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Original Article

Modeling of ketoprofen release from a mucoadhesive orodental gel for better control of dental pain and gingivitis

Dayana Samy Aboul Makarem*[1], Ahmed Mahmoud Abdelhaleem Ali[2], Rasha Mohamed Kharshoum[2] and Sadia Ahmed Tayel[3]

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Misr International University, Egypt
[2]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Beni Suef University, Egypt
[3]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Egypt

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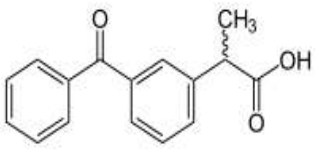
ABSTRACT

This research paper addressed the formulation and performance of a mucoadhesive gel containing the anti-inflammatory drug ketoprofen. Various polymers were used in the formulation at different levels together with different types of crosslinking additives. The compatibility between ketoprofen and the employed polymers was tested using differential scanning calorimetry (DSC). Sustained release profiles were obtained from gels containing pluroic F127, carbopol981 and polycarbophil. Fast release was obtained from sodium alginate and HPMC at low levels. Response surface modeling of the release data indicated that the optimum ketoprofen release rates (44-58 %) were obtained from gel formulations containing carbopol 981 at 1% w/w level. Gel formulations containing sodium alginate (5 % w/w) released more than 40 % of their content of ketoprofen within two hours. The fastest rate was obtained from formulations containing hydroxylpropyl methylcellulose (HPMC E15) where, more than 90 % of the drug content was released at polymer level of 20 % w/w as obtained from model optimized formulations. The clinical evaluation of the anti-inflammatory and analgesic action of the prepared formulations compared to commercial ketoprofen tablets indicated significant difference ($P < 0.05$) in pain intensity and swelling associated with ginigivitis in favor of the gel formulation over the oral tablet. Therefore, formulation of ketoprofen into a mucoadhesive orodental gel can be considered an easy and more effective alternative to oral solid dosage forms.

Keywords: Dental pain; Gingivitis; Ketoprofen; Mucoadhesive gel; Modeling; Optimization

INTRODUCTION

Ketoprofen is one of the nonsteroidal anti-inflammatory drugs (NSAIDs). The drug belongs to the propionic acid class. Its chemical formula is $C_{16}H_{14}O_3$ and the chemical name is (RS)2-(3-benzoylphenyl)-propionic acid. Ketoprofen has strong analgesic and antipyretic effects [1], it acts by inhibiting production of prostaglandin synthesis [2]. The absorption of ketoprofen is rapid and almost complete when given orally [3]. However the drug has a short terminal phase half-life of 2 - 4 hours [4].



Ketoprofen binds extensively to plasma proteins namely albumin, metabolized as glucouronides in the liver and excreted mainly in urine [3]. Substantial concentrations of the drug are attained in synovial fluid. It has been formulated in different dosage forms such as tablets, capsules, suppositories, intramuscular injections, topical gels worldwide [5]. Orodental pain and gum

Corresponding Author Address: Dayana Samy Aboul Makarem, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Misr International University, Egypt; E-mail: dayana.dayana201@gmail.com

inflammation are common illness in most populations and require great care and fast medical treatment. Severe orodental pain may be encountered following tooth extraction, which is often termed phantom pain, other types of pain might not be related to infections or inflammation such as atypical odontalgia or persistent orodental pain [6]. This latter type is often caused by neuropathic alteration of the trigeminal nerve. Orodental films containing an anti-inflammatory drug ketorolac were prepared and used as pain relief formulations [7]. Liquigel formulations containing a variety of analgesic model drugs e.g. ibuprofen, ketoprofen and acetaminophen demonstrated faster onset of post operative dental pain relief than the tablet formulations [8]. Clinical evaluation of the anti-inflammatory and pain relief efficacy of nonsteroidal anti-inflammatory drugs has been studied extensively in literature especially on the musculoskeletal systems [9-11] and dental pain [7, 12, 13]. However, rare research studies focused on the gingival inflammation, tenderness and swelling [14, 15] and none of these studies addressed modeling of release behavior from the anti-inflammatory gels. Therefore, this study involved the preparation and characterization of ketoprofen mucoadhesive dental gel using various muco-adhesive polymers. Modeling of the release behavior was also undertaken to optimize the formulation and predict the appropriate release profile for better control of gum inflammation and relief of associated pain.

MATERIALS AND METHODS

Materials: Ketoprofen was obtained as a free sample from Adwia Pharmaceutical Company, Cairo Egypt. Polycarbophil, Carbopol 981, Chitosan, Hydroxypropyl methylcellulose (HPMC-E15), Poloxamer 407 (Pluronic F127) and Sodium Alginate were purchased from Sigma Aldrich, US through the Egyptian Import Office, Nasr City, Cairo, Egypt. All other reagents were of analytical grade and were used as obtained.

Compatibility study between Ketoprofen and gel forming excipients: The compatibility between ketoprofen and various excipients used for gel formation was evaluated using differential scanning calorimetry (DSC). Samples of pure ketoprofen, various excipients and 1:1 physical mixtures (5 mg each) were individually filled into aluminium flat bottomed pans and heated in DSC-60 instrument (Schimadzu, Japan) in an atmosphere of nitrogen to eliminate the oxidative and pyrrolytic effects. The heating temperature was set between 20 – 300 ^{o}C with a heating rate 10^{o}C/minute.

Preparation of ketoprofen gels: The weighed amount of ketoprofen (50 mg) was dispersed in 100 mL beaker containing 5 mL phosphate buffer pH 6.8. The calculated amounts of polymers according to the specified ratios (see Table 1) were added and the mixture was placed on a magnetic stirrer for 10 minutes until all drug particles are dissolved and the polymers were completely hydrated forming a clear homogenous solution. To obtain the gel consistency various additives were prepared according to each polymer. For gel formulations containing polycarbophil or carbopol, 1% triethylamine was prepared and used as the gel forming addititive. For formulations containing Pluronic F127 or sodium alginate, 1% CaCl2 solution was prepared and used as the gelling additive. For Chitosan formulations, 1 % acetic acid solution was used as the gel forming additive. No additives were used for formulations containing HPMC and the gel was obtained directly after mixing of ingredients.

Determination of the rheology of Ketoprofen gels: The rheological properties of the prepared ketoprofen gel formulations was evaluated using DV2T Brookfield digital viscometer (Brookfield, USA) attached to a computer operated using a software program rheocalc-T (Brookfield Engineering Lab. USA). The displayed information included viscosity (cP), temperature (°C), shear rate/stress, % torque, spindle/speed and step program status. The collected data were processed by the rheocalc program and the rheograms were displayed (see Fig. 4).

In-vitro dissolution properties: The release profiles of ketoprofen from the prepared gel formulations were evaluated using USP Appratus-II paddle dissolution tester (Hanson, Research, USA). The weighed amounts of gel equivalent to 5 mg ketoprofen were placed in a small watch-glass (5 cm in diameter) and covered with a stainless steel wire mesh. This assembly was then transferred to the bottom of 900 mL capacity dissolution flask. The dissolution medium was composed of pH5.8 phosphate buffer at a temperature of 37 ± 0.05 C. At short time intervals 5 mL samples were withdrawn for analysis and replaced with fresh medium. The UV absorbance of taken samples was performed at a wave length of 260 nm.

Modeling of the release behavior: The release of ketoprofen from the prepared gel formulations was subjected to a modeling software program INForm (Intelligensys, UK). This model generating and predictive tool is based on artificial neural network and genetic algorithms to detect cause-effect relationship and predict the outputs of training data

[16]. The independent variables included the gel forming polymer type, level, crosslinker type and level as well as the drug concentration. The measured dependent variables were the percentage of ketoprofen dissolved from the gel formulations after 60 (Q60) and 120 minutes (Q120), respectively. Data were divided into three data sets; training, testing and validation data sets. The multilayer perceptron (MLP) network embedded into the modeling program was used for model training to build up the cause-effect relationships as well as relative weights and importance between input variables and output properties. Ten percent of data records were selected for testing the predictability of the model and another 10 % were used for model validation [17]. The nominal input variables were given numerical values (codes) to be recognized by the program. Polymer type variable was coded as; 1, 2, 3, 4, 5 and 6 for carbopol 981, polycarbophil, pluronic F127, sodium alginate, chitosan and HPMC E15 respectively. The crosslinker additive type was coded as; 7, 8, 9 and 10 for triethylamine, 1% CaCl2 solution, 1% acetic acid solution and phosphate buffer pH5.8, respectively. The artificial neural network structure I(5)-H(2)-O(1) was used for model training (linking inputs and the out-put property). The structure demonstrated; five nodes representing the input layer, two nodes in the hidden layer and one node in the output layer. The default model training rapid back-propagation algorithm (RPROP) was used for model training. After encoding of the nominal parameters and converting them to numerical values the data sets were introduced into the modeling software for starting the model training step (see Table 2).

Clinical evaluation of ketoprofen gel: A comparative clinical study was conducted at the out-patient dental clinic in Beni-Suef over a period of 2 weeks to evaluate the efficacy of ketoprofen gel formulations. The patients were divided into two groups receiving either the muco-adhesive ketoprofen gel or ketoprofen 50 mg tablets (Ketolgin® 50). The patients (having dental pain and gum inflammation) were asked to put the muco-adhesive gel on the affected area over the gingival tissue inside the mouth 3 times daily. The second group was asked to take the ketolgin® tablets 3 times daily. Patients (males and non-pregnant females) aged between 18 to 60 years were evaluated before and after initiation of therapy (i.e. on day 0, then day 2 and day 7) for the following parameters: Pain intensity, pain during chewing, swelling and tenderness. A four point scale (0-absent, 1-mild, 2 moderate, 3 severe) was used to evaluate the results [18]. Exclusion criteria included patients requiring surgical intervention, those with a history of allergy to NSAIDs, patients on oral NSAIDs for 3 days or more prior to enrollment and patients receiving systemic corticosteroids within 1 week of beginning of the study [19]. Pregnant and lactating mothers and children under 12 years of age were also excluded from this study.

RESULTS AND DISCUSSION

Compatibility studies: The obtained thermograms (Fig. 3) of pure ketoprofen indicated a sharp melting endotherm at 98 °C which is in accordance with data reported in the literature on ketoprofen [20]. The thermograms of the polymers demonstrated broad endotherms without sharp melting which indicated the amorphous nature of the polymers. The physical mixtures of ketoprofen with the gel forming polymers (1:1) demonstrated similar melting endotherm to that of pure ketoprofen which suggest stable mixtures of the drug with the polymers. However, pluronic F127 physical mixture with ketoprofen showed a different melting endotherm at 50 C which occurred at lower temperature that that of pure ketoprofen (98 °C) or pure pluronic (60 °C), respectively (see Fig. 2). This observation may suggest physical interaction between ketoprofen and the polyethylene-polypropylene block copolymer possibly by fast dissolution of the drug particles into the melted polymer.

Rheological behavior: The results of rheology of the samples indicated non-newtonian flow for all formulations (see Fig.4). Plastic flow behavior was observed in formulations F1-F6 containing carbopol 981, polycarbophil or pluronic F127 as polymers at low level of drug content (1%) and low level of additive (5-10 drops). When the drug load was increased to 2% w/w (F7-F10), the flow was changed to the pseudo-plastic type whilst the formulations containing pluronic F127 (F11 and F12) retained their plastic flow properties. Formulations F13-F16 containing sodium alginate (5-10 %w/w) demonstrated pseudo-plastic flow properties. Chitosan formulations (F17-F20) showed plastic flow behavior whilst HPMC formulations (F21-F24) demonstrated pseudo-plastic flow pattern.

In-vitro release studies: The results of ketoprofen release from the prepared gel formulations indicated sustained release behavior in most formulations where less than 30 % of the drug were released after 2 hours (see Fig. 5). Some formulations were able to release more than 40 % of ketoprofen after 2 hours (F1, F7, F15, F21 and F23). The maximum drug released (90 %) after two hours was obtained from formulation F23 containing HPMC E15 at a level of 20 % w/w.

Modeling of the release profiles: Training of the data resulted in a good model with high training and testing correlation coefficient R^2 for Q60 (89.4, 88.6) and Q120 (80.8, 78.7), respectively (see Table 3). The value of R^2 represents how much of variance of the dependent variable is accounted for in the model. When the experimental Q60 and Q120 were plotted versus the model predicted counterparts high linear regression coefficients (r^2) were also obtained (0.90 and 0.80) which suggest highly trustable model (see Fig. 6).

Optimization of the release performance was achieved by selecting three desirable ranges for the % released after 1 and 2 hours; as follows 65-75 % and 75-85 %; 70-80 % and 75-85%; 75-85% and 85-90 % for Q60 and Q120, respectively. Three optimized solutions were predicted by the model (see Table 3). The obtained optimumm solutions suggested formulation of the gel using Chitosan (code 5) at a concentration of 4.36 % using 18 drops of 1 % acetic acid crosslinking additive (code 9) and drug concentration of 1% to get 70 % and 77.7 % drug release after 60 and 120 min., respectively. High percentage of drug release can be obtained from the same suggested formula but at lower polymer level (2%) as shown in Table 4. The highest percentage of released ketoprofen can also be obtained, if HPMC was used as the gel forming polymer at a level of 18.48 % w/w.

Clinical evaluation: In this study, the two groups showed improvement in various parameters studied (Pain intensity, pain during chewing, swelling and tenderness. Treatment with Ketoprofen gel prepared according to formula (F23), containing 2% ketoprofen and 20 % w/w HPMC, proved to be more effective and faster in pain and inflammation relieve than orally given Ketoprofen 50 mg tablets (see Table 5). Ketoprofen gel prepared according to formula (F23) was more efficient in reducing the mean scores of all tested parameters in Gingivitis indicating significant difference ($P < 0.05$) between the gel and tablet formulations. These results are in good agreement with the reported literature about the topical anti-inflammatory activity of ketoprofen [21].

CONCLUSION

The above findings indicate that formulation of ketoprofen into mucoadhesive oral gel is an effective approach for fast relief of dental pain and gum inflammation compared to the traditional oral tablet formulation. Modeling of the drug release behavior demonstrated that the optimum release rate was achieved using chitosan or HPMC as gel forming polymers at 4.5 and 20 % w/w respectively. The type and level of crosslinking additive also proved to be important variables in controlling the release behavior of ketoprofen from the gel formulations. The drug loading was found to be less important compared to polymer type and concentration in the formulation. Hence, model optimized mucoadhesive gels containing ketoprofen can be used effectively to control dental pain and gum inflammation.

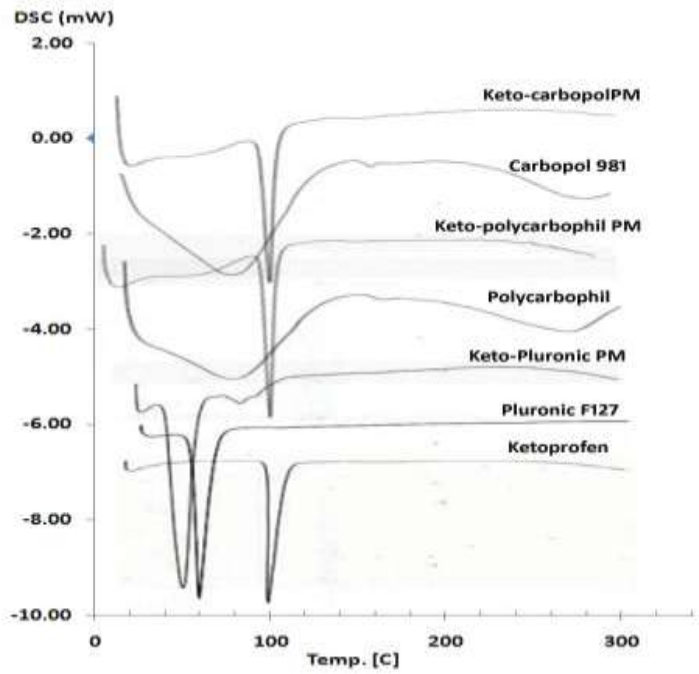


Fig. 2 DSC thermogram of ketoprofen, pluronic F127, polycarbophil and carbopol 881 and their physical mixtures

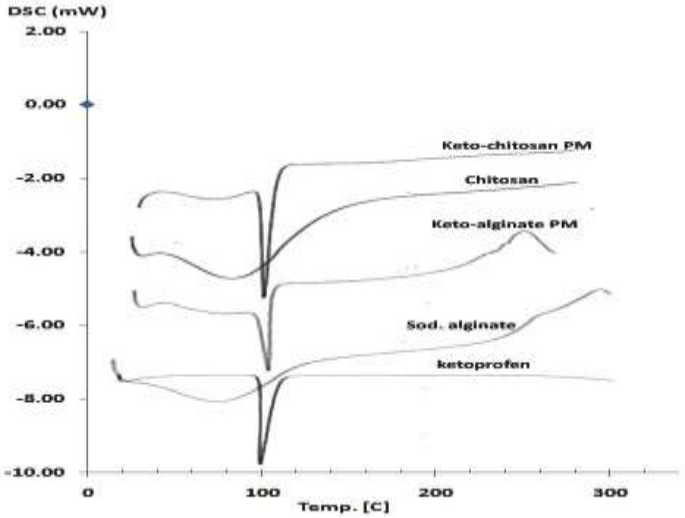


Fig. 3 DSC thermogram of ketoprofen, sodium alginate, chitosan and their physical mixtures

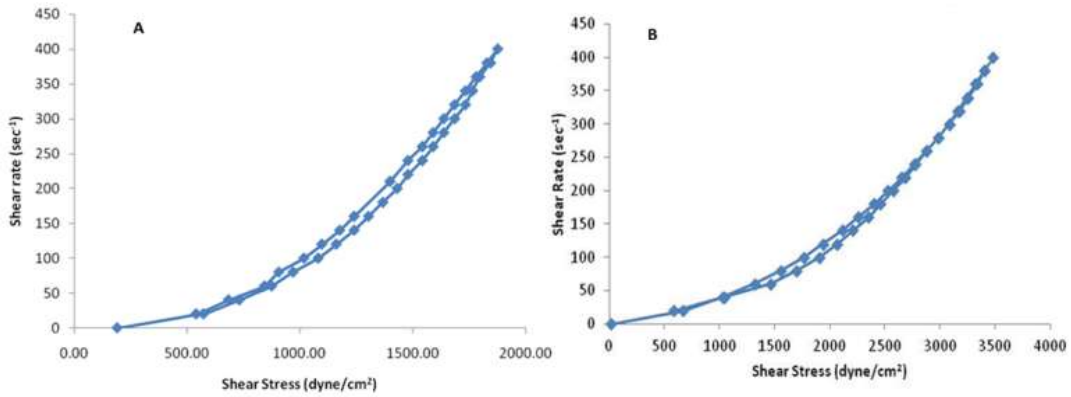


Fig.4 Rheograms of (A) formula F2 containing 2 % w/w carbopol 981and (B) formula F14 containing 10 % w/w sodium alginate

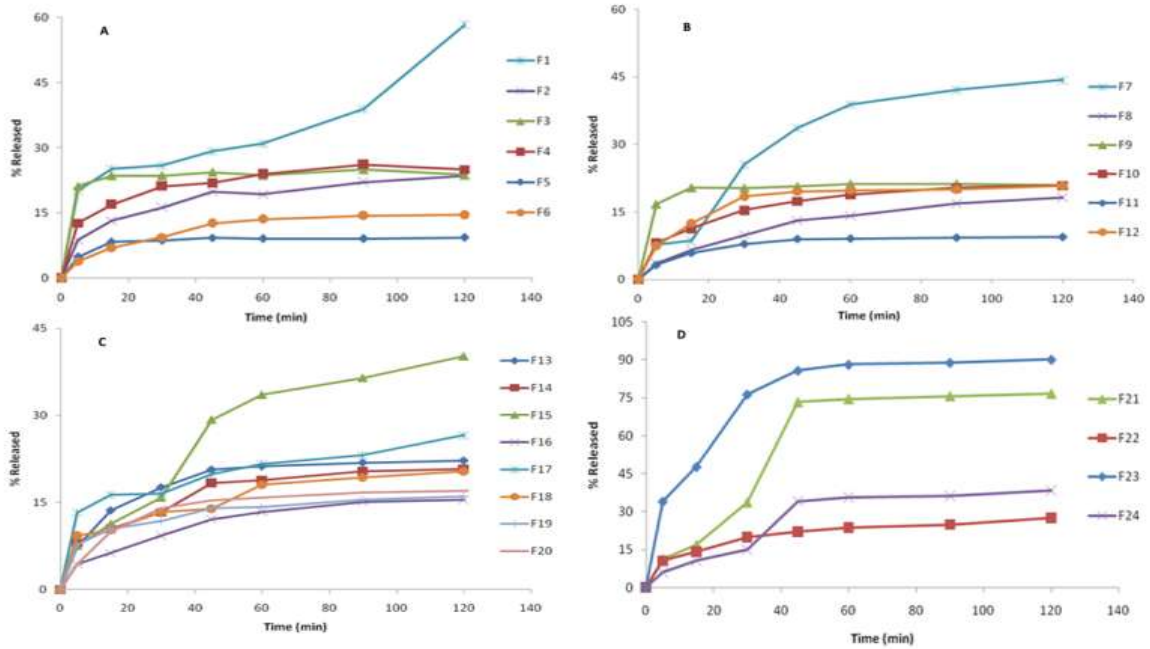


Fig. 5 % Ketoprofen released from gel formulations F1-F6 (A); F7-F12 (B); F13-F20 (C) and F21-F24 (D)

Table 1. Representative composition samples for ketoprofen gel formulations before encoding

Formula	Drug conc. (%)	Polymer type	Polymer conc. (%)	Additive type	Drops of additive	Q60	Q120
F1	1.00	Carbopol 981	1.00	Triethylamine	5	31.00	58.31
F2	1.00	Carbopol 981	2.00	Triethylamine	5	19.34	23.55
F3	1.00	Polycarbophil	1.00	Triethylamine	5	23.70	23.78
F4	1.00	Polycarbophil	2.00	Triethylamine	5	24.00	25.00
F5	1.00	Pluronic F127	25.00	1% CaCl2	10	9.10	9.40
F6	1.00	Pluronic F127	30.00	1% CaCl2	5	13.61	14.56
F12	2.00	Pluronic F127	30.00	1% CaCl2	5	19.81	20.82
F13	1.00	Sod. alginate	5.00	1% CaCl2	40	21.21	22.2
F16	2.00	Sod. alginate	10.00	1% CaCl2	30	13.41	15.5
F17	1.00	Chitosan	8.00	1 % acetic acid	60	21.65	26.6
F20	2.00	Chitosan	4.00	1 % acetic acid)	60	15.81	16.98
F24	2.00	HPMC E15	30.00	Buffer pH 5.8	0	35.80	38.52

Table 2. Representative sample of model training data set after encoding of nominal parameters

Formula	Inputs					Outputs	
	Drug conc. (%)	**Polymer type**	**Polymer Conc. (%)**	**Additive type**	**Drops of additive**	**Q60**	**Q120**
F1	1.00	1.00	1.00	7.00	5.00	31.00	58.31
F2	1.00	1.00	2.00	7.00	5.00	19.34	23.55
F3	1.00	2.00	1.00	7.00	5.00	23.70	23.78
F4	1.00	2.00	2.00	7.00	5.00	24.00	25.00
F5	1.00	3.00	25.00	8.00	10.00	9.10	9.40
F6	1.00	3.00	30.00	8.00	5.00	13.61	14.56
F13	1.00	4.00	5.00	8.00	40.00	21.21	22.20
F14	1.00	4.00	10.00	8.00	30.00	18.9	20.80
F15	2.00	4.00	5.00	8.00	40.00	33.6	40.24
F16	2.00	4.00	10.00	8.00	30.00	13.41	15.50
F17	1.00	5.00	8.00	9.00	60.00	21.65	26.60
F18	1.00	5.00	4.00	9.00	60.00	18.03	20.37
F19	2.00	5.00	8.00	9.00	60.00	14.23	16.10
F20	2.00	5.00	4.00	9.00	60.00	15.81	16.98
F21	1.00	6.00	20.00	10.00	0.00	74.50	76.65
F22	1.00	6.00	30.00	10.00	0.00	23.76	27.62
F23	2.00	6.00	20.00	10.00	0.00	88.20	90.22
F24	2.00	6.00	30.00	10.00	0.00	35.80	38.52

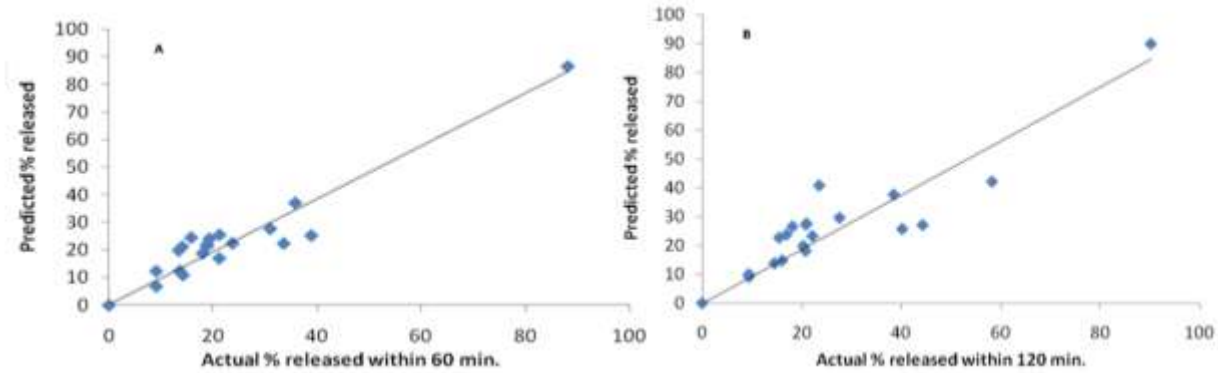


Fig. 6 actual versus model predicted percentage of ketoprofen released from gel formulations after 60 minutes (A) and 120 minutes (B)

Table 3. Model generated statistics for training and testing data sets

Property	Source of variation	Sum of Squares	Degrees of freedom	Mean sum of squares	Computed F ratio
	Model	4939.35	15.00	329.29	1.65
	Error	599.89	3.00	199.97	
	Total	5673.53	18.00		
Q_{60}	Covariance term	Sum of Errors			
	134.281	0.110637			
	Train Set R-squared	89.43 %			
	Test Set R-squared	88.66 %			
	Model	5565.74	15.00	371.05	0.83
	Error	1335.1	3.00	445.03	
	Total	6965.88	18.00		
Q_{120}	Covariance term	Sum of Errors			
	65.05	0.05			
	Train Set R-squared	80.83 %			
	Test Set R-squared	78.70 %			

Table 4. Model optimized solutions for the release of ketoprofen from gel formulations

Solution	Desirability	X1	X2	X3	X4	X5	Y1	Y2
		Drug conc. (%)	Polymer type	Polymer conc. (%)	Additive type	Drops of additive	Q60	Q120
Population 1	1.00	1.00	5.00	4.36	9.00	18.34	70.53	77.70
Population 2	1.00	1.00	5.00	2.09	9.00	18.34	72.55	81.69
Population 3	1.00	2.00	6.00	18.48	10.00	10.50	79.63	88.24

Table 5: Mean scores of ketoprofen gel and ketoprofen tablets on clinical parameters in case of gingivitis

Parameters	Ketoprofen gel			Ketoprofen tablets		
	Day 0	Day 2	Day 7	Day 0	Day 2	Day 7
Pain Intensity	2.50 ± 0.03	1.50 ± 0.11	0.20 ± 0.14	2.80 ± 0.25	2.00 ± 0.13	0.50 ± 0.05
Pain during chewing	2.70 ± 0.10	2.00 ± 0.30	0.80 ± 0.11	2.92 ± 0.15	2.30 ± 0.50	1.00 ± 0.22
Swelling	2.60 ± 0.34	2.10 ± 0.12	0.10 ± 0.11	2.80 ± 0.22	2.40 ± 0.11	0.25 ± 0.20
Tenderness	2.00 ± 0.13	1.20 ± 0.15	0.30 ± 0.08	2.50 ± 0.13	1.40 ± 0.06	0.40 ± 0.07

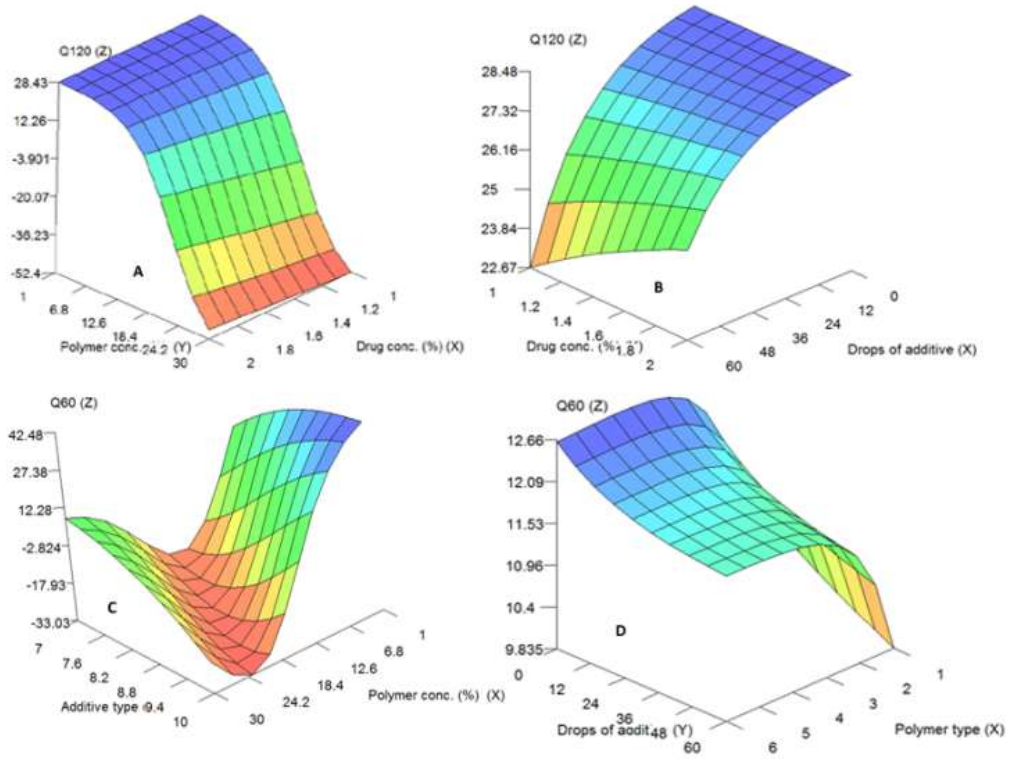


Fig. 7 Response surfaces generated by the modeling software for ketoprofen release from different gel formulations describing relationship between polymer and drug concentrations (A); drops of additives and drug concentration (B); drops of additive and polymer concentration (C) drops of additive and polymer type (D) and percentage drug released

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