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Research article

Evaluation of factors affecting the microencapsulation of mefenamic acid with cellulose acetate phthalate

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ABSTRACT

Modeling, one of the tools of Design of Experiments (DoE), was employed to achieve an optimum set of parameters for the microencapsulation of mefenamic acid (MA) with cellulose acetate phthalate (CAP). A two-level full factorial design was utilized to run the experiments with several factors being investigated simultaneously. Modified emulsion solvent evaporation was the method of choice to formulate the microcapsules. Microscopic evaluation of the surface characteristics of the microcapsules was conducted using stereomicroscope and SEM. Regression analysis was performed to evaluate the effects of the factors - polymer:drug ratio(X_1), amount of emulsifier(X_2), and stirring rate(X_3) - to percent yield, particle size, drug entrapment efficiency, and release kinetics. The microcapsules exhibited spherical shape with rough surface. Percent yield ranged from 77.33% to 92.39% among the formulations. Particle size ranged from 290.12 to 1162.12 µm, with stirring rate being a significant factor. Drug entrapment efficiency (DEE) ranged from 63.55 to 96.86%, with amount of emulsifier, and its combined effects of polymer:drug ratio and amount of emulsifier being the significant factors. Using the predicted model, a desired particle size of 561.77 µm and a DEE of 93.70% can be achieved by setting X_1 to 1.25:1, X_2 to 4 mL, and X_3 to 650 rpm. The release kinetics of most formulations best fit the Korsmeyer-Peppas Model. With all these information, it can be concluded that the factors under study may significantly affect the *in vitro* performance of the MA microcapsule.

1. INTRODUCTION

Microencapsulation is the packaging technology of solids, liquid or gaseous material with thin polymeric coatings, forming small particles called microcapsules. These particles release the core containing the drug in the ideal place and at the ideal time. Microencapsulation techniques could then provide protection against drug degradation, reduction of ulcerogenic side effects, and accurate control of rate of drug release through time.

Challenges in microencapsulation include low drug entrapment efficiency (DEE) and low production yield[1]. These may be addressed by experimental designs and optimization

techniques such as factor-screening experiments[2]. Mathematical models showing the combined effects of the factors and their interactions may be provided[3]. The advantages of factorial designs include (1) provision of wider inductive basis to draw inferences about the process, and (2) reveals interactions of factors in the study. Changing one factor at a time is tedious and does not guarantee attainment of the optimum set of parameters for microencapsulation[4].

To date, there are no studies employing a full factorial design on the optimization of mefenamic acid (MA) formulated as microcapsules using cellulose acetate phthalate (CAP) as polymer. This study investigated several factors that may affect the performance of MA microcapsules *in vitro* using mathematical modeling. MA served as the test drug in the formulation of microcapsules because of its short half-life and poor aqueous solubility. These characteristics of a drug justify the choice for modified emulsion solvent evaporation method to formulate the microcapsules. CAP was used as it is capable of providing gastric mucosal protection against NSAIDs. Two levels of each factor were used and responses such as morphology, percent yield, particle size, DEE, and release kinetics of the microcapsules were evaluated. Moreover, two-level factorial design was selected as it was economical in terms of resources utilization and allowed analysis of factor effects in a shorter period of time.

2. MATERIALS AND METHODS

2.1. Materials

MA and CAP were obtained from Sigma Aldrich, Inc. (Singapore). Tris buffer (pH of 9), dichloromethane, acetone, and ethanol were obtained from JT Baker Chemicals (New Jersey, USA). Span 80 and liquid paraffin were obtained from Theo-Pam Trading Corporation (Philippines).All solvents and reagents used were of analytical grade.

2.2. Preparation of MA microcapsules

The experimental designs in Tables 1 was used as basis for the formulation experiments. The minimum and maximum levels were obtained from several studies on factors affecting microencapsulation[5,6,7]. Microcapsules were prepared through oil-in-oil emulsion solvent evaporation method using CAP as the coating material. Two grams of MA were dispersed in the mixed solvent system of 18 mL acetone and 2 mL ethanol (polymer solvent) where 1.50 or 2.50 grams of CAP (X_1) were pre-dissolved. The mixture was emulsified and stirred in a 400 mL liquid paraffin and with addition of 2mL or 4mL Span 80 (X_2) under stirring at 500 or 1050 rpm (X_3) using Heidolph (Model RZR-2022, Kelheim, Germany) for 30 minutes. A 100 mL of dichloromethane, which served as a polymer non-solvent, was added to harden the microcapsules and stirring was continued for 30 minutes. The microcapsules were then collected by filtration and washed with three portions of 30 mL of dichloromethane to remove any remaining oil residues and were air dried for 24 hours.

2.3. Morphology of MA microcapsules

The surface characteristics of the microcapsules were observed with a stereomicroscope using ScopeImage 9.0 (X5) software and Quanta 450® scanning electron microscope. The surface morphology of samples was described using USP chapter <776> optical microscopy. Per formulation, one hundred particles were measured using a stereomicroscope coupled with Scopelmage 9.0 (X5) software.

2.4. Percent (%) yield

The yield of the microcapsules was calculated by dividing the actual weight of the MA microcapsules over the theoretical weight of MA and polymer, multiplied by 100.

2.5. Drug entrapment efficiency (DEE)

The microcapsules were dissolved in acetone to determine the concentration of MA using UV spectrophotometry at 350 nm. DEE (%) was calculated by dividing the quantity of MA in the microcapsules by the theoretical quantity of MA present in the microcapsules, multiplied by 100.

2.6. Characterization of the release profile

Dissolution was carried out using a USP Dissolution Apparatus 1 at 37°C and 100 rpm, using 900 mL of pH 9 Tris buffer[6]. Samples were withdrawn at appropriate intervals (0.25, 0.50, 1, 2, 3, 5, and 6 hour). Since a different solvent was used, a new

Table 1. Characteristics and assay of MA microcapsules

Formulation	Factors			Shape and Surface Characteristics	*Particle Size* (Mean ± SD), µm	Percent Yield (%)	Drug Entrapment Efficiency (Mean ± SD), %
	Polymer: Drug Ratio (X_1)	Amount of Emulsifier (mL) (X_2)	Stirring Rate (RPM) (X_3)				
1	1.25:1	4	1050	*Spherical, Columnar, Rough*	354.54 ± 72.41	88.07	90.53 ± 0.25
2	1.25:1	4	500	*Spherical, Rough*	791.23 ± 149.75	78.66	96.86 ± 0.21
3	1.25:1	2	1050	*Spherical, Rough*	594.31 ± 93.36	85.15	92.87 ± 0.10
4	1.25:1	2	500	*Spherical, Rough*	1026.27 ± 186.84	88.59	82.82 ± 0.16
5	0.75:1	4	1050	*Spherical, Agglomerate, Rough*	290.12 ± 53.25	92.39	71.08 ± 0.14
6	0.75:1	4	500	*Spherical, Agglomerate, Rough*	405.01 ± 74.78	82.14	63.55 ± 0.88
7	0.75:1	2	1050	*Spherical, Columnar, Rough*	360.06 ± 58.41	82.25	84.97 ± 0.22
8	0.75:1	2	500	*Spherical, Rough*	1162.12 ± 348.60	77.33	94.77 ± 0.27

Note. The minimum and maximum levels were obtained from studies[5-7] on factors affecting microencapsulation.

Table 2. Fitting the parameters of the in vitro release data to various release kinetic models of mefenamic acid microcapsules from different formulations

Code	Zero Order		First Order		Higuchi Equation		Korsmeyer-Peppas Equation			Hixson-Crowell Equation	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K_P	n	R^2	K
F1	0.8377	9.7619	0.9240	0.2335	**0.9331**	30.973	0.9243	38.3089	0.4707	0.9102	0.2662
F2	0.5302	7.6129	**0.7553**	0.2202	0.6665	25.662	0.6759	49.5222	0.3998	0.6792	0.2338
F3	0.4703	6.6472	0.6251	0.1642	0.6047	22.66	**0.6415**	46.6444	0.3896	0.5730	0.1848
F4	0.6148	10.1900	**0.7990**	0.3305	0.7683	34.2480	0.7691	44.4120	0.5396	0.7407	0.3336
F5	0.9482	13.6670	0.9661	0.3811	**0.9952**	42.094	0.9565	26.4302	0.7621	0.9865	0.4024
F6	0.6919	7.3438	0.9063	0.9470	0.8109	23.901	0.8532	72.6440	0.2185	**0.9255**	0.6865
F7	0.8173	5.6017	0.8825	0.1614	0.9038	17.709	**0.9471**	55.7828	0.1668	0.8682	0.1739
F8	0.7482	8.057	0.8802	0.2794	0.8478	25.936	**0.9206**	54.2608	0.2996	0.8523	0.2775

l_{max} was determined for MA. Drug concentration in the samples was measured using a UV spectrophotometer at 286 nm. The graph obtained was analyzed in terms of initial burst concentration, overall rate of release, and final concentration after the last time point. The release profiles were analyzed using different mathematical models: Zero-order kinetics, First-order kinetics, Higuchi

model, Korsmeyer-Peppas model, and Hixson-Crowell model. The plots of the kinetic models were generated using Microsoft Excel® 2016 16.0. The coefficient of determination (R^2) closest to 1 represents the most appropriate model to describe the mechanism of drug release, while a lower kinetic constant (K) indicates a slower rate of release.

2.7. Statistical analysis

The effects of the factors – polymer:drug ratio (X_1), amount of emulsifier (X_2), and stirring rate (X_3) – on the responses (mean particle size and DEE) were analyzed using regression analysis. Polynomial equations were generated using regression analysis (MiniTab® version 18.1). An alpha of 5% was considered significant. Main effects and interaction plots were generated using MiniTab® version 18.1. Prediction profiles using JMP® 13.1 were also generated.

3. RESULTS

3.1. Morphology of MA microcapsules

Figures 1a and 1b present the photographs of the microcapsules of each formulation when viewed under a stereomicroscope. All formulations had non-uniform sizes. Most of the formulations were of spherical shape. Formulations 1 (F1) and 7 (F7) were columnar in shape. F5 and F6 showed agglomerates and spherulite particles.

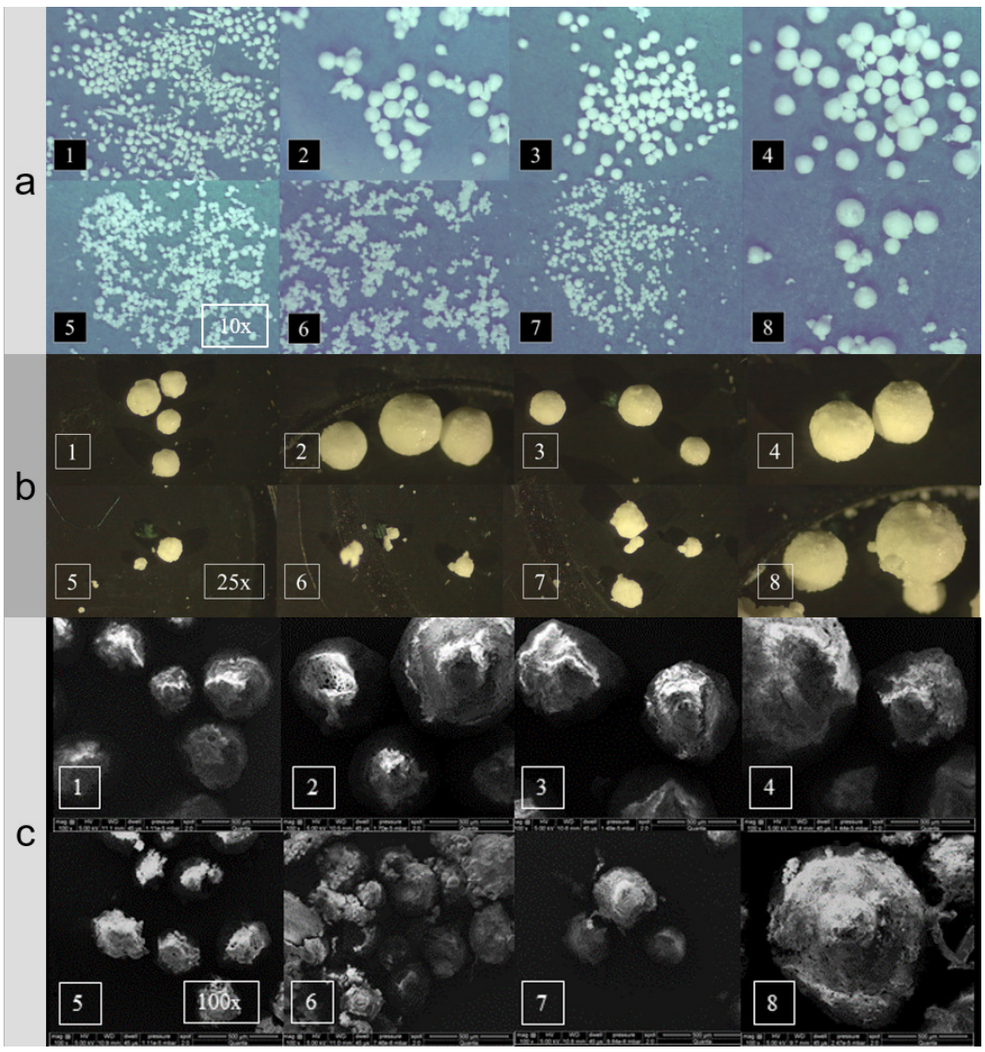

Figure 1. Photographs of microcapsules from F1 to F8 at 10x, 25x, and 100x magnifications

Observations under SEM (Figure 1c) reveal that all formulations had a rough surface morphology. spherical and smooth surface characteristics of the microcapsules were desired as shape and surface of the microcapsules may contribute to their uniform dissolution rate.

Table 1 shows the mean particle size of the formulated microcapsules. F5 and F8 exhibited the smallest and largest mean particle size, respectively.

3.2. Percent yield and DEE

Table 1 shows the percent yield and DEE of each formulation. F8 and F5 showed the lowest and highest percent yield, respectively. F6 and F2 demonstrated the lowest and highest DEE, respectively.

3.3. Statistical considerations

3.3.1. Particle size

The effects of each factor on particle size are presented in Figure 2. X_3 was shown to have the greatest effect on particle size followed by X_2 then X_1. Particle size was proportional to the increase in X_1 evidenced by the positive slope of the line. An inverse relationship may be considered between particle size and X_2 and X_3.

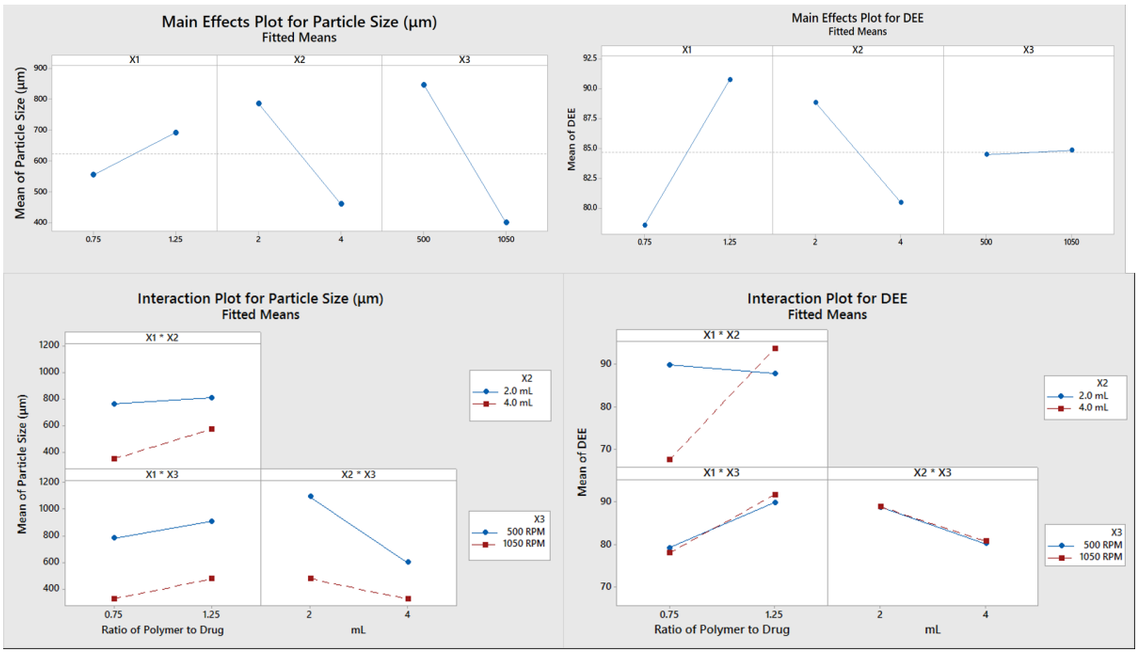

Figure 2. Plots showing main effects and interaction of factors affecting the particle size and DEE of microcapsules

The effects of interacting factors on particle size are presented in Figure 2. The interactions tested were X_1 and X_2, X_1 and X_3, and X_2 and X_3. All graphs showed parallel lines, which indicate that the effects of the said interactions on particle size were not significant.

Regression analysis of the full model revealed that no significant interactions were observed. The generated equation for the full model was particle size (µm) = $2783 - 322X_1 - 579X_2 - 1.83X_3 + 176X_1{*}X_2 + 0.09X_1{*}X_3 + 0.310X_2{*}X_3$. Backward elimination of the insignificant terms in the model was done since p-values of the coefficients were all greater than 0.05. The reduced model showed that X_3 had a significant effect on particle size ($p < .05$). The model was reduced to particle size (µm) = $1740 - 162.7X_2 - 0.812X_3$.

The prediction profile in Figure 3 shows that to achieve an optimum particle size of 561.77 µm, the optimum set of parameters for the X_2 and X_3 had to be 4 mL and 650 rpm, respectively. The profile is visually represented using a surface plot in Figure 3.

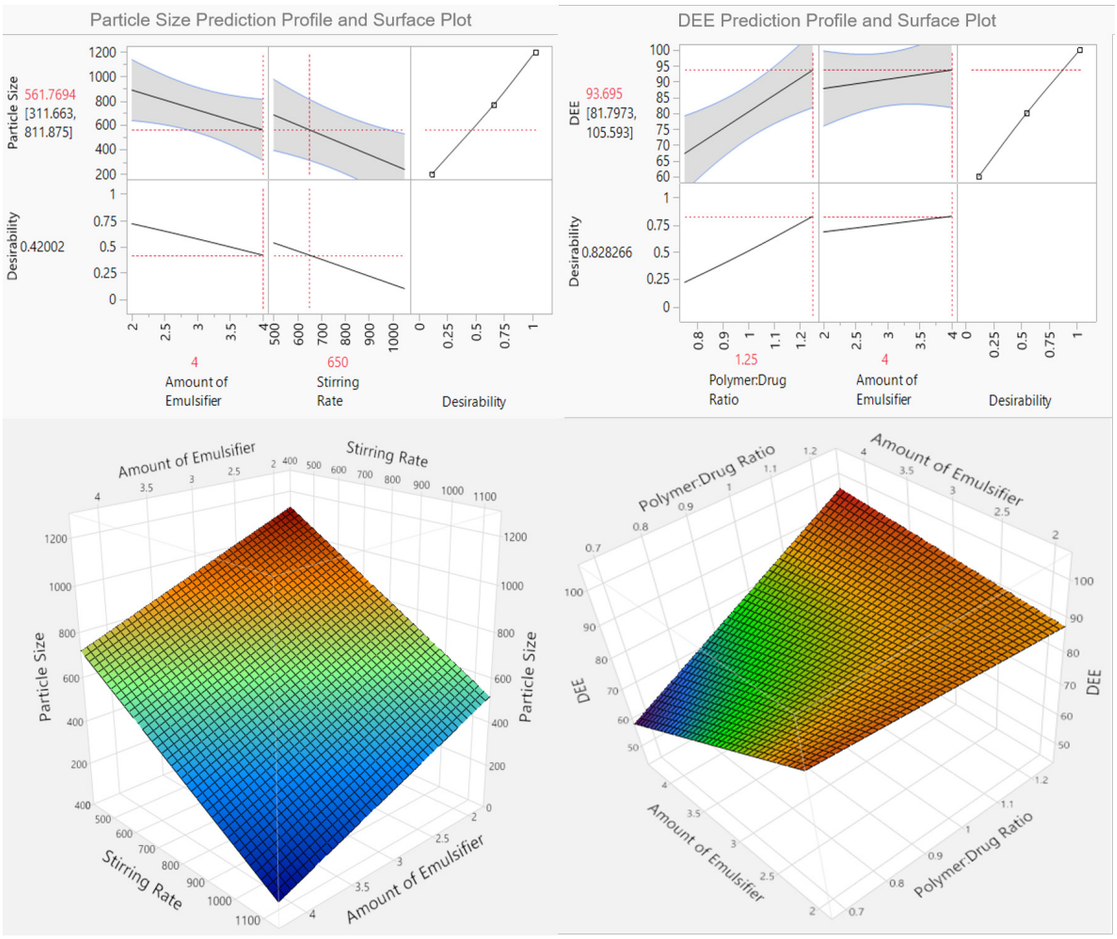

Figure 3. Prediction profile and surface plot of factors affecting particle size and DEE

3.3.2. Drug entrapment efficiency (DEE)

The effects of each factor on DEE are presented in Figure 2. DEE was proportionally affected by an increase in the X_1 as evidenced by the positive, steep slope of the line. However, an inverse relationship was observed between DEE and X_2. Factor X_3 did not significantly affect DEE as evidenced by its line being parallel with the x-axis.

The effects of interacting factors on DEE are presented in Figure 2. Intersecting lines as observed in X_1 and X_2, and X_1 and X_3 indicate that an interaction existed between these factors that an interaction existed between these factors.

Regression analysis of the full model revealed that no significant interactions were observed at $\alpha = .05$. The generated equation for the full model was DEE (%) = $167.0 - 69.3X_1 - 32.9X_2 - 0.0115X_3 + 28.4X_1*X_2 + 0.0109X_1*X_3 + 0.0004X_2*X_3$. Model reduction was done to eliminate insignificant coefficients.

The reduced model showed that X_1*X_2 had significant effect on drug entrapment efficiency ($p < .05$). The generated equation after model reduction was DEE (%) = $158.1 - 60.9\ X_1 - 32.58\ X_2 + 28.41\ X_1*X_2$.

The prediction profile in Figure 3 shows that the optimum set of parameters for X_1 and X_3 had to be 1.25:1 and 4 mL, respectively, to achieve the desired DEE of 93.70%. The profile is visually represented using a surface plot in Figure 3.

3.4. Characterization of the release profile

Figure 4 shows the dissolution profiles of the eight formulations and the commercially available immediate release capsule of MA. All formulations were more than 70% dissolved after

6 hours. Only F6 was completely dissolved after the set dissolution time. The graph also shows that F1 and F5, which exhibited the smallest size of particles, released MA at a slower rate compared with other formulations.

Table 2 shows the coefficients of determination and release constants for the different formulations. The highest coefficient of determination for each formulation demonstrates the dominant mechanism controlling the release of MA from the microcapsules. F1 and F5 were observed to follow the Higuchi equation. F2 and F4 demonstrate that the mechanism controlling their release was First-order. F3, F7, and F8 best fit the Korsmeyer-Peppas equation. Lastly, the dominant mechanism for Formulation 6 was Hixson-Crowell.

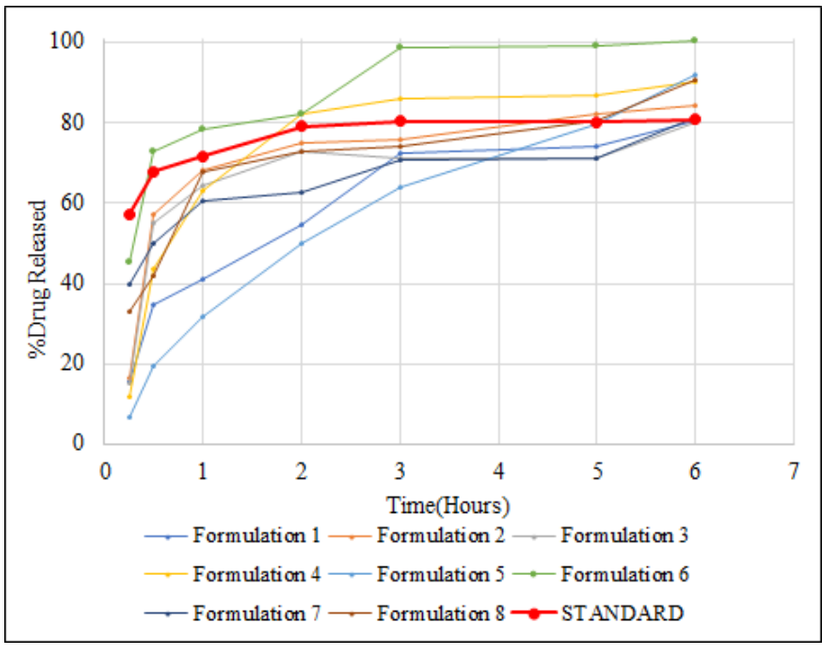

Figure 4. Percent of Mefenamic acid released from the various microcapsule formulations

4. DISCUSSION

4.1. Morphology of MA microcapsules

4.1.1. Shape and surface morphology

Based on Figure 1, most formulations appeared to have microcapsules that have rough surface and spherical in shape. It was also observed that smaller particles had higher tendency to agglomerate. Increasing the solubility difference between the polymer solvent and non-solvent can improve the surface morphology of microcapsules[8]. Acetone-ethanol:Dichloromethane was the polymer solvent:non-solvent pair used in this study. Other non-solvents such as n-hexane and cyclohexane can be used in place of dichloromethane since CAP is less soluble in them. Furthermore, the release rate of drugs from the microcapsules increased when solubility parameter difference was decreased. This may be due to the differences in surface morphology. Lower solubility differences between solvents produces rough surface and sponge-like morphology where the drug molecules can easily penetrate, diffuse, and be released to the media[8]. All formulations had rough surface morphology; therefore, its rate of release is expected to be faster when compared to standard microcapsules. However, since solvent: non-solvent pair was not factor and these was a lack of MA microcapsule standard in this study there is not enough data to prove these findings.

4.1.2. Particle size

Increasing the polymer concentration results to a larger particle size. This is attributed to increased viscosity leading to larger emulsion droplet size[9]. An increase in viscosity results to slower diffusion rate of non-solvent to polymer solution[6], consequently resulting to a larger size of microcapsules obtained.

Based from several studies, increasing the amount of emulsifier decreases the size of the resulting microcapsules. Emulsifiers such as Span 80 reduce the tendency of the droplets to coalesce, forming larger droplets. Span 80, a non-ionic surfactant, employs steric stabilization to inhibit the tendency of the internal phase to coalescence and forming larger droplets. It is adsorbed on the surface of dispersed phase droplets in an emulsion and provides a physical barrier for particle interactions[10]. As these droplets approach into close proximity, repulsive forces arise, keeping the particles apart. This leads to the stabilization of the microspheres[7,9].

Decreasing the stirring rate by half produced large microcapsules. This was also observed from the study[7] using diclofenac sodium as test drug and ethyl cellulose. The formation of large size microcapsules was attributed to a decrease in shearing force when mixing at lower stirring rate.

4.2. Percent yield

The effects of the factors on percent yield were not subjected to full-factorial analysis since other extraneous variables could have significantly affected the responses. However, based on Table 1, it was observed that the formulation with the highest percent yield had the smallest particle size (F5) and the formulation with the lowest percent yield had the biggest particles (F8). This low percent yield can be attributed to the increased viscosity of the solutions resulting to difficulty in transferring the solution from the syringe[5]. Increasing the viscosity of the solution can also result to a decreased diffusion rate of the drug and polymer solvents (acetone and ethyl alcohol 9:1) in the emulsion thus forming bigger droplets and consequently particle size[6]. Optimizing the formulation to decrease the viscosity of the solution can increase the yield of microcapsules.

4.3. Drug entrapment efficiency

The results of the experiment showed that an increase in polymer concentration led to an increase in DEE[11]. High viscosity was a result of the high concentration of the polymer. The contribution of a high polymer concentration to the encapsulation efficiency can be interpreted in two ways. The first mechanism was thought to be due to the rapid precipitation of the polymer when highly concentrated on the surface of the dispersed phase and prevents drug diffusion across the phase boundary. Secondly, the high concentration increases viscosity of the solution and delays the drug diffusion within the polymer droplets[12].

DEE decreased as the amount of emulsifier increased. This may be due to fact that increase in emulsifier concentration leads to stabilization of small droplets and results in smaller capsules[13]. The reader is referred to the previous section for a detailed discussion of the stabilization of an emulsion due to decrease in droplet size.

Our study revealed a decrease in particle size and DEE with an increase in stirring speed. Increasing the stirring rate had negative effect on drug entrapment efficiency[14]. This can be explained by production of a finer dispersion of droplets when higher stirring rates are applied and, consequently, by the formation of smaller microcapsules[15]. However, in the discussion of the factorial analysis, the effect of stirring rate on DEE was not statistically significant.

4.4. Statistical considerations

4.4.1. Particle size

The combined effects of the factors on particle size are presented in Figure 2. Any interaction of factors that is significant takes precedence over the main effects of the two factors involved in the interaction[16]. Inclusion of three-way interactions was not possible due to lack of degrees of freedom to perform the statistical test. Individual or combined factors did not have significant effects on particle size.

The regression analysis of the main factors and interactions generated a full model. Backward elimination was conducted to determine the factors that do not significantly affect particle size. A series of regression analysis was conducted by eliminating the factor with the highest p-value from the model until a refined model had been generated. A regression analysis was again performed which only included X_2 and X_3 as factors. The calculated p-value of the model was less than α. This means that the refined model explained the

variation in the responses. Lack of fit test was used to determine whether the model does not adequately describe the relationship between the factors and the outcome. This test is done on reduced models that do not include interactions of factors. The lack of fit test showed that the model fits the given set of data. The coefficient of multiple determination ($R^2 = 0.78$) indicated that the refined model predicts up to 78% of the variation in the response.

The generated model can be used to determine the optimum combination of experimental factors for an optimum particle size of microcapsules (Figure 3).

4.4.2. Drug entrapment efficiency

The main effects plot for DEE in Figure 2 strengthened the aforementioned discussion on the effects of the factors on DEE. The larger the slope, the greater the effect of the factor to the response[17]. Inclusion of three-way interactions was not possible due to lack of degrees of freedom to perform the statistical test. Both X_1 and X_2 had significant effects on DEE. Looking at the interaction plot in Figure 2, it was observed that there was an interaction between X_1 and X_2. Lines that cross on interaction plots indicate that there is interaction between variables[17]. It was also worth noting that the lines cross on the plot of X_1 and X_3. The interaction of X_1 and X_3 had higher hierarchy (or lower p-value) than X_3. Thus, X_3 cannot be removed without removing the said interaction.

To test whether the interaction between X_1 and X_2 was significant, a regression analysis for the reduced model for DEE was performed. The interaction between X_1 and X_2 had significant effect on DEE. X_2 was retained as a term even if its p-value > α since it was part of the interaction term X_1*X_2 which was statistically significant.

The calculated p-value of the model was less than α. This means that the refined model explained the variation in the responses. The generated model can be used to determine the optimum combination of experimental factors that can lead to higher drug entrapment efficiencies. The coefficient of multiple determination ($R^2 = 0.85$) indicated that the model predicts up to 85% of the total variations in the response could be attributed to the factors.

4.4.3. Mathematical modeling

At the end of the regression analysis, two polynomial equations were generated:

$$\text{Particle Size } (\mu m) = 1740 - 162.7\ X_2 - 0.812\ X_3$$

$$\text{DEE } (\%) = 158.1 - 60.9\ X_1 - 32.58\ X_2 + 28.41\ X_1*X_2$$

The sign of each coefficient shows how the related factor influences the response[4]. A positive coefficient corresponds to an increase (synergistic effect) in response as the factor moves from low level to high level; the contrary is obtained (inverse relationship/antagonist effect) if the coefficient is negative.

The prediction profile (Figure 3) predicted the amounts of the factors needed to maximize the particle size of the microcapsules. Considering the allowable mixing speed of the mixer, the observed particle agglomeration at particle sizes less than 450 μm, and high DEEs at higher particle sizes, the predicted particle size was expected to be 561.77 μm if 4 mL of emulsifier was used and if the stirring rate was set to 650 rpm.

Figure 3 shows the predicted amounts of the factors needed to maximize the DEE of the microcapsules. The desirability was set to maximum. If X_1 was set to 1.25:1 and X_2 was set to 4 mL, the predicted DEE may be 93.695%.

In addition, each surface plot represents the number of combinations of the two-test variable and shows the regression equation. The plots were useful to describe and analyze the relationship between factors and responses.

4.5. Dissolution studies

All formulations were more than 70% dissolved after 6 hours. Most formulations satisfied the criteria on dissolution for extended-release tablets[18]. The tolerance should be between 50% and 80% after 6 hours. Only F6 was completely dissolved after the set dissolution time. This can be attributed to the very low drug entrapment efficiency of the said formulation.

The different formulations showed manifold shaped curves. All had different rates of release which were further described using mathematical models. A relatively high variability between dissolution trials was observed with an average standard deviation of 10.68% and a coefficient of variation of 24.67%. The computed coefficient of

variation did not pass the acceptance criteria of ±10%[19]. The variability can be attributed to the high variability in particle size and drug entrapment efficiency within formulations.

Similarity and difference factors computed also showed that all formulations had significantly different dissolution profile against the standard. All formulations except for F6 had lower initial burst concentrations than the standard. Lower initial burst concentrations release indicates a slower rate of release. The low DEE and particle size of F6 caused a faster rate of release.

It was also observed that formulations with smaller microcapsules had slower release of MA compared to those formulations with larger microcapsules. Increasing the polymer:drug ratio also decreased the rate of release of MA.

4.6. Mechanism of release of MA

The coefficients of determination obtained were lower than 0.95. However, the kinetic equation with the highest coefficient of determination or fit was still used to describe the release.

The mechanism of drug release for F2 and F4 was observed to be of first-order. This indicated that the release of drug in the microcapsules were concentration-dependent[20]. This type of release is often observed in sustained-release dosage forms; however, a constant fraction of drug-released was not observed in both formulations which was also expected in first-order release.

The appropriate model to demonstrate the release mechanism of F1 and F5 was that of Higuchi. Microcapsules that best fit this model implies that the release is diffusion controlled and follow the Fick's law[20]. F3, F7, and F8 best fit the Korsmeyer-Peppas equation. The release kinetics of microcapsules can be further interpreted using the release exponents (n) generated. The release exponent of all three formulations was less than 0.43 which meant that the transport mechanism involved was Fickian-diffusion. In diffusion-controlled systems, the polymeric chains either by inherent semi-permeability or by swelling forms pores into which the drug can diffuse and be released into the media. Majority of the formulations, namely 1,3,5,7 and 8 were diffusion controlled. Theoretically for these formulations, increasing the polymer: drug ratio will form a less porous matrix or reservoir; thus, reducing the rate of release. This trend was observed in F1 and F5 under Higuchi model. F1 had higher polymer:drug ratio; thus, a lower kinetic constant and slower rate of release. This was also observed between F3, F7, and F8; wherein, F3 had the slowest rate of release.

Formulation 6 fits best the Hixson-Crowell model, which meant that drug release was limited by the dissolution of the polymer in the fluid, changes in surface area and diameter of the microcapsules[20]. For this formulation, a bigger particle size meant slower drug release.

Overall, the mechanisms of drug release for majority of the formulations (namely 1,3,5,7 and 8) were diffusion controlled. All of these formulations except for F8 have high stirring rates. The high X_3 may have aided the formation of a robust membrane which is less prone to erosion. On the other hand, the formulations with slower X_3 namely F2, F4, and F6 followed the dissolution-controlled and concentration-dependent release mechanism. The membranes formed for these formulations were more prone to erosion and dissolution. It cannot be concluded however, that X_1 and X_2 had an effect on the release profiles of the formulations since no relationships were observed.

5. CONCLUSIONS

With all these information, it can be concluded that the factors under study can significantly affect the *in vitro* performance of the MA microcapsule. These factors can be manipulated to improve the results of the responses. We would like to recommend the conduct of an experiment that utilizes the predicted values of variables to be used. The experimental response should be then compared to the predicted response to verify the validity of the model. For the progress of this study, it is recommended to further develop a dosage form where microcapsules can be incorporated to increase validity of comparison with existing formulations.

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Conflict of interest (If any)
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Ethical approval

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