curve of Ketorolac tromethamine in 0.1N HCL**

The powder sample of Ketorolac tromethamine, Eudragit RS100 and physical mixture of Ketorolac tromethamine and polymer (Eudragit RS100) was kept in dryer to make moisture-free. The dried sample of powders were separately mixed and triturated with dry potassium bromide. This mixture was placed in a DRS assembly sample holder. The infrared spectrum was recorded at 500 to 4000 cm^{-1} (Shimadzu8400S, Japan).

Physical characterization and pellets sphericity

The micrometrics properties such as Carr's index, Hausner's ratio and angle of repose of the floating pellets were determined. The pellets friability was studied using USP friability test apparatus (Raval *et al.*, 2013; Patil *et al.*, 2017; Nandgude *et al.*, 2006). 10 g of the pellet formulations was kept into friabilator, and after 200 revolutions, the percentage weight loss was determined (Roche Friability Tester, India). The pellets hardness was determined using digital hardness tester (Veego, India) (Muley *et al.*, 2016). Pellets sphericity was determined by measuring the feret diameter (FD) and perpendicular diameter (PD) of pellets by Vernier calliper (Salve *et al.*, 2019). It is calculated in terms of aspect ratio (AR), i.e. (ratio of longest FD to longest PD).

Particle Size distribution analysis

The particle size analysis of the KT pellets was deter-

mined by mechanical sieve shaker (Make-Kumar). A series of BSS standard sieves no 10, 12, 16, 22, 36, 44, and 60 were arranged in decreasing aperture size order. An accurately weighed amount of drug-containing pellets from each batch were kept on the upper most sieve. The sieves were shaken for a ten minutes time period and the material retained on each sieve was weighed separately (P *et al.*, 2016). Graph of mean size vs % weight retained was plotted to analyse pellet size distribution.

Drug Content

KT pellets equivalent to 10mg were crushed in mortar pestle and transferred into 100ml of methanol in volumetric flask. The mixture for thirty minutes time period was sonicated to allow complete extraction of a drug (Etman *et al.*, 2008). The solution was filtered and assayed spectrophotometrically (Shimadzu 1800, Japan) at 322 nm to determine the percent drug content.

Scanning electron microscopy (SEM)

The surface morphology of uncoated and optimized coated KT pellets was examined by scanning electron microscope (Amrutkar *et al.*, 2012). SEM analysis was performed using Carl Zeiss Supra 5, Germany Scanning Electron Microscope (Pagariya and Patil, 2013). The pellets samples were placed directly onto aluminium stages and for 1 min were sputter-

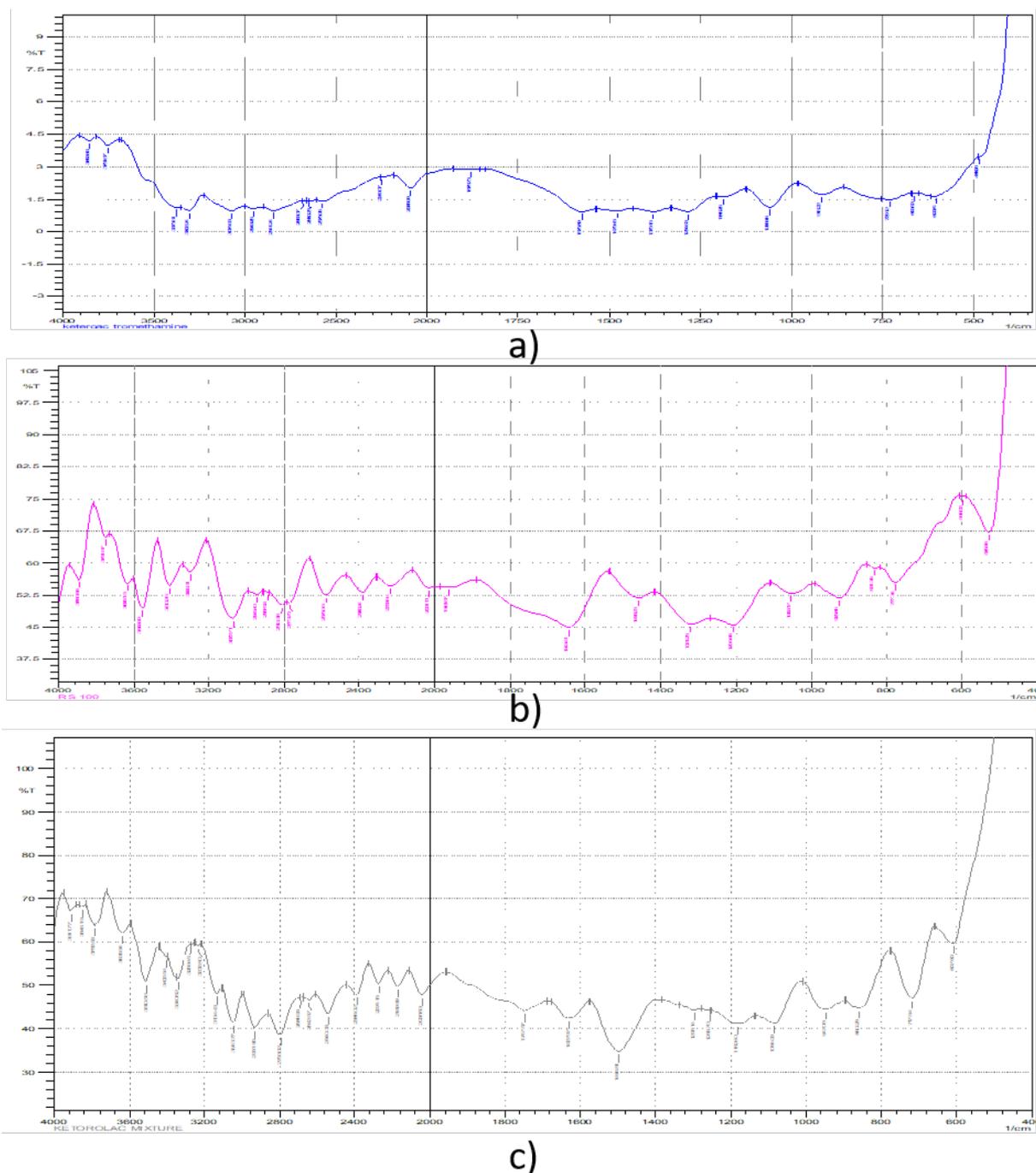


Figure 2: IR spectrum of (a) Ketorolac tromethamine (b) Eudragit RS 100 (c) Physical Mixture.

coated under an argon atmosphere with gold /Palladium mixture. The pellet samples were placed onto stubs by double-sided adhesive tape.

In vitro buoyancy studies

Floating lag time (FLT), i.e. the time taken by the pellets to come over the surface and total time period for which pellets floated over the surface, i.e. total floating time was determined. 100 unit floating pellets were kept in USP Type-II dissolution apparatus on 50 rpm. The dissolution medium used was 0.1N

HCl $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. FLT was determined by visual inspection. The floating pellet percentage was determined by the following equation (Loganathan *et al*, 1993).

$$\text{Floating pellets (\%)} = \frac{\text{number of floating units at measure time}}{\text{initial floating units number}} \times 100$$

In vitro drug release studies

Drug release behavior of KT pellets was studied by USP Dissolution Apparatus-II (Veego DA-8D, India). KT Pellets (equivalent to 10 mg of drug) were

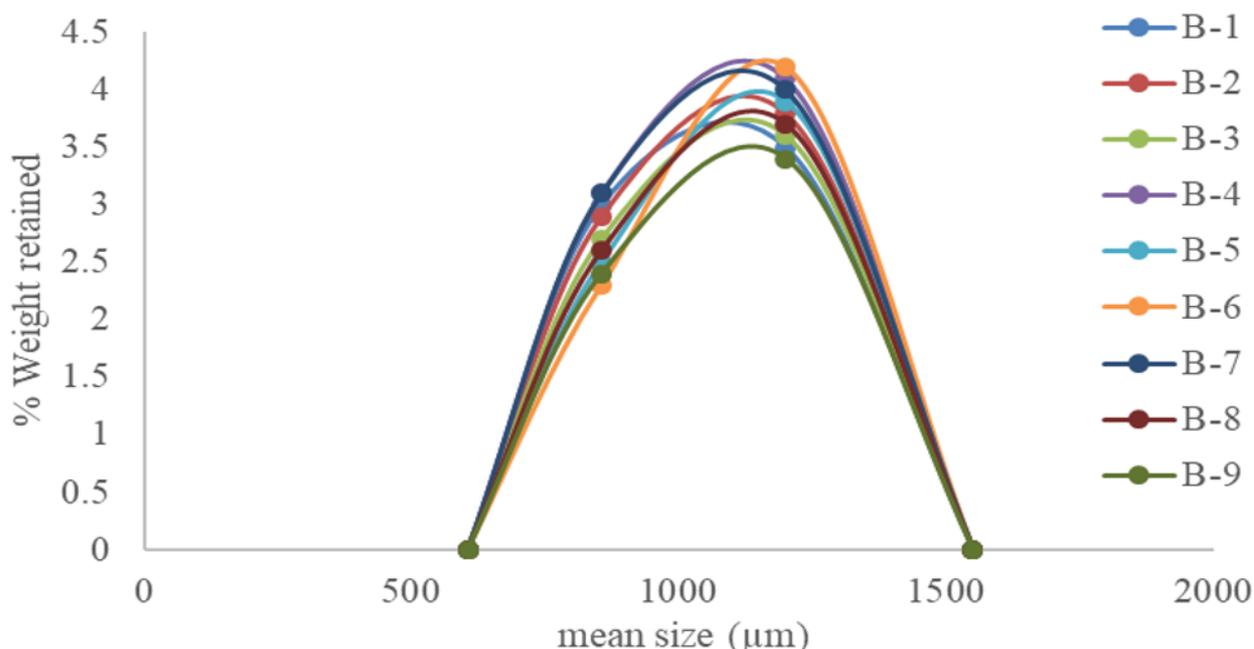


Figure 3: Particle size distribution curve of pellets (B-1 to B-9).

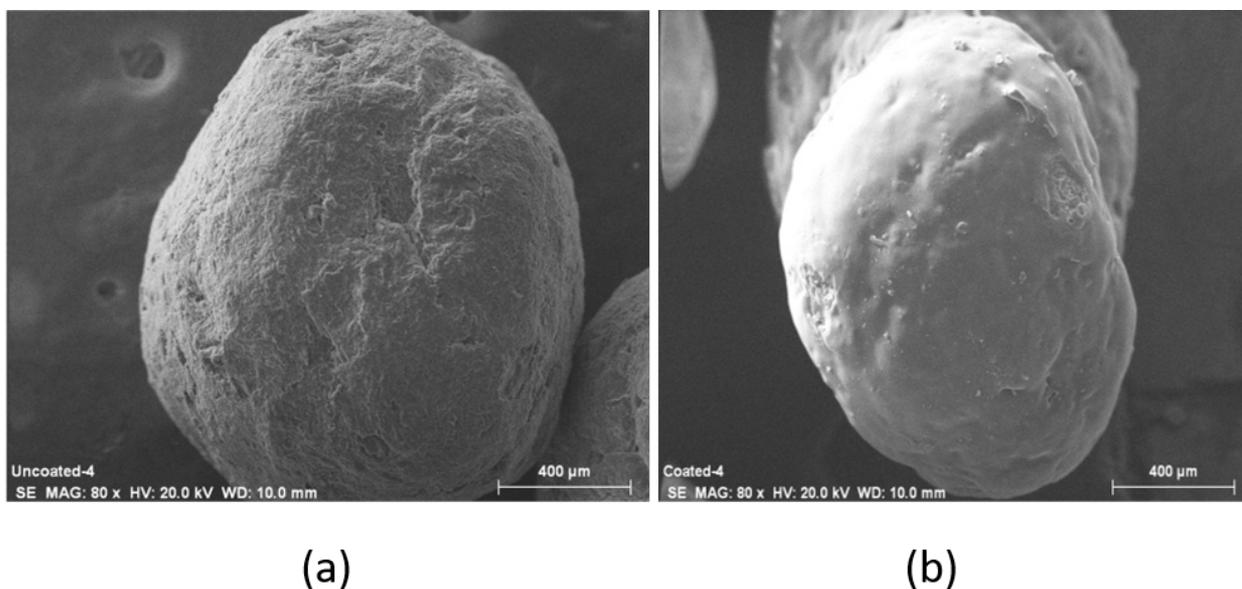


Figure 4: Scanning electron microphotographs of (a) uncoated KT pellets and (b) KT pellets coated with Eudragit RS100 polymer at 80X magnification.

accurately weighed and transferred to 900 ml of 0.1N HCl dissolution medium maintain at $37 \pm 0.5^\circ\text{C}$ on 50 rpm. 5 ml aliquot was withdrawn and to maintain sink condition immediately replaced with the addition of same volume of fresh 0.1N HCl. The aliquot was filtered and at 322 nm absorbance was measured using UV spectrophotometer (Shimadzu 1800, Japan) to determine the drug concentration (Klausner *et al.*, 2003; Diggikar *et al.*, 2018; Muley *et al.*, 2017).

RESULTS AND DISCUSSION

UV Spectrum of Ketorolac tromethamine in 0.1 N HCl

The λ_{max} of KT in 0.1 N HCl was observed to be 322 nm. The calibration curve of KT was obtained in 0.1 N HCl at the respective λ_{max} value, as indicated in (Figure 1).

Fourier Transform Infra-Red (FTIR) spectrum

The IR spectrum of KT and Eudragit RS100 was obtained, as indicated in (Figure 2). The interpreta-

Table 2: Composition of experimental formulation

| Batch Number | NaHCO ₃ : HPMC K4M | Eudragit RS100 (%) |
|--------------|-------------------------------|--------------------|
| B-1 | 2:1 | 15 |
| B-2 | 2:1 | 5 |
| B-3 | 2:1 | 10 |
| B-4 | 1:1 | 15 |
| B-5 | 1:1 | 5 |
| B-6 | 1:1 | 10 |
| B-7 | 1:2 | 15 |
| B-8 | 1:2 | 5 |
| B-9 | 1:2 | 10 |

Table 3: Physical characterization of pellets batch (B-1 to B- 9)

| Batch number | Angle of Repose (°) | Carr's Index (%) | Hausner's Ratio | Hardness (Kg/cm ²) | Friability (%) | Aspect ratio |
|--------------|---------------------|------------------|-----------------|--------------------------------|----------------|--------------|
| B-1 | 29.85±0.2 | 7.54±0.32 | 1.08±0.03 | 3.6±0.06 | 0.31±0.01 | 1.3 ±0.03 |
| B-2 | 24.51±0.3 | 9.5±0.64 | 1.10±0.01 | 2.3±0.04 | 0.40±0.02 | 1.15 ±0.02 |
| B-3 | 29.85±0.5 | 7.93±0.53 | 1.08±0.04 | 2.2±0.08 | 0.36±0.03 | 1.19 ±0.05 |
| B-4 | 25.56±0.3 | 14.49±0.26 | 1.16±0.02 | 2.20±0.03 | 0.53±0.03 | 1.09 ±0.04 |
| B-5 | 21.60±0.5 | 8.82±0.45 | 1.09±0.05 | 2.3±0.04 | 0.29±0.04 | 1.30 ±0.09 |
| B-6 | 28.63±0.7 | 10.14±0.12 | 1.11±0.01 | 2.7±0.04 | 0.43±0.03 | 1.11 ±0.01 |
| B-7 | 26.59±0.6 | 12.18±0.22 | 1.12±0.2 | 1.7±0.3 | 0.19±0.05 | 1.08 ±0.09 |
| B-8 | 27.20±0.3 | 13±0.19 | 1.16±0.7 | 1.8±0.5 | 0.24±0.03 | 1.03 ±0.02 |
| B-9 | 28.19±0.7 | 9.47±0.53 | 1.10±0.7 | 2.10±0.3 | 0.37±0.05 | 1.13 ±0.07 |

Table 4: Floating and drug release (B1 - B9).

| Batch Number | Floating lag Time (min) | % Drug release (6hr) |
|--------------|-------------------------|----------------------|
| B-1 | 5.5±0.1 | 61.86±0.4 |
| B-2 | 3.2±0.3 | 94.47±0.2 |
| B-3 | 4.9±0.4 | 81.01±0.3 |
| B-4 | 11.5±0.2 | 60.64±0.4 |
| B-5 | 7.1±0.1 | 94.13±0.2 |
| B-6 | 9.2±0.3 | 78.05±0.2 |
| B-7 | 17.4±0.2 | 57.68±0.4 |
| B-8 | 15.1±0.1 | 75.41±0.3 |
| B-9 | 13.2±0.4 | 89.31±0.3 |

Table 5: Numerical optimization (Batch code: B-2)

| Parameters | Constraints | Solution | Actual value | (experimental) |
|-----------------------------|-------------|----------|--------------|----------------|
| NaHCO ₃ :HPMCK4M | In range | (+1) 2:1 | 2:1 | |
| Eudragit RS100 | In range | (-1) 5 % | 5 % | |
| Floating lag time | Minimum | 3.19 min | 3.36 min | |
| % Drug release (6 h) | Maximum | 94.85 % | 95.15 % | |

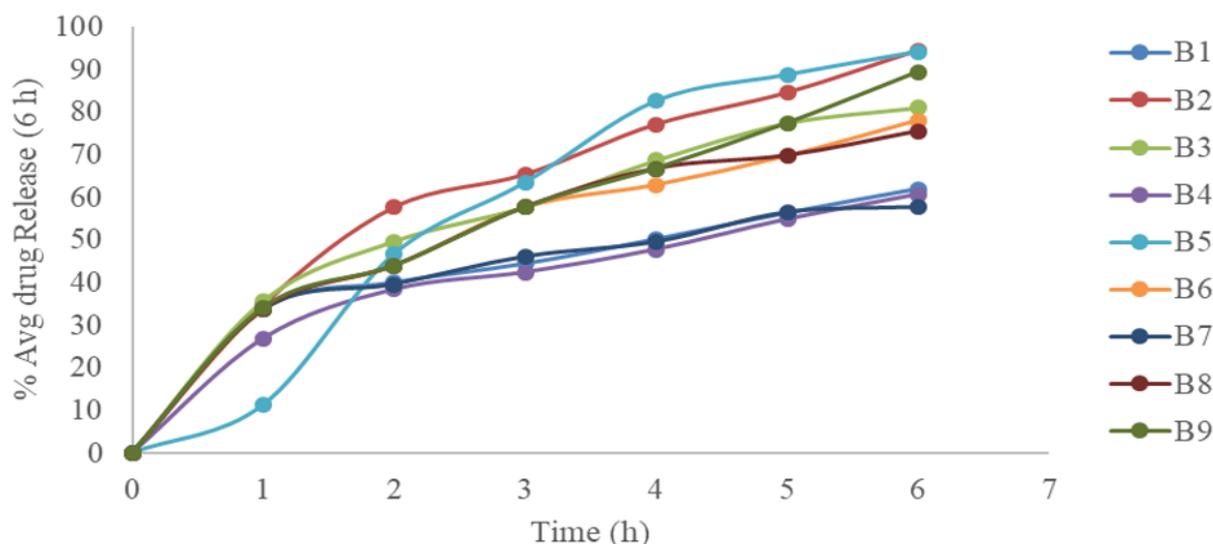


Figure 5: Percentage drug release in 6 h (B1 to B9).

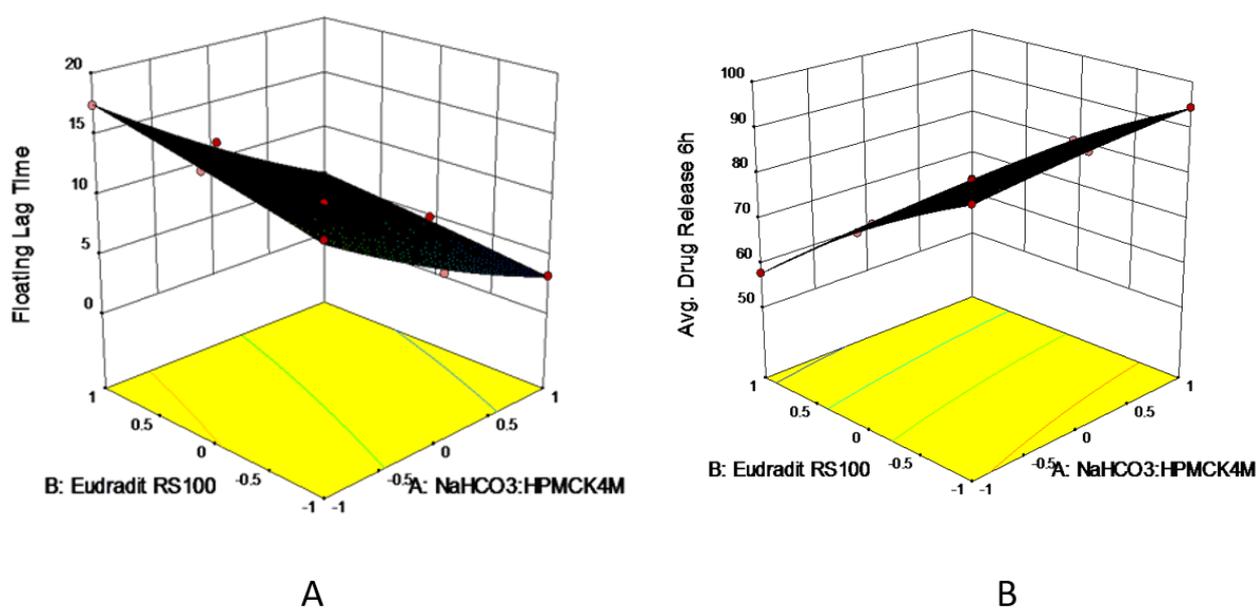


Figure 6: Response surface plots (A) Floating lag time and (B) percent drug release in 6 h.

tions of IR frequencies were done, and absorption bands are consistent with the structure of KT and Eudragit RS100. The FTIR spectra of pure drug showed functional peak at 3373 to 3302 cm^{-1} is (N-H stretching), 3074.63 (aromatic C-H stretching), 2949.26 , 2841.24 cm^{-1} (CH_2 asymmetric) and symmetric stretching of (CH_2 group), 1575.89 , 1700 cm^{-1} (carbonyl group), 1058.96 cm^{-1} (C-O single bond stretch) both (COH and CH_2OH), 729.12 , 663 cm^{-1} (monosubstituted aromatic C-H bond). The IR spectrum of Eudragit RS100 showed functional peak at 294 cm^{-1} (CH_3 , CH_2 asymmetric Stretching), 2887 cm^{-1} (CH_3 , CH_2 Symetretic stretching), 164 cm^{-1} (N^+ , CH_3 , CH_3 , CH_3 , CL^-), 1747 cm^{-1} ($\text{C}=\text{O}$, C_2H_5 Stretching). The FTIR spectra of drug excipient mix-

ture showed a characteristic peak of drug and Eudragit RS100 with a negligible shift in wavenumber indicated the compatibility of the drug with Eudragit RS100.

Physical characterization of pellets

Physical characterization studies of pellets indicated excellent flow properties of all the formulation batches having an angle of repose in the range $21.60 \pm 0.5^\circ$ to $29.85 \pm 0.5^\circ$, Carr's index $7.54 \pm 0.32\%$ to $14.49 \pm 0.26\%$ and Hausner's ratio in the range of 1.08 ± 0.03 to 1.16 ± 0.07 . The aspect ratio of pellets obtain was near to unity indicated sphericity of pellets. Hardness and friability obtained was in the range of 1.7 ± 0.3 to $3.6 \pm 0.06\text{ Kg/cm}^2$ and $0.19 \pm 0.05\%$ to $0.53 \pm 0.03\%$ shown in (Table 3).

Particle size distribution analysis of pellets

The particle size distribution study of pellets indicates narrow size distribution in which most of the pellets are in size range of 800 μ m to 1200 μ m, as shown in (Figure 3).

Drug Content

The drug content for all pellet formulation batches was measured by UV spectroscopy method and observed in the range of 96.35 \pm 0.9% to 98.91 \pm 0.75% showed that the coating onto the pellets can also produces good reproducibility in drug content.

Scanning electron microscopy (SEM)

The surface morphology of KT uncoated pellets and coated pellets was studied through SEM. The uncoated KT pellets surface was wrinkled and rough, whereas the Eudragit RS100 polymer-coated pellet showed smoother surface indicate in (Figure 4a and Figure 4b).

In vitro buoyancy

The floating studies reveal that with an increasing amount of NaHCO₃: HPMC K4M FLT decreases, on the other hand, floating lag time increases with an increasing amount of Eudragit RS100. The coated pellets showed floating lag time in the range of 3.2 min to 17.4 min. Indicated in (Table 4). The prepared floating pellet formulations showed acceptable floating behaviour of which 80–95% of pellets remained buoyant till 6 h.

In vitro drug release

The in vitro drug release behaviour of coated pellets was studied. The drug release obtained in the range of 57.68 \pm 0.4 % to 94.47 \pm 0.2 % in 6 h indicated in Table 4 and Figure 5. The drug release studies indicated that as the Eudragit RS100 polymer coat increases the drug release was decreased. The higher coat leads to get thicker membrane over pellets, which retarded dissolution medium penetration and hence sustained drug release was obtained. Figure 5 shows,

Optimization of formulation

The ANOVA results were obtained for the selected dependent variables for all nine batches of prepared formulations. The observed responses, i.e. FLT and drug release in 6 h, were fitted into different models using Design Expert[®] 11 software. The best-fitted model was found to be a quadratic model. The regression equation for each response was also generated.

Regression equations of the fitted quadratic model:

$$\text{Floating lag time } (Y_1) = 9.34 - 5.35 X_1 + 1.82 X_2 - 0.48 X_1 X_2 + 0.61 X_1^2 - 0.095 X_2^2 \dots (1)$$

$$\text{Drug release } (Y_2) = 78.30 + 2.49 X_1 - 16.29 X_2 - 0.24 X_1 X_2 - 0.68 X_1^2 - 1.50 X_2^2 \dots (2)$$

It was found that the independent variables X₁ (NaHCO₃: HPMC K4M) and X₂ (Eudragit RS100) had a negative and positive effect on Y₁ (floating lag time). From equation (1) negative coefficient of X₁ indicated a decrease in floating lag time with an increase in the ratio of (NaHCO₃: HPMCK₄M) concentration and positive coefficient of X₂ indicated an increase in a floating lag time with an increase in Eudragit RS100 concentration. From equation (2) more pronounced negative coefficient of X₂ was observed indicated a decrease in percent drug release as Eudragit RS100 concentration increases. The response surface plots indicating the relative effect of the amount of NaHCO₃: HPMC K4M and Eudragit RS100 on FLT (Y₁) and percent drug release (Y₂) of KT pellets are shown in Figure 5A and Figure 5B, respectively. Figure 6 shows,

Optimization and validation

The desirability approach under numerical optimization technique was used to recognize the optimum values of the independent variables for the formulation (Amrutkar *et al.*, 2012). The optimized formulation was identified by applying constraints, i.e. a minimum value of FLT and maximum value of drug released in 6 h. The suggested batch based upon the highest desirability value was selected indicated in Table 5. The suggested value of FLT and drug release was observed to be in near proximity to the experimental value. Figure 6 shows,

CONCLUSIONS

The gastroretentive multiparticulate drug delivery system of Ketorolac tromethamine by gas generation technique was successfully designed and optimized. The identification and purity of drug was confirmed by conducting infrared spectroscopy and ultraviolet spectroscopy studies. A 3² factorial design was employed for optimization of the concentration of NaHCO₃: HPMC K4M and Eudragit RS100. The study reveals the significant effect of NaHCO₃: HPMCK4M and Eudragit RS100 polymer coat on floating character and drug release behaviour. As the concentration of sodium bicarbonate increases FLT decreases, whereas the increasing concentration of Eudragit RS100 decreases the drug release. The floating multiparticulate pellets batch containing NaHCO₃: HPMC K4M in the ratio of 2:1 with 5% Eudragit RS100 coating showed FLT of 3.2 min and 95.15% average drug release in 6 h. 80–95% of pellets showed buoyancy till the period of 6 h. The sustained release gastroretentive floating pellets of Ketorolac tromethamine were obtained and could be

effectively used in the delivery of drug with less irritant effect on the gastric mucosa.

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