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Research paper

Study of formulation variables influencing the drug release rate from matrix tablets by experimental design

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Abstract

Experimental design was utilized to simultaneously investigate the effect of varying the type of diluent (insoluble Calcium phosphate or water-soluble arabic gum) and the diluent/matrix ratio on the drug release behaviour from both lipophilic (glyceryl behenate, Compritol®) or hydrophilic (hydroxypropylmethylcellulose) matrix tablets. Ketoprofen, theophylline and sodium sulphadiazine were selected as model drugs on the basis of their respectively very low, medium and high water-solubility, in order to evaluate the influence of this parameter as well. The selected response variables were the dissolution efficiency (i.e. the area under the dissolution curve) after one and six hours and the time necessary to dissolve 10% drug. Tablets obtained by direct compression of drug-diluent-matrix ternary mixtures prepared according to the experimental plan provided for by an asymmetric screening matrix, were tested for drug release properties using a USP paddle apparatus. Graphic analysis of the effects allowed identification, for each examined drug, of the formulation factors active on the selected responses and determination of the proper level of the variables to be selected for the response improvement. The different results obtained with the three examined drugs pointed out the role of the drug solubility in determining the influence of formulation parameters on drug release rate from matrix tablets.

Keywords: Experimental design; Asymmetric screening matrix; Matrix tablets; Drug release rate; Formulation optimisation

1. Introduction

Polymeric materials have been widely used in order to opportunely modify and modulate the drug release from solid pharmaceutical dosage forms such as sustained-release or controlled-release matrix tablets. However, a large number of factors, including the chemical–physical properties of the raw materials (both drug and excipients), the composition and the component's relative amounts in the formulations, as well as the manufacturing process parameters, can influence the drug release behaviour from the final products [1–4]. Therefore, complex, expensive and time-consuming pre-formulation studies are often necessary for the development of a product with the required release properties. Moreover, although an incremental improvement can be achieved through successive approximation experiments by means of a classic mono-varied approach, it is not possible to establish when and whether the optimal formulation has been actually obtained, nor to identify and quantify possible interaction effects among the variables.

Statistical experimental design methodologies are powerful, efficient and systematic tools in the design of pharmaceutical dosage forms, allowing a rational study of the influence of formulation and/or processing parameters on the selected responses with a shortening of the experiment time and an improvement in the research and development work [5–7]. The main objective of the experimental design strategies is to plan experiments in order to obtain the maximum information regarding the considered experimental domain with the lowest number of experiments [8]. Moreover, the multi-varied strategy of experimental design enables the simultaneous evaluation of the influence of the different variables involved in any process, being therefore particularly useful when, as in the case of pre-formulation studies, multiple factors have to be evaluated contemporaneously.

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In particular, optimisation by means of statistical experimental design methodologies has been successfully applied in the development of different kinds of modified-release dosage forms, allowing a quick and efficient quantification and prediction of the effects of formulation changes on the considered crucial responses [9–14].

Thus, the aim of the present paper was to evaluate, by means of a multi-varied experimental design methodology, the influence of both the type of diluent and matrix excipients and of the diluent/matrix ratio on the drug release behaviour from matrix tablets. Ketoprofen, theophylline and sodium sulphadiazine were selected as model drugs on the basis of their respectively very low, medium and high water-solubility, in order to evaluate the influence of this parameter as well. The selected response variables were the dissolution efficiency (i.e. the area under the dissolution curve) after one and six hours and the time necessary to dissolve 10% drug.

The proposed experimental design strategy should allow a rapid evaluation and identification of the parameters important in determining the drug release rate from matrix tablets, providing a powerful support for their rational selection during pre-formulation studies and thus shortening the time necessary for the development of effective dosage forms with the desired drug release behaviour.

2. Materials and methods

2.1. Materials

Ketoprofen (KETO), theophylline (THEO), Na sulphadiazine (NaSDZ), and hydroxypropylmethylcellulose (MW ≈ 86 kDa, methoxyl content 28–30%, hydroxypropoxyl content 7–12%, viscosity 3500–5600 cP of a 2% aqueous solution at 20 °C) (HPMC) were purchased from Sigma (St. Louis, MO, USA). Compritol® 888 ATO (USP-NF glyceryl behenate) was a gift from Gattefossé (Saint Priest, F). Arabic gum (A.G.) and Calcium hydrogen phosphate dihydrate (CaP) were supplied by Merck-Schuchardt (München, D).

2.2. Software for experimental design

The software NEMRODW was used for generation and evaluation of the statistical experimental design [15].

2.3. Preparation of tablets

For each drug with each matrix (Compritol or HPMC), eight different formulations were prepared, by varying the type of diluent (CaP or A.G.) and the matrix/diluent w/w ratio, always keeping the drug amount (20% w/w) and the total tablet weight constant, according to the experimental design matrix proposed by the NEMRODW software. Tablets were prepared by direct compression (with a hydraulic press at a force of $1.5t\,cm^{-2}$) of the components previously sieved (75–150 μm) and mixed for 15 min in a Turbula apparatus (Turbula mixer TA 2, Willy A. Bachofen Maschinenfabrik, Switzerland). The mixtures were checked for blend uniformity prior to tabletting (coefficient of variation (C.V.) of the mixing index $<5\%$). Weight uniformity of the tablets was controlled (Mettler, type AE 50) (C.V. $<2\%$).

2.4. Drug release studies

Drug release was recorded for 6 h using a USP rotating paddle fully automated apparatus (SOTAX AT7, Basel, CH), by adding each tablet to 1000 ml of unbuffered water (pH ≈ 6) thermostated at 37 + 0.5 °C and stirred at 50 rpm. Medium from each individual vessel is circulated continuously by means of a peristaltic pump through each of a series of flow cells located in the cell compartment of a UV/Vis spectrophotometer (Perkin–Elmer Lambda 2). Drug released amount was measured at predetermined time intervals by spectrometric assay at 261.0 nm (KETO), 271.5 nm (THEO) and 264.0 nm (Na-SDZ), respectively. The whole system is controlled by an external PC whose Windows-based dissolution software (Perkin–Elmer PEDS®) automatically collects and analyses drug release data. Sink conditions were maintained throughout the test. Each experiment was performed in triplicate (C.V. $<5\%$). Dissolution efficiency (D.E.) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [16].

3. Results and discussion

In the present study, experimental design methodology was exploited for systematically evaluating the effect of varying the type of diluent and matrix excipients and the matrix/diluent ratio on drug release from matrix tablets, with the aim of identifying the most significant factors in determining its release rate and establishing their best levels for optimizing the considered experimental responses. Toward this purpose, two products with opposite properties, i.e., the lipophilic Compritol (which is the ester of glycerol and behenic acid) and the hydrophilic HPMC were selected as matrix-forming materials for sustained release solid dosage forms. Their direct compressibility and binding properties as well as, respectively, the insolubility or swellability in water, confer them with good matrix-building abilities [17–19]. With the same rationale, two different excipients, i.e. CaP and A.G. were chosen as insoluble and water-soluble model diluents, respectively, being both suitable for preparing tablets by direct compression. Finally, in order to also evaluate the role of drug solubility on its release rate from matrix tablets, three

Table 1
Eight-run asymmetric screening matrix

Trials	Variable U_1 (type of diluent)	Variable U_2 (matrix/diluent)
1	1	1
2	2	2
3	1	2
4	2	3
5	1	4
6	2	4
7	1	5
8	2	5

model drugs with different water solubility, i.e. the poorly-soluble KETO (0.24 mg/ml), the moderately soluble THEO (8 mg/ml) and the highly soluble NaSDZ (500 mg/ml) were chosen.

Among the different release parameters utilized in the literature as response variable to describe and optimise drug release behaviour [10,11], the following were selected as the most representative:

Y_1: time to dissolve 10% of drug ($t_{10\%}$)
Y_2: dissolution efficiency at 60 min (% w/w) (DE60)
Y_3: dissolution efficiency at 360 min (%) (DE360).

The parameters $t_{10\%}$ and dissolution efficiency at 60 min were chosen to achieve information about the initial drug release rate, whereas the final dissolution efficiency (DE360) as indicative of the total amount of drug released.

The effect of different levels of each independent variable on the considered responses was studied. The independent variables evaluated for each examined matrix (HPMC and Compritol) and for each considered drug (KETO, THEO and Na-SDZ) and their respective levels were:

U_1 diluent type: CaP; A.G.
U_2 matrix/diluent (w/w ratio): 70/10; 60/20; 50/30; 40/40; 30/50.

A qualitative model [20] was hypothesised among response and factors under study that contained one constant plus, for each factor, a number of terms equal to its number of levels minus one:

$$y = b_o + A_1x_1 + B_1x_2 + B_2x_2 + B_3x_2 + B_4x_2$$

In particular, A_1 is the coefficient relative to the effect on the response of the level change of the factor U_1 and $B_1 - B_4$ are the coefficients relative to the changes of level of the factor U_2.

In order to evaluate the effects on the response of variations in the factor levels, an asymmetric screening design was used [6,21]. The asymmetric screening design allows a rapid examination of factors at different numbers of levels, thus it can be used when the number of levels of each factor is different. This specific design normally derived from symmetrical designs [22,23] and in this case the resulting matrix was constituted by 18 experiments. In order to reduce the number of experiments, the exchange algorithm was applied [6,24]. Given a set of feasible experiments and the number of runs, this algorithm determines a D-optimal design characterized by a lower number of experiments but equally able to give a good quality of information. In the present case, the D-optimal design contained eight experiments (Table 1). Six independent studies were performed, two for each drug with each matrix-forming material, using matrix tablets prepared by always keeping the drug amount constant (20% w/w) and varying the diluent type and the matrix/diluent ratio, according to the same general experimental plan (Table 1) . For each series of studies, the drug release experiments were carried out in a randomised order.

The experimental plans and the obtained responses for the three examined drugs are reported in Tables 2–4, whereas, by way of example, the release profiles of KETO from the different matrix tablet formulations with HPMC or Compritol are shown in Fig. 1.

Statistical evaluation of the experimental results processed with the NEMRODW software made it possible to obtain the desired information about the weight of each level of each factor on the considered responses.

In particular, the graphic analysis of the effects [25] was used to evaluate the different effect of factor levels and determine the suitable level of the variable to be selected for optimising the considered response. The results of

Table 2
Experimental plan and observed responses for KETO–HPMC and KETO–Compritol tablets with Ca phosphate (CaP) or arabic gum (A.G.) at different matrix/diluent (w/w) ratios

Trials	U_1 (diluent)	U_2 (matrix/diluent)	Matrix: HPMC			Matrix: Compritol		
			Y_1 ($t_{10\%}$)	Y_2 (DE60)	Y_3 (DE360)	Y_1 ($t_{10\%}$)	Y_2 (DE60)	Y_3 (DE360)
1	CaP	70/10	173	2.60	9.71	119	3.76	12.30
2	A.G	60/20	165	2.69	10.63	46	6.22	22.73
3	CaP	60/20	151	2.84	10.72	135	3.60	11.33
4	A.G	50/30	128	3.07	12.69	43	6.71	29.16
5	CaP	40/40	70	5.38	15.34	189	2.72	9.19
6	A.G	40/40	92	3.95	15.38	39	7.65	32.44
7	CaP	30/50	56	6.11	17.05	197	2.35	8.91
8	A.G	30/50	25	7.94	23.65	31	8.60	37.47

Table 3
Experimental plan and observed responses for THEO–HPMC and THEO–Compritol tablets with Ca phosphate (CaP) or arabic gum (A.G.) at different matrix/diluent w/w ratios

Trials	U_1 (diluent)	U_2 (matrix/diluent)	Matrix: HPMC			Matrix: Compritol		
			Y_1 ($t_{10\%}$)	Y_2 (DE60)	Y_3 (DE360)	Y_1 ($t_{10\%}$)	Y_2 (DE60)	Y_3 (DE360)
1	CaP	70/10	283	1.89	6.98	290	1.20	3.62
2	A.G	60/20	89	3.97	15.09	63	5.09	19.11
3	CaP	60/20	277	1.96	7.09	280	1.37	3.81
4	A.G	50/30	75	4.40	17.30	60	5.28	20.51
5	CaP	40/40	265	2.10	7.36	270	1.57	4.52
6	A.G	40/40	37	6.96	22.38	55	5.59	21.23
7	CaP	30/50	215	2.61	8.31	220	1.80	5.67
8	A.G	30/50	29	8.03	24.03	50	5.95	22.56

the graphic analysis of the investigated factors related to the $t_{10\%}$ and DE360 responses for the different drug-Compritol and drug-HPMC tablets examined are presented in Figs. 2–7. It must be pointed out that for the statistic treatment of the data, the DE360 response, in the case of THEO-HPMC tablets, and the $t_{10\%}$ response, in the case of NaSDZ–HPMC and NaSDZ–Compritol tablets, were transformed into their reciprocals (1/DE360 and $1/t_{10\%}$). Data transformation was applied since a statistical evaluation, pointed out that using the original responses, the regression models obtained had a non-constant variance, that was stabilized using the reciprocal of the responses [26].

Graphic analysis of effects is a simple experimental design tool in which the changes of levels that are active on the response correspond to the bars that exceed the dotted vertical lines, which represent the experimental error (Figs. 2–7a). In particular, coefficient A_1 indicates the effect on the response moving from level 1 to level 2 of factor U_1. Coefficient B_1 indicates the effect on the response moving from level 1 to level 2 of factor U_2; B_2 indicates for the same factor the effect on the response moving from level 1 to the level 3; B_3 refers to the 1–4 level change and, finally, B_4 to the 1–5 level change. Once the active level changes are pointed out, it is possible to individuate the suitable levels with another graph in which the effects of each tested level on the response are reported (Figs. 2–7b). In this graph the length of the bars is correlated with the effect of the level on the response: the bars with maximum length are those relative to the levels that determine a maximization of the response. Bars with similar length indicate that the change in the factor levels is not statistically significant for the observed response [25].

Starting from these figures, it is possible to select, for each drug, the best level of each factor for each considered response. In particular, for each variable, the level to select is indicated by the highest or lowest bar, depending on the considered response have to be maximized (DE360) or minimized ($t_{10\%}$), respectively. This is, for example, the case of KETO tablets with HPMC as polymeric matrix (Fig. 2), where it is clear that the effect of the two levels of factor U_1 (CaP or A.G.) on the considered responses is not statistically important. In contrast, the change in level of the other factor (matrix/diluent ratio) was statistically significant, and the results indicated that for optimising the selected responses (i.e. for minimizing $t_{10\%}$ and maximizing DE360), the 30/50 (w/w) HPMC/diluent ratio should be used. Interestingly, opposite results were obtained when using Compritol as matrix-forming material (Fig. 3). In fact, in this case, changes in the matrix/diluent (w/w) ratio were not important, whereas the diluent type was statistically significant, and the relative bars indicated that the soluble excipient should be used for optimising both the considered responses. These different results can be explained on the basis of the different nature of the two matrices and of the lipophilic character of the drug. In fact, the dissolution and subsequent diffusion of KETO through the hydrophilic HPMC matrix tablets is particularly unfavourable and, therefore, the progressive replacement of HPMC by an inert

Table 4
Experimental plan and observed responses for NaSUL–HPMC and NaSUL–Compritol tablets with Ca phosphate (CaP) or arabic gum (A.G.) at different matrix/diluent w/w ratios

Trials	U_1 (diluent)	U_2 (matrix/diluent)	Matrix: HPMC			Matrix: Compritol		
			Y_1 ($t_{10\%}$)	Y_2 (DE60)	Y_3 (DE360)	Y_1 ($t_{10\%}$)	Y_2 (DE60)	Y_3 (DE360)
1	CaP	70/10	92	4.77	12.74	163	2.58	10.46
2	A.G	60/20	78	4.76	15.11	119	3.11	14.53
3	CaP	60/20	142	4.29	10.34	240	2.13	7.87
4	A.G	50/30	83	4.55	14.72	130	2.96	13.28
5	CaP	40/40	400	2.58	6.33	400	1.56	5.22
6	A.G	40/40	92	4.36	13.58	133	2.80	13.01
7	CaP	30/50	400	2.47	6.19	400	1.42	4.71
8	A.G	30/50	120	3.78	11.94	153	2.58	11.42

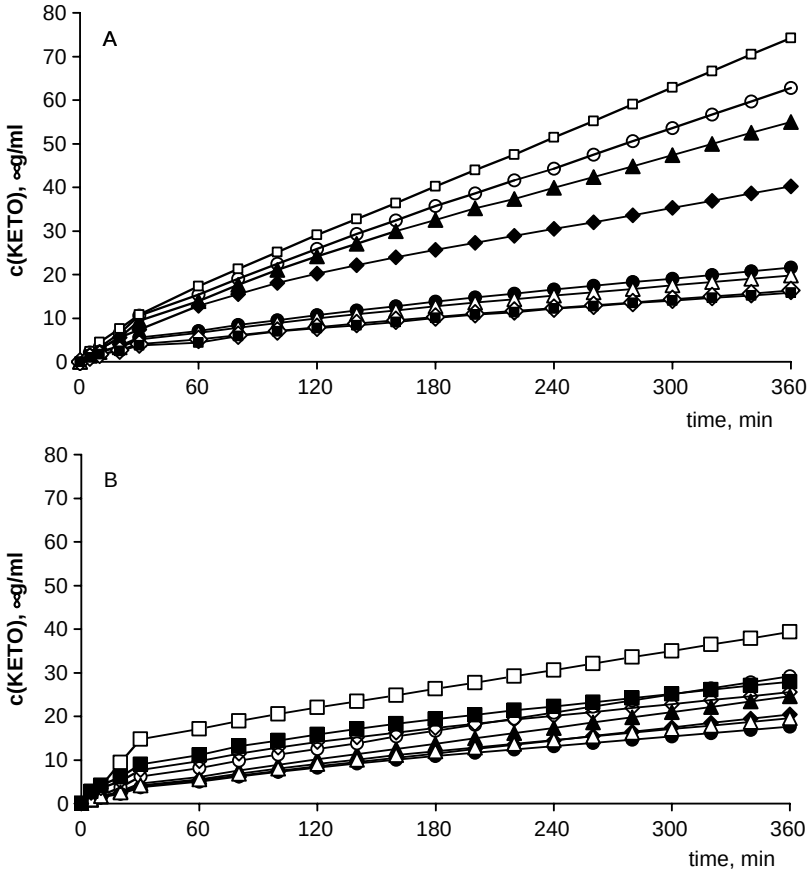

Fig. 1. Release curves of ketoprofen (KETO) from matrix tablet formulations with HPMC (A) or Compritol (B). Key: ● (1); ♦ (2); △ (3); ▲ (4); ◇ (5); ○ (6); ■ (7); □ (8) (The numbers correspond to the tablet formulations reported in Table 1.)

diluent improves the drug release rate. Moreover the results indicated that this effect takes place with both the examined fillers, despite their different solubilities. Probably, the insoluble CaP acts by interfering with the gel structuring and hinders the gel-forming process of the matrix [27]. On the other hand, the soluble A.G. acts as a channelling agent, by rapidly dissolving and easily diffusing outward [28]. On the contrary, in the case of tablets with the lipophilic Compritol (due to the higher affinity of the hydrophobic KETO towards such matrix, through which the dissolved drug more easily diffuses) the type of diluent added was more important than the matrix/diluent ratio and it was the critical factor in determining the dug release rate. The presence of CaP or A.G. had opposite effects on the drug release rate: the former displayed a negative influence, by reducing the matrix erosion process and consequently hindering drug diffusion and release, whereas the latter had a positive effect, since, as in the case of HPMC tablets, its rapid dissolution allowed a decrease in tortuosity and/or an increase in the matrix porosity.

With regard to the THEO tablets, the graphic analysis of the effects showed that in the case of the HPMC matrix (Fig. 4), only the type of diluent was important and that,

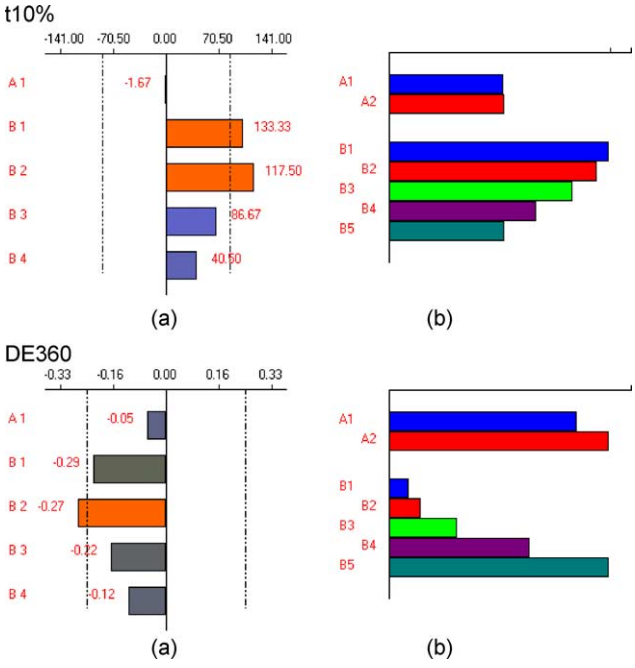

Fig. 2. KETO tablets with HPMC. (a) Graphic analysis of effects: A_1 coefficient relative to the change of level of the factor U_1 (diluent); B_1–B_4 coefficients relative to the change of levels of the factor U_2 (matrix/diluent ratio, w/w). (b) Response trend due to the different factor levels.

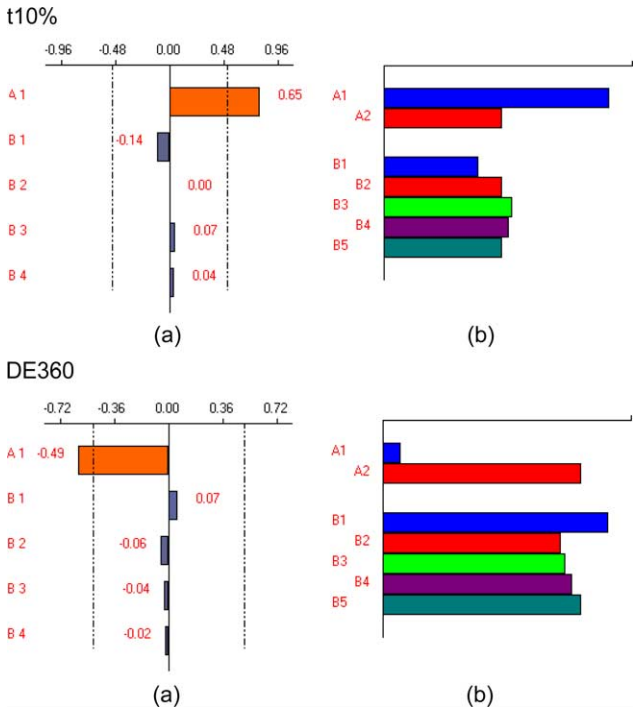

Fig. 3. KETO tablets with Compritol. (a) Graphic analysis of effects: A_1 coefficient relative to the change of level of the factor U_1 (diluent); B_1–B_4 coefficients relative to the change of levels of the factor U_2 (matrix/diluent ratio, w/w). (b) Response trend due to the different factor levels.

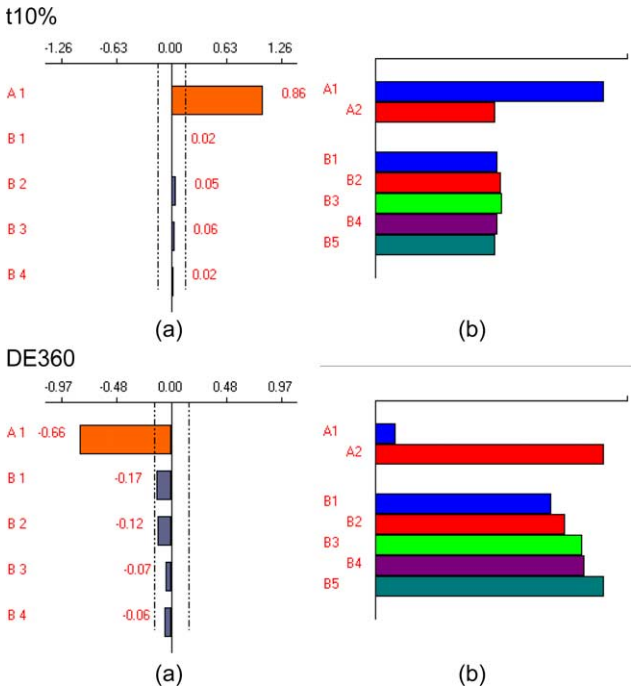

Fig. 5. THEO tablets with Compritol. (a) Graphic analysis of effects: A_1 coefficient relative to the change of level of the factor U_1 (diluent); B_1–B_4 coefficients relative to the change of levels of the factor U_2 (matrix/diluent ratio, w/w). (b) Response trend due to the different factor levels.

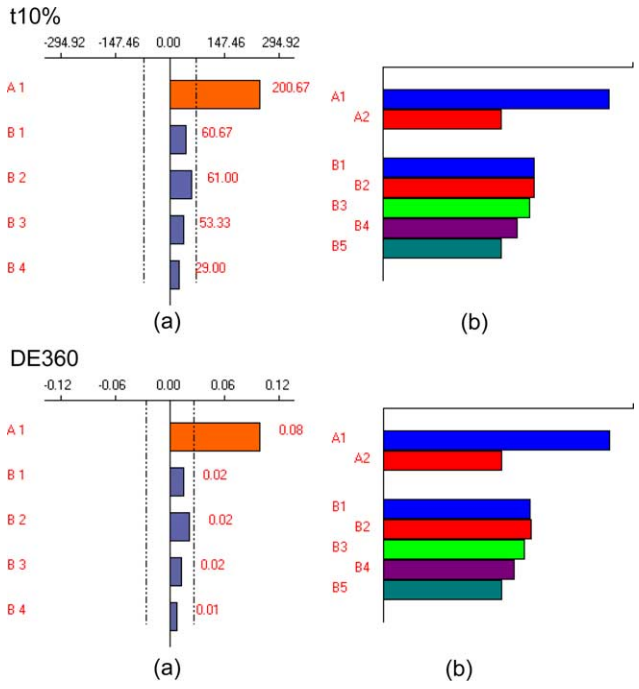

Fig. 4. THEO tablets with HPMC. (a) Graphic analysis of effects: A_1 coefficient relative to the change of level of the factor U_1 (diluent); B_1–B_4 coefficients relative to the change of levels of the factor U_2 (matrix/diluent ratio, w/w). (b) Response trend due to the different factor levels.

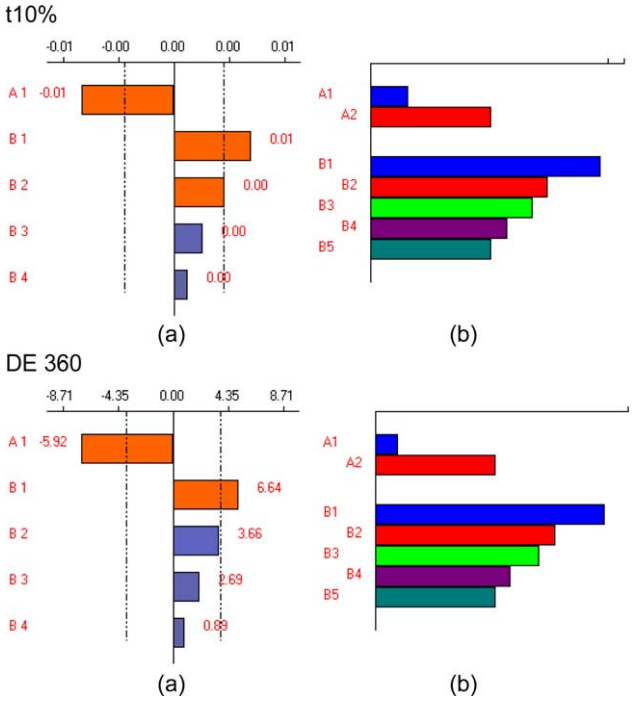

Fig. 6. NaSDZ tablets with HPMC. (a) Graphic analysis of effects: A_1 coefficient relative to the change of level of the factor U_1 (diluent); B_1–B_4 coefficients relative to the change of levels of the factor U_2 (matrix/diluent ratio, w/w). (b) Response trend due to the different factor levels.

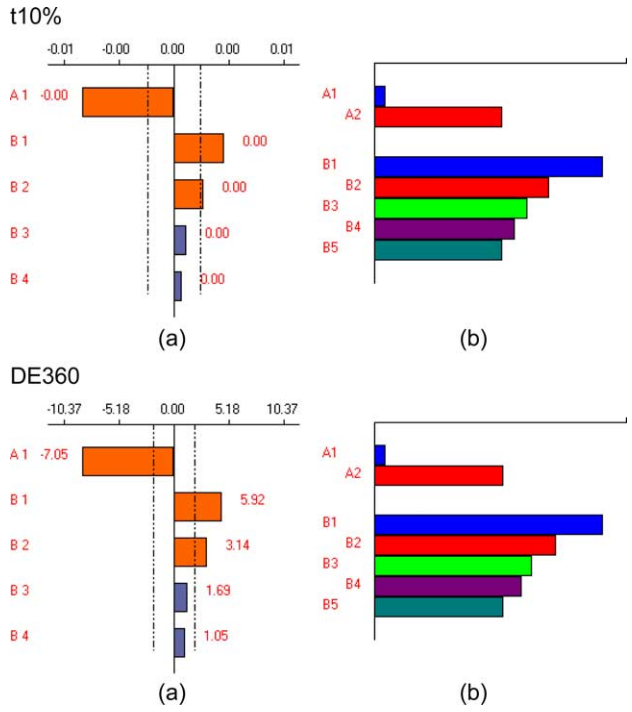

Fig. 7. NaSDZ tablets with Compritol. (a) Graphic analysis of effects: A_1 coefficient relative to the change of level of the factor U_1 (diluent); B_1–B_4 coefficients relative to the change of levels of the factor U_2 (matrix/diluent ratio, w/w). (b) Response trend due to the different factor levels.

in order to minimize $t_{10\%}$ and maximize DE, A.G. should be used. These same results were obtained also in the case of the Compritol matrix (Fig. 5), and were analogous to those observed for KETO–Compritol tablets. By contrast, the different results obtained with THEO-HPMC tablets, with respect to those with the KETO–HPMC tablets, can be attributed to the different solubility of the two drugs: in the case of the more water-soluble THEO, its diffusion through the hydrophilic matrix is not as unfavourable as for KETO and therefore the positive effect obtained by adding A.G. manifests itself independently on the HPMC/A.G. ratio. Moreover, whereas in the case of KETO, as expected, higher DE values were observed for Compritol than for HPMC tablets, similar DE values were instead obtained in the case of THEO with both the matrices. Such a result can be attributed to the well-balanced hydrophilic and lipophilic characteristics of this drug (oil/water partition coefficient 0.6 in comparison with 85 for KETO).

Finally, as for the NaSDZ tablets, with both HPMC (Fig. 6) and Compritol (Fig. 7) matrices, both $t_{10\%}$ and DE values were significantly affected by the type of diluent and the matrix/diluent ratio. Graphic analysis of the effects indicated that, in order to optimize the responses, independently of the type (hydrophilic or lipophilic) of the matrix, A.G. should be used as diluent, with a 70/10 (w/w) matrix/diluent ratio. Evidently, also in this case the presence of the water-soluble excipient was favourable; however, in contrast to the case of KETO tablets, the highest matrix/diluent ratio was the most effective combination. It can be reasonably hypothesized that NaSDZ, due to its good water-solubility, rapidly dissolves and then the presence of high amounts of the hydrophilic diluent could be not only unnecessary, but also have a competitive effect and reduce the drug dissolution rate from matrix tablets. Moreover, the unexpectedly similar values of DE obtained with both HPMC and Compritol matrices, in spite of their opposite properties and the very high water-solubility of the drug, could probably be attributed to the excessive affinity of NaSDZ for the hydrophilic matrix; in fact, it can give rise to the formation of possible drug-polymer interactions which could in-turn reduce the drug release rate. Such hypothesis is supported by the demonstrated ability of HPMC to have hydrogen bonding interactions with various drug molecules [29–31]. The mechanisms of the hypothesized NaSDZ–HPMC interaction are currently under investigation.

4. Conclusion

Experimental design strategy has shown to be a very useful tool in pre-formulation studies aimed at the development of sustained-release formulations based on matrix-tablets, allowing a rapid, systematic and reliable screening to identify and quantitatively define the significant factors influencing the drug release.

In particular, graphic analysis of the effects enabled identification for each examined drug of the formulation factors active on the selected responses, i.e. $t_{10\%}$ and DE, and determination of their best level for the response optimisation.

Moreover, the different results observed with the different examined drugs underlined the role of drug solubility in determining the influence of formulation parameters on its release rate from the tablets. In fact, for example, only in the case of KETO–HPMC tablets, the addition of the water insoluble excipient CaP did not have a negative effect on the drug release rate with respect to the water-soluble one. Furthermore, even though the presence of A.G. always had a favourable influence, the optimal matrix/diluent (w/w) ratio was very different passing from 30/50 for KETO tablets to 70/10 for NaSDZ tablets.

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