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Optimization of preparation method for ketoprofen-loaded microspheres consisting polymeric blends using simplex lattice mixture design

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ABSTRACT

In the present investigation, simplex lattice mixture design was applied for formulation development and optimization of a controlled release dosage form of ketoprofen microspheres consisting polymers like ethylcellulose and Eudragit®RL 100; when those were formed by oil-in-oil emulsion solvent evaporation method. The investigation was carried out to observe the effects of polymer amount, stirring speed and emulsifier concentration (% w/w) on percentage yield, average particle size, drug entrapment efficiency and *in vitro* drug release in 8 h from the microspheres. Analysis of variance (ANOVA) was used to estimate the significance of the models. Based on the desirability function approach numerical optimization was carried out. Optimized formulation (KTF-O) showed close match between actual and predicted responses with desirability factor 0.811. No adverse reaction between drug and polymers were observed on the basis of Fourier transform infrared (FTIR) spectroscopy and Differential scanning calorimetric (DSC) analysis. Scanning electron microscopy (SEM) was carried out to show discreteness of microspheres (149.2 ± 1.25 μm) and their surface conditions during pre and post dissolution operations. The drug release pattern from KTF-O was best explained by Korsmeyer-Peppas and Higuchi models. The batch of optimized microspheres were found with maximum entrapment (~90%), minimum loss (~10%) and prolonged drug release for 8 h (91.25%) which may be considered as favourable criteria of controlled release dosage form.

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1. Introduction

Ketoprofen (2-(3-Benzoylphenyl) propionic acid), a nonsteroidal anti-inflammatory drug (NSAID) used in chronic disorders such as spondylitis, osteoarthritis and rheumatoid arthritis [1,2]. Its short biological half-life (2 − 3 h) directs frequent administration [3] of doses to relief pains in chronic inflammatory ailments which causes nausea, vomiting as unabsorbed remaining amount of drug between two dosing causes the irritation to gastrointestinal tract (GIT) membrane owing to insolubility of drug [4]. To overcome these associated adverse effects and to avoid problems of short half-life ketoprofen may be considered as a suitable candidate for developing prolonged release dosage form (microspheres), which may meet up therapeutic objective, patient acceptance and drug management [5].

Over the last two decades commonly reported methods of preparing ketoprofen-loaded microspheres include spray drying [6,7], emulsion cross-linking [8], ionotropic gelation [9], complex coacervation [10], melt dispersion [11], quasi emulsion solvent diffusion method [12,13] and emulsion solvent evaporation [14]. Among these methods, emulsion solvent evaporation (oil-in-oil, o/o) has many advantages such as cost effectiveness [15], simplicity, success with poorly aqueous soluble drug, and production of microspheres with relatively high drug loading [16], increase of surface area for better release and requirement of only mild conditions such as ambient temperature and constant stirring [17]. This method had not been much used to prepare ketoprofen-loaded microspheres [14,18–21]. Ethylcellulose polymers are recognized as 'generally regarded as safe' (GRAS) and used widely in tablet coatings, controlled-release coatings, microencapsulation, granulation, and in taste masking [22]. Ethylcellulose microspheres suffer from too slow and incomplete drug release as it is not porous type [23]. The coupling of permeable polymer with ethylcellulose can modify drug release profile [24]. Eudragit®RL 100 is the copolymers of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make this polymer permeable [25]. The nature of polymers greatly influences the rate of diffusion of drug molecules from the matrix of microspheres [26,27].

Conventional experimentation is empirical and lengthy and it involves a good deal of efforts as the effect of each variables was evaluated separately. Conventional method based on trial and error often lacks reproducibility, validity and versatility as this is not validated statistically. So its success frequently relies on the statistical knowledge and the working experience of the formulation scientist [28,29]. Software based statistical tool analyzes the effects of the interactions among different variables under investigation [30]. Many design methods are there to optimize the conditions of this method which are selected

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judiciously [31]. In factorial design levels of the factors are chosen under individual frame/limit. The factor levels can be fixed too within a composition (either % or fraction of the whole) [32]. This is used generally in the cases of composition of materials involved to prepare a product. Therefore, mixture design is found suitable where all fractions of the components must sum to unity and is known as simplex lattice mixture design (SLMD). The advantage of this design is that it requires least number of experimental runs [29,33–35].

The published data on modelling of microencapsulation of ketoprofen embedded in Eudragit®RL 100, a more permeable polymer, along with Ethylcellulose is conspicuously rare to our knowledge. Ketoprofen needs to be formulated as controlled release dosage form in a better way for post-operative patients in order to enhance its potentiality and to negate drawbacks of frequently administered dosage forms. The aim of this study was to design formulation criteria of controlled release dosage form of ketoprofen and the main objective was to examine the effects of independent variables, *i.e.*, amount of polymer, stirring speed and emulsifier's (Span 80) concentration on the responses such as percentage yield, particle size, drug entrapment efficiency and *in vitro* drug release in 8 h span from microspheres with the help of models and response surfaces generated by simplex lattice mixture design and to optimize the process variables to achieve the desired criteria in final product. Other objectives were to validate models and characterizations of products formed by emulsion solvent evaporation method.

2. Materials and methods

2.1. Materials

Ketoprofen (MW = 254.281) was purchased from Yarrow Chem Products (Mumbai, India). Ethocel (Ethylcellulose, viscosity range 18–22 mPa·s, ethoxyl content 48.0–49.5%, Dow) and Eudragit®RL 100 (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate polymer, MW approx. 150,000) were kindly donated by Colorcon Asia Pvt. Ltd. (Goa, India) and Evonik India Pvt. Ltd. (Mumbai, India) respectively. Span 80 (MW 428.61, HLB value 4.7; Loba Chemie Pvt. Ltd., India), Acetone (Merck Specialties Pvt. Ltd., India), methanol (Merck Specialties Pvt. Ltd., India), light liquid paraffin (density 823 kg/m^3 at 25 °C, viscosity 29.15 mPa·s at 25 °C; measured in our Laboratory) (Ranbaxy Fine Chemical Ltd., India) and petroleum ether (Ranbaxy Fine Chemical Ltd., India) were purchased and used as received without any further purification. All other reagents and solvents used were of analytical grade.

2.2. Experimental design

In the present study, the simplex lattice mixture design (SLMD) was used to evaluate the effect of amount of polymer (X_1, mg), stirring speed (X_2, rpm) and emulsifier (span 80) concentration (X_3, % w/w) on the responses: yield (%), average particle size (μm), drug entrapment efficiency (%) and cumulative drug release after 8 h (%) from microspheres. In contrary individual levels (actual amounts) used for each factor here, we used fractions of each level and sum of contributory fractions makes one always, *i.e.* 0.5 + 0 + 0.5 = 1 [30]. The factors, levels (in terms of coded value), and matrix of the experimental design were outlined in Table 1. These levels (coded) were ascribed to each of three factors. Design was generated by using Design-Expert®7 trial version software (Stat-Ease Inc., Minneapolis, USA). The measured response function (Y) of the mixture model was explained by using following quadratic equation [36]:

$$Y = \sum_{i=1}^{q} \beta_i x_i + \sum \sum_{i<j}^{q} \beta_{ij} x_i x_j \quad (1)$$

where, Y is the response variable; β_i and β_{ij} are the regression coefficients of pure component and interaction components respectively; x_i is the variable and $x_i x_j$ represents the interaction between variables.

In this study, total 14 runs were conducted of which six pure component blends, four binary blends, and four ternary blends. A coded level of simplex lattice mixture design was shown in Fig. 1. Analysis of variance (ANOVA) was used to estimate the significance of the model and to remove the non-significant terms ($p > 0.05$). F-test and Lack of Fit values confirm the applicability of the model. The best fit equations for all the responses were obtained after removing the non-significant terms [28]. A numerical optimization technique based on desirability function approach was used to optimize the compositions of formulation. However, optimization of all variables at the same time is not possible at a time because several responses may be applicable to do the same when one response may antagonize other [37]. During numerical optimization software suggests numerous check point solutions within the experimental domain along with optimized formulation. In view

Table 1
Design matrix and observed values of response.

Variables Level (code)	Low (0)	High (1)
Amount of polymer (mg) (X_1)	500	1500
Stirring speed (rpm) (X_2)	800	1200
Span 80 Conc. (% w/w) (X_3)	1	3

Polymer used (80% Ethylcellulose and 20% Eudragit®RL 100) but total amount of polymer varies

Run order	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3	Response 4
	Code						
	Amount of polymer (X_1)	Stirring speed (X_2)	Emulsifier concentration (X_3)	Yield (Y_1), %	Particle size (Y_2), μm	DEE (Y_3), %	Rel 8 h (Y_4), %
1	0.5	0	0.5	91.64 ± 1.17	160 ± 4.01	89.53 ± 4.00	89.67 ± 1.49
2	1	0	0	93.05 ± 1.79	181.93 ± 2.53	91.92 ± 5.98	86.06 ± 1.27
3	0	0	1	77.07 ± 2.53	94.73 ± 2.83	81.21 ± 5.84	96.25 ± 1.24
4	0	0	1	77.97 ± 1.38	110.07 ± 3.41	81.01 ± 5.51	96.09 ± 2.69
5	0	1	0	79.03 ± 1.45	91.93 ± 3.24	80.00 ± 6.56	96.92 ± 1.34
6	1	0	0	92.47 ± 1.59	175.33 ± 5.52	92.93 ± 4.94	86.96 ± 1.70
7	0.5	0.5	0	87.96 ± 1.10	150 ± 1.78	88.00 ± 5.74	88.98 ± 1.36
8	0	1	0	76.10 ± 1.87	79.93 ± 3.16	82.02 ± 5.13	96.48 ± 1.97
9	0.667	0.167	0.167	92.10 ± 1.68	162 ± 3.86	90.42 ± 4.32	88.44 ± 1.11
10	0.167	0.667	0.167	82.12 ± 1.90	112.33 ± 2.20	83.00 ± 5.21	92.95 ± 1.12
11	0.333	0.333	0.333	85.20 ± 1.55	121.87 ± 1.36	85.10 ± 4.82	89.76 ± 1.00
12	0.167	0.167	0.667	80.98 ± 1.09	116.07 ± 3.44	82.05 ± 2.67	91.63 ± 1.02
13	0.5	0.5	0	89.44 ± 1.17	155.47 ± 1.63	89.99 ± 7.35	91.08 ± 1.11
14	0	0.5	0.5	74.97 ± 1.31	77.27 ± 3.07	78.99 ± 6.37	95.05 ± 1.26

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