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Research Article

Semibatch Production of Pharmaceutical Grade Magnesium Stearate: A Statistical Approach

Fractional factorial design was employed to investigate the effect of feed composition and the major operating variables on the production of pharmaceutical grade magnesium stearate in a double decomposition process. The studied variables were initial stearic acid concentration, initial sodium hydroxide concentration, initial magnesium sulfate concentration, as well as reactor temperature at the time of NaOH addition (the first reaction temperature) and reactor temperature during magnesium sulfate addition (the final reaction temperature), pH of the solution at the end of reaction (final pH). The moisture content of the cake produced after filtration and the yield of magnesium stearate in the dried cake (assay), were the most important responses investigated as a function of feed and operating variables and these were optimized through statistical analysis. The results of the study showed that both magnesium sulfate and NaOH had high positive effects on the final pH, with a nonsignificant effect of the other main factors being observed. Increasing the NaOH concentration and the first reaction temperature led to an increase in the assay production, whereas the binary interaction of stearic acid and NaOH revealed a negative effect. The acid as well as NaOH concentrations exhibited positive influence on the moisture content of the filtered cake. Finally, the simplex optimization method was used to obtain the optimal conditions. The results of the study were successfully adapted to the large scale production of pharmaceutical grade magnesium stearate and pharmaceutical grade product was produced meeting the standards required.

Keywords: Experimental design, Fractional factorial design, Pharmaceutical products

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1 Introduction

Magnesium stearate is an alkali earth metal soap in a white solid powder state at room temperature. The commercially available magnesium stearate products are mixtures of different fatty acid salts (stearin) mainly including stearic acid and palmitic acid, which can be derived either from animal fats or from vegetable oils, although the vegetable source of stearin has not been studied intensively [1–5]. This material is widely used by chemical industries for different purposes as a slip additive in molding compounds and ABS resins, as a moisture separator in fire extinguishing powders, essential components or as rubber separating agents, in foodstuffs, as stabilizers for PVC, and as defoaming agents in cosmetic preparations. The substance also has other applications due to its extremely effective lubricating properties even at the lowest effective concentration, which prevents ingredients from sticking to process equipment during the compression of chemical powders into solid tablets [6, 7].

Magnesium stearate is also a commonly used chemical in pharmaceutical industries. Since magnesium stearate is widely regarded as harmless and safe for human consumption, it is often used as a filling agent in the manufacture of medical tablets and capsules. Therefore, it is essential to quantify its structural stability under ambient temperature and normal humidity conditions. The chemically unstable anti-caking agent may have a serious impact on production processes or on the storing conditions of pharmaceutical products and tablets. In order to avoid such deficiencies with the chemicals used in the

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pharmaceutical industry, high quality raw materials, especially with regard to heavy metal impurities, are required in the production of pharmaceutical grade magnesium stearate (PGMS) [8–11].

Recently, the demand for stearates from vegetable sources has increased, mainly for applications in foods, pharmaceuticals, and cosmetics due to the bovine spongiform encephalopathy (BSE) problem, even though stearin from tallow is largely deactivated during its production. Pharmaceutical quality material must fulfill the requirements of the European, Japanese, and U.S. pharmacopoeias [1].

There are three basic methods in commercial use for the manufacture of metallic fatty acid soaps. They are designated the double decomposition process, the fusion process, which includes the related slurry process, and the metal-acid reaction process. The double decomposition process involves two basic reactions: (1) reaction of aqueous caustic and the fatty acid to form sodium soap dissolved in an aqueous phase, and (2) reaction of the sodium soap with an inorganic metal salt to form the metal soap. The fusion process involves the reaction of fatty acid and metal oxide, hydroxide, or acetate to form the metal soap. The metal-acid reaction process involves the reaction of the free metal in powdered form with the fatty acid to form the polyvalent metal soap. Of the three methods of production, the first, or double decomposition method, is the most widely used, especially in the preparation of stearates and palmitates of aluminum, calcium, lead, zinc and magnesium. The fusion process is generally not used when the metal oxides or metal hydroxides do not react rapidly with the organic fatty acid, and where raw materials are not available with a high degree of purity. The metal-acid reaction process is the least widely used of the three commercial processes [2–4]. The properties of the magnesium stearate formed from the different manufacturing processes may vary considerably. On the other hand, the raw materials and product preparation procedure are the most important factors in the overall process [12].

Although, the product may be easily found on the market, during the execution of the current literature review, it soon became apparent that only limited process information was available in the literature with respect to higher quality PGMS. Therefore, it seems that there is a need to look at the production process of PGMS in a detailed manner in order to report the process conditions leading to high quality products.

In this study, an attempt is made to produce PGMS in a semi-batch process by the double decomposition process and to investigate the effect of feed and operational variables on the production process by considering the following two-step reactions:

$$C_{17}H_{35}COOH + NaOH \rightarrow C_{17}H_{35}COONa + H_2O \quad (1a)$$

$$2C_{17}H_{35}COONa + MgSO_4 \rightarrow (C_{17}H_{35}COO)_2Mg + Na_2SO_4 \quad (1b)$$

In step (1a) of the process, the organic acid is saponified by using caustic solution. In step (1b), the resulting alkali soap is precipitated by addition of a solution of a water-soluble metal salt, e.g., magnesium sulfate.

A statistical approach is also developed to design the proper experiments and to analyze the results for obtaining the optimal process conditions for the PGMS production. In this part of the study, the half-fractional factorial design was adapted to determine the effects of parameters and their binary interactions on the production process and properties of the product.

2 Experimental Design

One of the most effective economical and valuable tools for the study and optimization of chemical products and processes is the statistical factorial design. In recent years, researchers have used fractional factorial design (FFD) to minimize the cost of experiments and derive the optimum conditions in the

Table 1. Selected levels of variables for the experimental design.

Variable Level	C_{acid} [kg/m^3] (A)	C_{NaOH} [kmol/m^3] (B)	T_1 [°C] (C)	C_{MgSO4} [kmol/m^3] (D)	T_F [°C] (E)
Low(−1)	50	2	65	1.5	50
High(+1)	200	3.5	85	2.33	65

Table 2. The 2^5 fractional factorial table with the three responses.

No of Exp.	(X_A)*	(X_B)	(X_C)	(X_D)	(X_E)	Final pH (Y_1)	Assay (Y_2)	Moisture (Y_3)
1	+1	+1	+1	+1	+1	8.65	4.78	65.32
2	−1	+1	+1	+1	−1	7.68	5.32	56.84
3	+1	−1	+1	+1	−1	7.32	4.14	63.21
4	−1	−1	+1	+1	+1	7.51	4.12	55.46
5	+1	+1	−1	+1	−1	8.1	4.47	65.23
6	−1	+1	−1	+1	+1	7.65	5.64	57.64
7	+1	−1	−1	+1	+1	7.32	5.45	62.32
8	−1	−1	−1	+1	−1	7.95	4.14	53.21
9	+1	+1	+1	−1	−1	6.79	4.63	64.56
10	−1	+1	+1	−1	+1	7.12	5.45	50.65
11	+1	−1	+1	−1	+1	6.97	4.65	63.12
12	−1	−1	+1	−1	−1	6.95	4.17	51.26
13	+1	+1	−1	−1	+1	7.22	5.24	64.17
14	−1	+1	−1	−1	−1	6.84	5.23	57.64
15	+1	−1	−1	−1	−1	6.32	4.65	59.41
16	−1	−1	−1	−1	+1	6.52	4.32	54.21
17	0	0	0	0	0	7.20	4.80	59.6
18	0	0	0	0	0	7.40	4.63	58.2
19	0	0	0	0	0	6.96	4.97	60.5

* *XA* to *XE* are the coded values of variables *A* to *E*, respectively.

presence of different variables affecting the quality of the final product. FFD is among the most widely used types of design for product and process design and for process improvement. A major use of FFD is in the screening experiments that are usually performed at the early stages of a process [13–17]. In this study, a five factor, two-level, half-fractional design ($2^5/2$) is carried out to investigate the effect of the mentioned variables on the three important responses, i.e., solution final pH, moisture content in the filtered cake and assay (magnesium stearate in the dried cake).

On the base of statistical design, this kind of fractional factorial design performs resolution V in which the main effects are not confounded with binary interaction effects. Therefore, it is possible to independently derive the effect of each single variable and each binary interaction. The selected variables and their levels are shown in Tab. 1 and include some medium compositions, e.g., initial concentration of stearic acid (SA), sodium hydroxide (SH) and magnesium sulfate (MS) and environmental factors, e.g., temperature set of the first reaction and the final reaction[1)]. Tab. 2 shows selected experimental variables and a 2^{5-1} fractional factorial design for conducting 16 experimental trials. In this table, the elements +1 (high level) and –1 (low level) represent the coded different levels of independent variables examined. In this research, another experiment was conducted at the medium level of variables coded by element 0, with three replications in order to investigate the reproducibility and error analysis of the experiments [17].

3 Experiments

3.1 Materials

Stearic acid, sodium hydroxide and hydrated magnesium sulfate with chemical formula $MgSO_4{\cdot}7H2O$, are the reactants used in the experiments. The variable parameters in this study are selected as: A – stearic acid concentration, B – sodium hydroxide concentration, C – first reaction temperature, which is the reactor temperature set during addition of SH (T_1), D – hydrated magnesium sulfate concentration, E – final reaction temperature which is the reactor temperature set during addition of MS (T_F). These factors are considered as the major variables in this research because of their effects on the process and the quality of the final product [1].

3.2 Experimental Setup and Procedure

The experiments were carried in an IKA® Laboratory reactor type LR 2000 P system variant (pressure) LR 2000.75 laboratory setup. The reactor is equipped with a mechanical mixer, pH meter, thermal sensor and a data acquisition system.

The experiments in Tab. 2 were carried out with a small-scale 2 L capacity. The procedure of the PGMS production involved first adding the SA into the reactor filled with deionized water at the initial temperature of 85 °C. The SH solution was then pumped to the reactor by a peristaltic pump with a controlled flow rate of 0.03 mL/min. The resultant solution was mixed by a mechanical agitator at 100 rpm. The reactor temperature was adjusted to the desired temperature, T_1. After 30 min, magnesium sulfate was gradually added with a flow rate of 0.05 mL/min for 50 min and the temperature was set to its final level, T_f. After 20 min, the final pH was measured and the filtration process was started. The produced cake was filtered and washed with deionized water. After measurement of the moisture in the filtered cake it was transferred to the dryer. After drying, the assay was reported on the basis of magnesium weight percentage in the dried cake. The pH of the solution was measured with an electrical pH meter, while the assay composition and the moisture content were measured according to the USP [1].

On the basis of the experiments, by changing the variables A to E for each experimental trial, 19 different runs were carried out to produce PGMS and at the end of each run, three different responses, i.e., final pH, assay and the moisture content of the cake were measured and presented in Tab. 2.

4 Results and Discussion

After performing the experimental runs, the three response variables were detected and the results are presented in Tab. 2. The effects of each single and binary interaction were calculated using Eq. (2) for the effect of A:

$$\text{Effect of } A = \frac{1}{8}\left(\sum_{i=1}^{8} y_i^{A+} - \sum_{j=1}^{8} y_j^{A+}\right) \tag{2}$$

y_i^{A+} is the response for the high level of A in the i^{th} trial. y_j^{A-} is the response for the low level of A in the j^{th} experiment. The effects are exhibited in bar-chart type format in Figs. 1–3, for final pH of the solution, the assay and the moisture content of the filtrated cake, respectively. In Figs. 1–3, variables with high positive or negative effects, have a significant effect on the response whereas those parameters with low absolute effects show no significant effect on the results, although statistical hypothesis tests need to be performed to derive the signifi-

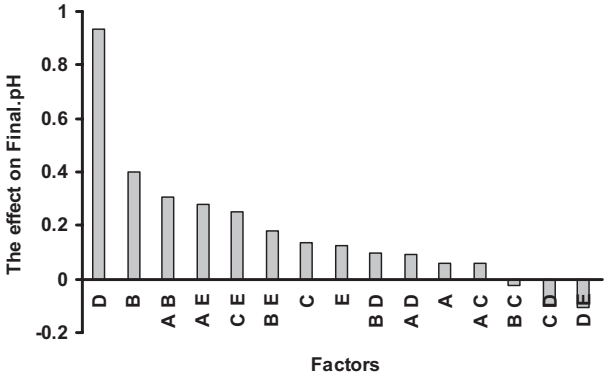

Figure 1. The effect of single and binary factors on the final pH.

1) List of symbols at the end of the paper.

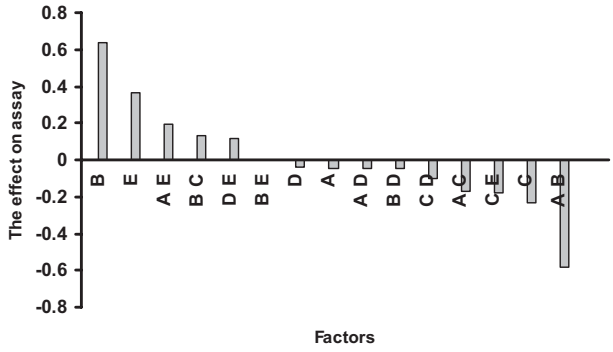

Figure 2. The effect of single and binary factors on the assay.

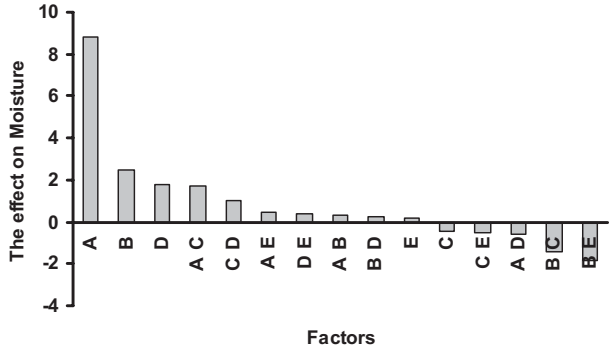

Figure 3. The effect of single and binary factor on the moisture.

Table 3. The effects and coefficients for final pH.

Term	Effect	Coeff. (β_i)	Standard dev. of coeff.	*T*-value	*P*-value	signification
Constant	7.28789	0.04841	150.55	0.000		
A	0.05875	0.02938	0.05275	0.56	0.616	NS
B	0.39875	0.19937	0.05275	3.78	0.032	S
C	0.13375	0.06688	0.05275	1.27	0.294	NS
D	0.93125	0.46563	0.05275	8.83	0.003	S
E	0.12625	0.06313	0.05275	1.20	0.317	NS
AB	0.30875	0.15437	0.05275	2.93	0.061	PS
AC	0.05875	0.02938	0.05275	0.56	0.616	NS
AD	0.09125	0.04562	0.05275	0.86	0.451	NS
AE	0.28125	0.14063	0.05275	2.67	0.076	PS
BC	–0.02625	–0.01312	0.05275	–0.25	0.820	NS
BD	0.09625	0.04812	0.05275	0.91	0.429	NS
BE	0.18125	0.09063	0.05275	1.72	0.184	NS
CD	–0.09875	–0.04938	0.05275	–0.94	0.418	NS
CE	0.25125	0.12562	0.05275	2.38	0.097	PS
DE	–0.10625	–0.05312	0.05275	–1.01	0.388	NS

cance of each parameter relative to the random error of the experiments.

The combination of the five variables in each response, allowed the introduction of the first-order polynomial model consisting of single and binary factors to estimate 15 coefficients (β_i, β_{ij}) and one constant (β_0) with three degree of freedom, as shown in Eqs. (3) and (4):

$$Y = \beta_0 + \sum \beta_i X_i + \sum \beta_{ij} X_i X_j + \varepsilon \quad (3)$$

$$\beta_A = \frac{1}{2}(\text{effect of } A) \quad (4)$$

The effects and coefficients are tabulated in Tabs. 3–5 for each response.

The student's *T*-test was performed to determine the significance of each variable employed, using the 95 % confidence level. The calculated *T*-values for each single and binary variable are presented in Tabs. 3–5 using Minitab (Ver.14) statistical software. The probability values, *P*, lower than 5 % revealed significant effects, those effects with $P > 10\,\%$ were recognized as nonsignificant effects and the variables with $5\,\% < P < 10\,\%$ were considered as possibly significant effects. In the following sections, each response is discussed separately [17].

4.1 Final pH

As shown in Tab. 3, in the range of studied parameters, MS and SH inlet concentrations (*D* and *B*) play the most important role in increasing the final pH of the product with a negligible effect on the other variables. Among the binary effects, although AE and CE show *p*-values within 0.05 and 0.10, they should not play any important role because none of main variables of *A*, *C* and *E* showed significant effects. The interaction of SA and SH inlet concentrations (*A* and *B*) with a *p*-value of 0.061 is rather considerable and is plotted in Fig. 4 where it is seen that to bring the pH value up to 7, working at a high level of both A and B would be recommended.

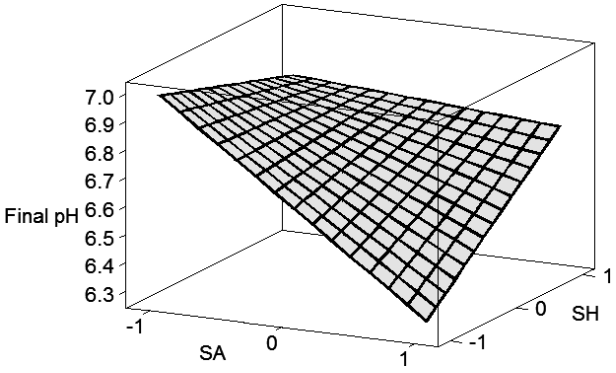

Figure 4. Interaction plot of stearic acid and NaOH concentration on the final pH.

4.2 Assay

As shown in Tab. 4 the effective main variables are *B*, *E*, and *C*, respectively. The inlet concentration of SH (*B*) and the final temperature (*E*) have positive influences on the essay. It seems that *B* improves the first reaction rate as well as a side reaction to produce $Mg(OH)_2$, which leads to increases in the assay, while *E* also enhances the second reaction rate leading to an increase in the assay. Increasing the first reaction temperature (*C*) showed a negative effect on the assay. This is attributed to the fact that the first reaction is exothermic and an increase in the reaction temperature enhances the reverse reaction rate. This may lower the concentration of sodium stearate leading to less PGMS production. The results of this study confirm that the range of selected MS concentration (*D*) exhibits no effect on the assay. It seems that the amount of *D* studied in this work was in excess of the base stoichiometry required to observe any significant effect on the rate in the second reaction.

Table 4. The effects and coefficients for assay by ANOVA.

Term	Effect	Coeff. (β_i)	Standard dev. of Coeff.	*T*-value	*P*-value	signification
Constant	4.7789	0.03228	148.07	0.000		
A	–0.0475	–0.0237	0.03517	–0.68	0.548	NS
B	0.6400	0.3200	0.03517	9.10	0.003	S
C	–0.2350	–0.1175	0.03517	–3.34	0.044	S
D	–0.0350	–0.0175	0.03517	–0.50	0.653	NS
E	0.3625	0.1813	0.03517	5.15	0.014	S
AB	–0.5825	–0.2913	0.03517	–8.28	0.004	S
AC	–0.1675	–0.0838	0.03517	–2.38	0.098	PS
AD	-0.0475-	–0.0237	0.03517	–0.68	0.548	NS
AE	0.1950	0.0975	0.03517	2.77	0.069	PS
BC	0.1350	0.0675	0.03517	1.92	0.151	NS
BD	–0.0500	–0.0250	0.03517	–0.71	0.528	NS
BE	0.0025	0.0012	0.03517	0.04	0.974	NS
CD	–0.1000	–0.0500	0.03517	–1.42	0.250	NS
CE	–0.1775	–0.0887	0.03517	–2.52	0.086	PS

According to the binary interactions, *AB* has the most significant interaction effect on the assay whereas *AE*, *CE* and *AC* have possible significant interactions on the assay. Fig. 5 shows the binary effect of *AB*. Although *A* did not show any remarkable influence on the assay, its binary effects with *B*, *C* and *E* could be quite important. As seen in Fig. 5, the assay production is influenced largely by the addition of *B* while maintaining a low level of *A*, where the side reaction to $Mg(OH)_2$ is favored. However, low levels of both *A* and *B* reduce the assay.

In Fig. 6 at high levels of *A*, increasing levels of *E* enhances assay production. It seems that additional acid reacts with MS at higher temperatures to improve the assay. In preparing

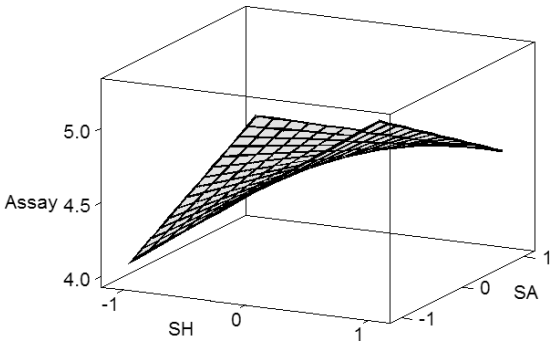

Figure 5. Interaction plot of stearic acid and NaOH concentration on the assay.

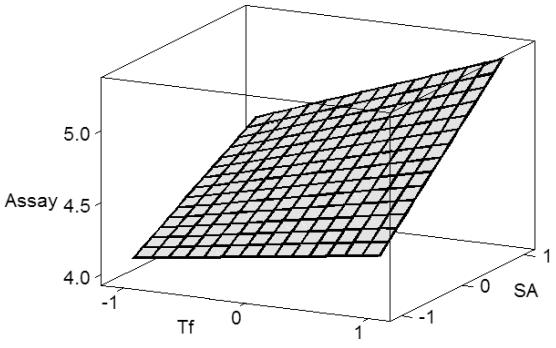

Figure 6. Interaction plot of stearic acid and final temperature on the assay.

PGMS, the assay is measured on the basis of weight percentage of magnesium in the dried cake. Therefore, the final product may contain traces of magnesium hydroxide precipitation. According to the USP, the presence of $Mg(OH)_2$ is unacceptable and would cause rejection of the product. Using a standard desirable assay from 4–5 by USP is a key factor to ensure minimal traces of $Mg(OH)_2$ in the final product.

4.3 Moisture in the Cake

As shown in Tab. 5, the most important single variables on moisture content of the cake are *A*, *B* and *D*. The concentration of inlet acid (*A*), leads to the formation of water and favors an increase in the moisture content inside the cake. SH produces water through the first reaction and MS, which is a hydrated material creates more moisture inside the cake. Two significant binary interactions of *AC* and *BE* are presented graphically in Figs. 7 and 8, respectively. Fig. 7 shows that the low inlet concentration of acid at high temperatures related to the first reaction leads to a low moisture content, whereas a high concentration of acid at higher temperatures for the first reaction enhances the moisture content. Fig. 8 presents the interaction of *B* and *E*, and reveals that a low final temperature with low level of SH decreases moisture, although the moisture content may be increased at low T_f with a high amount of SH present.

Table 5. The effects and coefficients for moisture by ANOVA.

Term	Effect	Coeff. (β_i)	Standard deviation of Coeff.	*T*-value	*P*-value	signification
Constant	59.0737	0.2350	251.39	0.000		
A	8.8125	4.4062	0.2561	17.21	0.000	S
B	2.4625	1.2312	0.2561	4.81	0.017	S
C	–0.4125	–0.2063	0.2561	–0.81	0.479	NS
D	1.7625	0.8812	0.2561	3.44	0.041	S
E	0.1875	0.0938	0.2561	0.37	0.739	NS
AB	0.3625	0.1813	0.2561	0.71	0.530	NS
AC	1.6875	0.8438	0.2561	3.29	0.046	S
AD	–0.5875	–0.2938	0.2561	–1.15	0.335	NS
AE	0.4375	0.2188	0.2561	0.85	0.456	NS
BC	–1.4125	–0.7063	0.2561	–2.76	0.070	PS
BD	0.2125	0.1062	0.2561	0.41	0.706	NS
BE	–1.8125	-0.9063	0.2561	-3.54	0.038	S
CD	1.0375	0.5188	0.2561	2.03	0.136	NS
CE	–0.5375	–0.2688	0.2561	–1.05	0.371	NS
DE	0.3875	0.1937	0.2561	0.76	0.504	NS

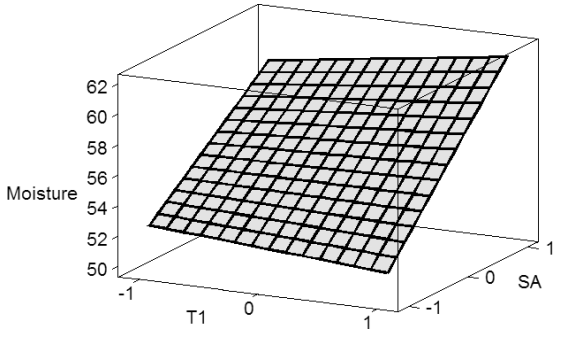

Figure 7. Interaction plot of stearic acid and first reaction temperature on the moisture.

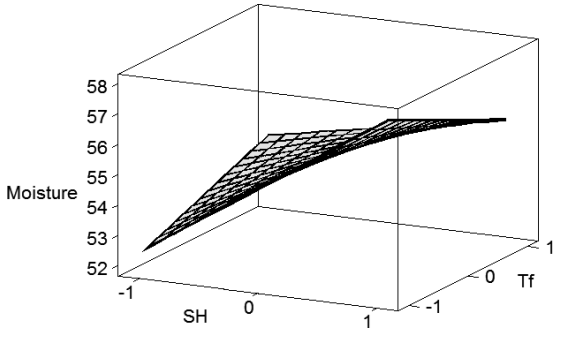

Figure 8. Interaction plot of NaOH concentration and final temperature on the moisture.

4.4 Optimization

In the final stage of the study, optimization was performed on the variables of the process to approach the target values reported by USP, in which the range of final pH should be 6–8, damp cake moisture from 40–60 % and assay from 4–5. The simplex optimization method was carried out on the model results to simultaneously derive the optimal conditions of the variables. These conditions were obtained and are tabulated in Tab. 6. According to Tab. 6, a final experiment was carried out based on the introduced optimal conditions at a large scale and the results are presented in Tab. 7. The experimental data are compared with the model predictions and close agreement is observed.

Table 6. The optimal conditions for preparing pharmaceutical magnesium stearate.

	Factor	Optimum value
Parameters	Stearic acid concentration, kg/m^3	80
	NaOH concentration, kmol/m^3	2.4
	NaOH adding temperature, °C	81.4
	concentration, kmol/m^3 $MgSO_4$	1.50
	Final temperature, °C	65
Responses	Final pH	6.78
	Assay, wt% Mg	4.35
	Moisture in damp cake, wt%	54.76

Table 7. Comparison between the optimal design data and experiment.

Factors	Optimal Value	Experimental Value	Relative absolute error
Final pH	6.78	6.9	0.017
Assay	4.35	4.63	0.060
Moisture	54.76	53.3	0.027

5 Conclusions

The fractional factorial experimental design method was employed in order to investigate the effect of the feed composition and the main operating variables on semi-batch production of pharmaceutical grade magnesium stearate by the double decomposition process. It is concluded from the results that the concentrations of magnesium sulfate and sodium hydroxide have a positive effect on the final pH, while the concentration of sodium hydroxide reveals the most positive effect on assay production. A negative influence of the first reaction temperature and positive effect of the final temperature on the assay are seen.

A polynomial is introduced to predict the quality and properties of the PGMS as a function of the operational parameters. In conclusion, the results of the study could be used as a

framework in the scale up of PGMS production with process design according to USP requirements.

Symbols used

T_1	[–]	first reaction temperature set
T_F	[–]	final reaction temperature set
y_i^{A+}	[–]	response at high level of A in i^{th} trial
y_j^{A-}	[–]	response at low level of A in j^{th} trial
β_0, β_i, β_{ij}	[–]	coefficients of the model

Abbreviations

SA	stearic acid
SH	sodium hydroxide
MS	hydrated magnesium sulfate

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