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INFLUENCES OF PROCESSING METHOD, FILLER TYPE AND APPLIED COMPRESSION FORCE ON PHARMACEUTICAL PROPERTIES OF KETOPROFEN ORAL MATRICES.

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ABSTRACT

The aim of this study is to investigate the possible individual and joined influences of processing method, filler type and applied compression force on the physical performance of HPMC based oral matrices using ketoprofen as a model drug. Design implemented was $3^{(3-1)}$ fractional factorial design where each of the investigated variables was examined at 3 different levels. Matrix tablets were prepared according to the design and were evaluated for their weight variation, friability and drug release properties. Results indicated that processing method and filler type were found to influence weight variation, friability and drug release attributes of different matrices either through their individual or joined effects ($p< 0.05$). Moreover, the joined influences of processing method and filler type on weight variation and friability properties were shown to be comparable to the negligible influence of the applied compression force on both properties. Whilst the influence of applied compression force on time for 50% drug release and dissolution efficiency properties of different matrices was proved to be profound ($p= 0.0154$), drug release kinetics (n) appeared to be the least affected matrix property by any of the variables investigated. The study highlighted the supremacy of the joined influence of processing method and filler type on different matrix properties in comparison to the individual influences of each variable alone, at least within the experimental domain of the present study.

KEYWORDS: Fractional factorial design, processing method, filler type, applied compression force, HPMC matrices, individual and joined influences.

INTRODUCTION

Hydroxypropyl methylcellulose based matrices are the most frequently applied technique to fabricate drugs into oral controlled release delivery systems which is attributed to simplicity, flexibility and reproducibility properties characterizing the manufacturing of these matrices.[1,2]

Numerous reports have addressed the individual influences of either formulation or processing variables on the concert of HPMC oral matrices.[3-5] However, cited researches dealing with the mutual influences of many variables on the performance of HPMC based oral matrices are scarce.[6, 7]

Undoubtedly, introduction of statistical design in formulation technology has drawn attention to the advantages of evaluating the joined influences of many formulations and processing variables using only a limited number of experimental runs instead of using large number of formulations to study the possible effects of each type of variable alone in conventional manner.

Making use of statistical design in a previous study, we were able to show how the joined effect of some formulation and processing variables might be more influential than the individual effects of each variable alone on the various attributes of HPMC matrices and, moreover, we emphasized on such mutual influences despite their statistical ignorance in some instances.[7]

This study is a part of research series addressing the importance of the mutual influences that some manufacturing and processing variables might jointly have on pharmaceutical properties of HPMC based oral matrices and, accordingly the present study aims at screening and evaluating the possible individual and mutual influences of two process variables (processing method and applied compression force) and one formulation variable (filler type) on pharmaceutical attributes of Ketoprofen loaded HPMC oral matrices using $3^{(3-1)}$ fractional factorial design.

MATERIALS AND METHODS

Materials

Working standard Ketoprofen (Zhejiang East Asia, China), anhydrous lactose (DFE Pharma, Germany), microcrystalline cellulose (grade 102, FMC Biopolymer, Ireland), dibasic calcium

diphosphate (Budenhem, Germany); purified talc (Imerys, Italy); colloidal silicon dioxide (Aerosil, Anatwerpen, Germany) and magnesium stearate (Greven, Netherland) were all Pharmaceutical grade products and were kindly donated by Azal Pharmaceutical Industry, Sudan. Hydroxypropyl methylcelluose (K4M HPMC, 4000cps) was a Pharmaceutical grade product of Feicheng Ruitai Fine Chemicals (China) and was generously donated by the Blue Nile Pharmaceutical industry, Sudan. Other materials and reagents were analytical grades obtained from different commercial sources.

Experimental design

According to the aim of the experiment, a 3^{3-1} fractional factorial design was selected as an experimental design, in which 3 variables, namely, manufacturing method, filler type and hardness (as indication for the applied compression force) were each examined at 3 different levels through 9 experimental runs. Levels selected for manufacturing method were direct compression (DC), dry granulation (DG) and wet granulation (WG) whereas grade 102 microcrystalline cellulose (MCC), anhydrous lactose (LA) and dibasic calcium diphosphate (DCD) were selected as levels for filler type and, moreover, hardness ranges of 7-9, 10-12 and 13-15 kg/cm2 were chosen as different hardness levels to indicate respective compression force applied (Table 1).

Preparation of matrix tablet formulations

For each experimental run, accurately weighed 20 g of ketoprofen, 14 g of HPMC and 17 g of either lactose (LAC), microcrystalline cellulose (MCC) or dibasic calcium diphosphate (DCD) were mixed together using porsaline-made mortar and pestle for 10 min. For runs prepared by direct compression method (FF1, FF2 and FF3), obtained powder blend was passed with 0.4 g of colloidal silicon dioxide and 1.6 g of purified talc through # 0.71 mm screen and mixed for 5 min. 1.8% w/w magnesium stearate was finally added and mixed gently for extra 2 min. Powder blend was then compressed under different forces by rotary press tableting machine (ZP7 rotary press, Shanghai Yali, China) equipped with size 9 mm flat punch to produce matrix tablets having different hardness levels.

For matrix formulations designed to be prepared by dry granulation (FF4, FF5 and FF6), the mixture blend of the drug, HPMC and the respective filler which was mixed with colloidal silicon dioxide and talc was compressed randomly with a large punch at random weight and high hardness to produce slugs. The slugs were granulated by crushing, passed through # 0.71

mm screen, mixed with magnesium stearate and processed into matrices as described before with direct compression method.

For matrix formulation runs that considered for production by wet granulation method (FF7, FF8 and FF9), the mixture of the drug, HPMC and the specified filler that previously mixed for 10 min was wetted by addition of suitable volume of purified water to form slightly wet mass which was forced through #16 mesh screen to obtain granules. Granules were then dried in a horizontal flow oven at 65 ºC for 50 min (DAIHAN Scientific Co. ltd, WOF- 155, Korea), passed with the colloidal silicon dioxide and purified talc through # 0.71 mm screen, mixed for 5 min and processed into matrices after addition of magnesium stearate as described with direct compression method.

In all runs, obtained matrices were of different hardness levels in the range 7-15 kg/cm^2, weighed 270 mg in average and contain 100 mg ketoprofen per unit matrix and.

Qualification of matrix tablets

Randomly selected samples of matrices from all formulation runs were subjected to different pharmacopoeial tests in order to determine and evaluate their pharmaceutical properties.

Matrix weight variation[8]

Randomly selected 20 matrix tablets of each run were weighed, mean value and relative standard deviations (% RSD) from the mean value for all matrices were calculated and compared to the allowed Pharmacopoeial limitations for weight variation.

Matrix friability[9]

For each run, 20 matrix tablets were weighed and tested in friabilator rotating at speed of 25 round per minute for 4 min (Electronic 902, India). Matrices were then de-dusted, re-weighed and friability was calculated as a percentage ratio of the loss in weight to the total weight of matrices before test conduction.

Matrix hardness[10]

The test was performed as per Ph. Eur. in which 10 randomly selected matrices from each formulation run were individually investigated for the force (in kg/cm2) required to break the matrix using Pharmatest® hardness tester (Hainbursg, Germany). The test was carried out to ensure settings of the applied compression force as a variable in the design.

In vitro drug release test[11]

The dissolution test was carried out using USP paddle apparatus set at 100 rpm (Pharmatest®, D- 63512, Hainbursg, Germany). Dissolution medium was 900 ml of phosphate buffer pH 6.8 maintained at 37 ± 0.5 ºC. For each formulation run 3 matrices were subjected to the test which was conducted for 12 hrs and 10ml dissolution samples were withdrawn at predetermined time intervals, filtered and assayed for the drug spectrophotometrically at λ_{max} 255nm (UV-vis spectrophotometer, Shimadzu®, Japan) against phosphate buffer as a blank.[11] The mean cumulative percentage of drug released was calculated and plotted against respective time interval to generate drug release profiles of different runs. For comparative purposes, time for 50% drug release ($T_{50\%\ rel}$) and dissolution efficiency of the first 4 hours (DE_{0-4}) for all formulation runs were calculated from the respective drug release profiles.

Determination of Ketoprofen release kinetics from different matrices

Dissolution data of all formulation runs were fitted to power law model in order to determine the diffusion exponent (n) that characterizes the drug release kinetics.[12] Suitability of the selected model to fit the dissolution data was assured using determination coefficient (r^2) and associated probability value (p).

Influences of different factors on physical performance of Ketoprofen matrices

Possible direct and combined influences of filler type, manufacturing method and matrix hardness on properties of different matrices were investigated at linear and quadratic levels using surface model fitting and regression techniques.

Statistical data analysis

Values for different properties of matrix tablets was presented as mean ± standard deviation whereas convergence of the measured mean values of properties with the stated Pharmacopoeial limits was evaluated using % relative standard deviation term (% RSD). Descriptive statistics relying on determination coefficient (r^2) and probability significance (p) were used to evaluate the efficiency of the power law model fitting during determination of the diffusion exponent (*n*) that characterizes drug release kinetics from all formulation runs.

Moreover, inferential statistics relying on regression analysis, residual regression, surface model fitting, analysis of variance and mathematical approaches were used to examine the power of the individual and combined influences that investigated variables have exhibited

on different attributes of the produced matrix tablets. Computations were aided by software computer package STATISTICA 8 (Statsofts Inc., USA) and in all cases, probability $p \leq 0.05$ was considered as a cutoff point for significant influences.

RESULTS AND DISCUSSION

layout and Pharmaceutical attributes of different experimental runs are enclosed in Tables 1, 2 , 3 and Fig. 3 whereas influences of investigated variables on different properties of produced matrices are summarized in Figures 1, 2, 4 and 5. It appears from the results that investigated variables have influenced the properties of yielded matrices in different manners which would be thoroughly considered in the following subsections.

Table I: Experimental runs layout for the 3^{3-1} fractional factorial design

Formulations	Manufacturing method [a]	Filler type [b]	Hardness range (kg/cm^2)
F1	DC	MCC	7-9
F2	DC	LAC	13-15
F3	DC	DCD	10-12
F4	DG	MCC	13-15
F5	DG	LAC	10-12
F6	DG	DCD	7-9
F7	WG	MCC	10-12
F8	WG	LAC	7-9
F9	WG	DCD	13-15

[a] *DC, DG and WG indicate direct compression, dry granulation and wet granulation, respectively;* [b] *MCC, LAC and DCD stand for microcrystalline cellulose, lactose and dibasic calcium diphosphate, correspondingly*

Influences of variables on matrices weight variation property

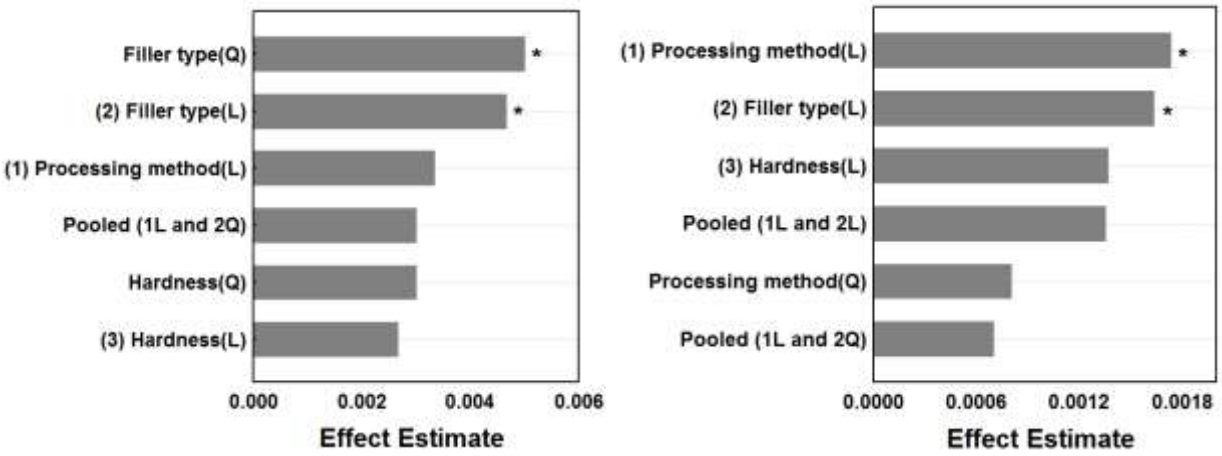
Displayed average weights of matrices among different formulations vary insignificantly around the theoretical matrix weight between 265.2 and 273.3mg (t' test, p=0.110) with %RSD ranged 2-3% (Table 2).

All batches appear within the accepted requirement for weight variation according to the category of <500 mg solid oral dosage form which requires maximum %RSD of 5% to fulfill the weight variation specification.[8]

Table 2: Weight variation, friability and hardness attributes of different matrix formulations

Formulations	Weight variation (mg) Mean (%RSD)	Friability (%) Mean ± SD	Hardness (kg/cm^2) Mean ± SD
F1	265.2 (2.1%)	0.43 ± 0.02	8.1 ± 1.0
F2	268.7 (2.8%)	0.61 ± 0.09	13.0 ± 0.7
F3	265.2 (3.0%)	0.66 ± 0.10	11.3 ± 1.3
F4	267.4 (2.1%)	0.41 ± 0.15	14.2 ± 1.0
F5	269.5 (3.0%)	0.56 ± 0.22	10.4 ± 0.5
F6	273.3 (2.3%)	0.71 ± 0.08	7.9 ± 0.8
F7	269.6 (2.0%)	0.37 ± 0.19	12.0 ± 0.3
F8	270.0 (2.6%)	0.48 ± 0.11	8.3 ± 0.8
F9	267.4 (2.3%)	0.33 ±0.07	14.9 ± 0.5

Among different factors investigated, only filler type (at both linear and quadratic setting) appears to have an influential effect on matrix weight variation (p= 0.0245) followed by that of the processing method and, moreover, the joined influence of processing method and filler type on weight variation property appears comparable to that of applied compression force as individual processing variable that indicated for by matrix hardness (Fig. 1a).

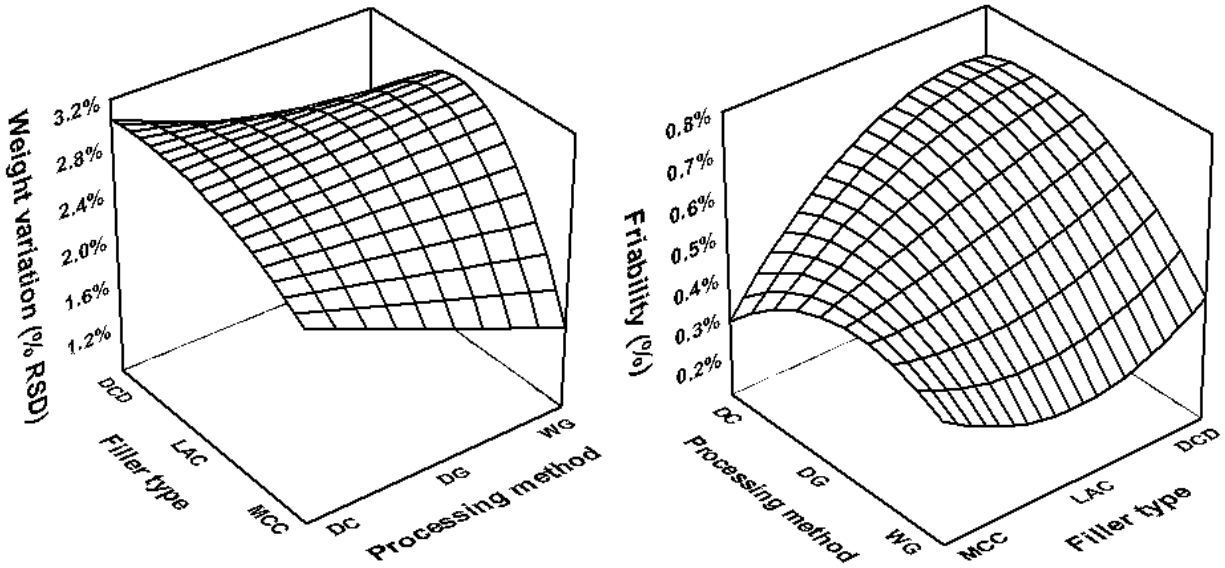


(a) ***(b)***

Fig. 1: Estimate of linear (L) and quadratic (Q) individual and pooled variables' effects on (a) weight variation and (b) friability attributes of different matrix formulations with * indicating significant effect at p< 0.05.

In general, variation of matrix weight is related mainly to the flowability of the powder blend prior compression where both filler used and manufacturing techniques are expected to affect the formulation flow criteria.

The results demonstrate that with utilization of either MCC or DCD as a diluent, the %RSD for weight variation tends to decrease especially with formulations processed by either dry or wet granulation method (F4, F6, F7 and F9) as summarized in Table 2 and illustrated in Fig. 2a. This might be attributed either to the granular nature of both diluents or to the granular yield of formulations associated with the two processing methods. The influence of processing method on weight variation property of matrix formulations is well documented,[7,13] however, with application of the less granular LAC as a diluent, %RSD measures a comparative higher value irrespective to the processing method utilized, indicating less consistent powder flow which promotes the chance for weight variation to occur (Fig. 2a).



(a) *(b)*

Fig. 2: Surface plots for the changing profiles of (a) weight variation and (b) friability of different matrices in response to the joined variation in filler type and manufacturing methods at matrix hardness of 10-12kg/cm^2

Interestingly, the influence of filler type on matrix weight variation is of curvature type rather than simple linear one (Figs. 1a and 2a). Such finding might support extra second order investigations of this variable which is beyond the scope of the present study.

Influences of variables on matrices friability property

Values of friability showed by different matrix formulation were considerably varied (one way ANOVA, $F_{cal} >> F_{crit}$) between 0.33 and 0.71% (Table 2) and despite that all matrices appear within the specified <1% limit for friability.[9]

Both filler type and processing method have revealed considerable linear influences on matrix friability (Fig. 1b) with the influence of processing method being more profound (p= 0.0281) than that of filler type (p= 0.0426).

Three directional surface plot for the changing profiles of matrix friability in response to variation in filler type and manufacturing methods at medium level of applied compression force (matrix hardness of 10-12 kg/cm^2) is shown in Fig. 2b. The figure clearly demonstrates that changing of processing method from DC to WG would result in production of matrices with low desired friability regardless to the filler used. Moreover, the plot signifies that when DC is selected as a manufacturing method, utilization of either MCC or LAC as a filler seems necessary to achieve matrices with desired low friability (Fig. 2b).

Observed low friability that associated with matrix formulations incorporating MCC as a filler (F1, F4 and F7) (Table 2) could be due to the high compactability and compressability properties of MCC.[14] Moreover, the observed association between WG as a processing method and the reduced matrix friability could possibly be explained in terms of the efficient intra and inter granular binder distribution offered by the method as compared to the DC one. On another instance, from Table 2, it might be obvious that formulations which measure a comparative low matrix friability (F9, F7 and F4, in descending order) are also those which compressed to a relatively high hardness level (12-14.9kg/cm^2). This observation might encourage the assumption of an inverse relation between applied compression force and matrix friability as previously reported.[14,15] In this study, however, the computed p-value that associated with the influence of hardness on matrix friability (p= 0.0975) persuades the statistical ignorance of such effect (Fig.1b), at least within the domain of the present experiment.

As with weight variation property, it should be noted also that the joined linear influence of processing method and filler type on matrix friability property appears more dominant than the individual quadratic influence of the processing method and comparable to that of the applied compression force as indicated for by matrix hardness (Fig. 1a).

Influences of variables on drug release properties of matrix formulations

Ketoprofen release profiles and characteristics of matrices within different formulations are shown in Fig. 3 and Table 3, respectively.

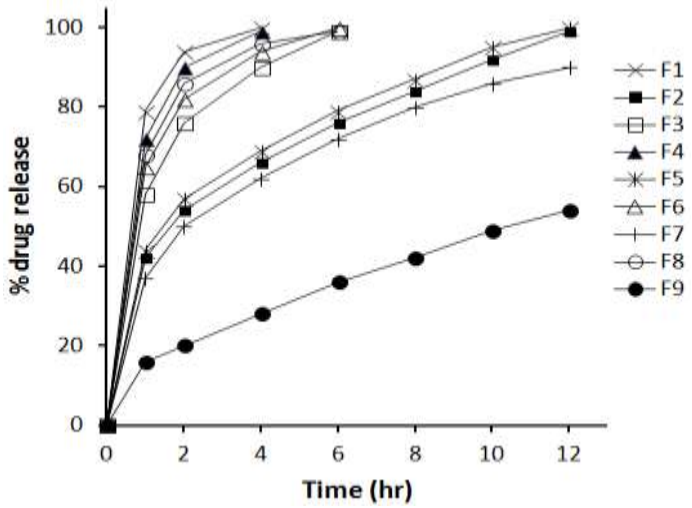


Fig. 3: Ketoprofen release profiles of different matrix formulations

It might be clear from Fig.3 that different matrix formulations revealed drug release of varying profiles where one formulation has retained the loaded drug over more than 12 hrs (F9), 3 formulations were capable to sustain the drug release over 12 hrs (F2, F5 and F7), 3 formulations sustained the release of loaded drug only for 6 hrs (F3, F6 and F8) and 2 formulations proved inferior with regard to sustaining the drug release (F1 and F4).

Consequently, displayed values of time for 50% drug release ($T_{50\%}$) which ranged between 30 and 624 min and dissolution efficiency after 4 hours ($DE_{0\text{-}4hrs}$) that ranged 0.19-0.80 were found to be substantially differ among different matrix formulations (p= 0.0103 and 0.005 for both attributes, respectively) (Table 3).

On the contrary to $T_{50\%\ rel}$ and $DE_{0\text{-}4hrs}$ properties, estimated values for diffusion exponent (n) that vary between 0.354 and 0.675 (Table 3) were computed as statistically comparable (p= 0.5637). The presented values of (*n*) indicate the Fickian drug diffusion as a regulator for drug release from these matrices.

Table 3: Drug release attributes of different matrix formulations

Formulations	$T_{50\%\ rel}$ (min) [a] Mean ± SD	$DE_{0\text{-}4hr}$ [b] Mean ± SD	Diffusion exponent (*n*)	r^2 [c]
F1	36 ± 8	0.80 ± 0.10	0.451	0.9911
F2	84 ± 12	0.47 ± 0.04	0.553	0.9898
F3	48 ± 10	0.66 ± 0.05	0.383	0.9993
F4	36 ± 4	0.77 ± 0.06	0.366	0.9989
F5	78 ± 11	0.50 ± 0.03	0.463	0.9976
F6	42 ± 7	0.73 ± 0.08	0.354	0.9899
F7	120 ± 17	0.44 ± 0.03	0.557	0.9908

F8	30 ± 6	0.75 ± 0.02	0.445	0.9990
F9	624 ± 12	0.19 ± 0.01	0.675	0.9889

[a] *Time for 50% drug release;* [b] *Drug dissolution efficiency after 4 hours;* [c] *Determination coefficient associated with power law model fitting.*

Both $T_{50\%}$ and $DE_{0\text{-}4hrs}$ of different matrices were shown to be considerably affected by the joined linear influence of processing method and filler type ($p< 0.05$ for the joined influence on both properties), as compared to the linear individual influence of both variables (Fig. 4).

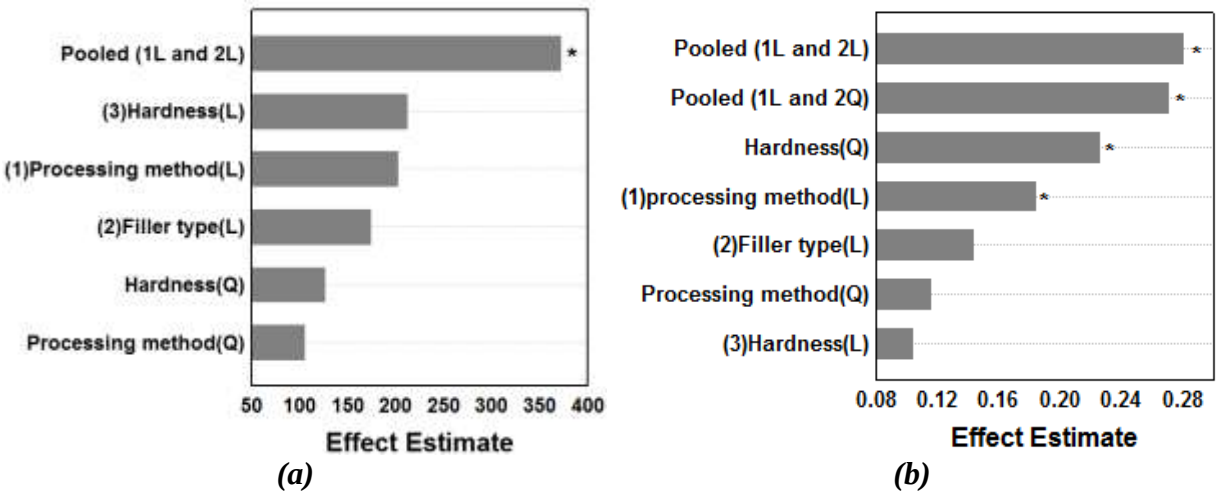
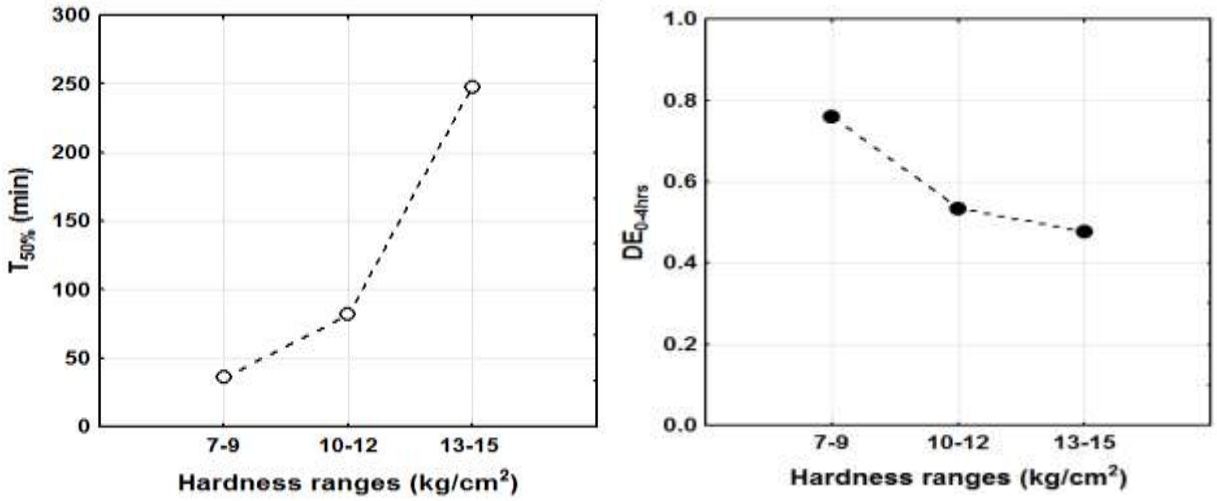


Fig. 4: Estimate of linear (L) and quadratic (Q) individual and pooled variables' effects on (a) $T_{50\%}$ and (b) $DE_{0\text{-}4hrs}$ attributes of the drug release of different matrix formulations with * indicating significant effect at $p< 0.05$

Moreover, unlike the case with $T_{50\%}$, matrix hardness and processing method were both demonstrated to have significant quadratic and linear influences, respectively, on $DE_{0\text{-}4hrs}$ property. Furthermore, neither the filler type (at any level) nor the processing method (at quadratic level) appear to exert considerable influences on both matrix properties ($p> 0.05$ for the influences of both variables) (Fig. 4). With the release kinetic (*n*), none of the investigated variable (at any individual or joined settings) demonstrate considerable influence on this property ($p> 0.05$ for the influences of all variables' setting). These findings encourage the assumption that some of investigated variables appear to influence Ketoprofen release profiles and attributes from different matrices without interfering with the drug release kinetics.

It appears from Tables 2 and 3 that formulations exhibited prolonged drug release characteristics (those with comparative long $T_{50\%}$ and small $DE_{0\text{-}4hrs}$) are those compressed to

a relative high hardness range (F2 and F9) or those incorporating either LAC or MCC and compressed to a medium hardness level (F5 and F7). Consequently, the role of matrix hardness on drug release characteristics is evidenced despite its statistical ignorance with $T_{50\%}$ property, as being illustrated in Fig. 5 for both properties.



(a) *(b)*

Fig. 5: Marginal means for (a) $T_{50\%}$ and (b) $DE_{0\text{-}4hrs}$ displayed by different matrix formulations in response to variation in applied compression force.

In a previous study, we reported a delaying influence of hardness on drug release characteristics in HPMC based matrices which was attributed to the anticipated impeding effect of hardness on matrix porosity and, consequently, on water permeation and movement of solvent fronts.[7] On the other hand, the effects of processing method on $DE_{0\text{-}4hrs}$ property of matrices that monitored in this study might be explained in terms of the dissimilar distribution profile of the matrixing agent (HPMC) that related to DC, DG and WG as processing methods. These findings are in accord with relevant published works on HPMC matrices.[16,17] Although filler type is demonstrated to has trivial influences on both characteristics of the drug release (Fig. 4), it is noteworthy that matrix formulation F7 which contains MCC (hydrophilic filler) and compressed to medium hardness level measured longer $T_{50\%}$ and consequently, smaller $DE_{0\text{-}4hrs}$ value when compared to other formulations incorporating the same filler and compressed to a lower or even higher hardness level (F1 and F4). In fact, this might be because of the agglomeration of HPMC as a consequence of addition of aqueous fluid involved in WG method which, in turn, retards the penetration of dissolution medium as a result of reduction of distance between particles induced by the agglomerated HPMC.[18] In another instance, the most delayed drug release of formulation 9

could possibly be due to the relative high hardness level and, moreover, to the water insolubility and non-swellability nature of the included DCD.

CONCLUSIONS

Among different factors investigated within the experimental domain of the present study, processing method and filler type confirmed to influence weight variation, friability and drug release attributes of different matrices either through their individual or joined effects. The joined influence of processing method and filler type on weight variation and friability properties was shown to be comparable to the negligible influence of the applied compression force on both properties. Whilst applied compression force proved to exert weighty influences on the extent of drug release property of the matrices, the release kinetics (*n*) was found to be the least affected matrix property by the investigated variables.

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