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RESEARCH PAPER

Effects of Manufacturing Process Variables on In Vitro Dissolution Characteristics of Extended-Release Tablets Formulated with Hydroxypropyl Methylcellulose

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ABSTRACT

The purpose of this study was to investigate the effect of three process variables: distribution of hydroxypropyl methylcellulose (HPMC) within the tablet matrix, amount of water for granulation, and tablet hardness on drug release from the hydrophilic matrix tablets. Tablets were made both by direct compression as well as wet granulation method. Three formulations were made by wet granulation, all three having the exact same composition but differing in intragranular:intergranular HPMC distribution in the matrix. Further, each formulation was made using two different amounts of water for granulation. All tablets were then compressed at two hardness levels. Dissolution studies were performed on all tablets using USP dissolution apparatus I (basket). The dissolution parameters obtained were statistically analyzed using a multilevel factorial-design approach to study the influence of the various process variables on drug release from the tablets. Results indicated that a change in the manufacturing process could yield significantly dissimilar dissolution profiles for the same formulation, especially at low-hardness level. Overgranulation could lead to tablets showing hardness-dependent drug-release characteristics. Studies showed that intergranular addition of a partial amount of HPMC (i.e., HPMC addition outside of granules) provided a significant advantage in making the formulation more robust over intragranular addition (i.e., that in which the entire amount of HPMC was added to the granules). Dissolution profiles obtained for these tablets were relatively less dependent on tablet hardness irrespective of the amount of water added during granulation.

Key Words: Matrix tablets; Dissolution; Intergranular; Intragranular.

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INTRODUCTION

Although developing a hydrophilic matrix tablet offers a simple and effective approach to formulate a drug for extended-release oral-dosage form, it requires a careful consideration of the physicochemical properties of the drug, polymer, and the excipients.[1–6] In addition to this, process variables like method of granulation, amount of binder added during granulation, use of high or low shear mixer, granule size distribution, compression force during tableting, etc., are also important.[7–17] Optimization of the formulation and the process variables is sometimes very tedious, expensive, and time-consuming. The present study demonstrates that optimization of the proportions of all ingredients in the formulation can be done on a small batch size of less than 100 g using a dry-blend–direct-compression approach. The dissolution profiles of the tablets made by this approach can be compared to a predetermined target-dissolution profile by using an appropriate dissolution method. Once the desired dissolution profile is achieved, this formulation can then be taken up for optimization of process variables. But for most formulations containing high amounts of active ingredient and/or polymer, dry-blend–direct-compression method is not a practical approach for large-scale production. So frequently, some other manufacturing process such as roller compaction, wet granulation, etc., has to be used. In this study, the optimization of process variables was focused on a wet-granulation method.

Until now, there have been many studies on the effect of polymer concentration on drug release through matrix tablets.[9,18–21] But there has been no study to show the effect of intra-:intergranular polymer distribution in the matrix tablet on drug release. It is believed that understanding the significance of HPMC distribution within the tablet matrix may help formulators to develop a better formulation. Hence, this approach is definitely worthy of further investigation.

In the present study, hydroxypropyl methylcellulose (HPMC) was used as the rate-controlling agent. Tablets made by dry-blend–direct-compression method that showed proximity to a predetermined target-dissolution profile were used as reference product. The percentage cumulative drug released (±standard deviation) in the target-dissolution profile were as follows: 1 hr: 34% (±1.1), 2 hr: 53% (±1.9), 4 hr: 77% (±2.9), and 8 hr: 95% (±3.2). Three formulations with the same composition as the reference tablets were made using wet-granulation method, but with each having a different intra-:intergranular HPMC distribution. Each formulation was made using two levels of water for granulation and was further compressed at two hardness levels. Dissolution studies were performed on these tablets. A multilevel factorial design was employed to study the effect of the three variables: intra-:intergranular HPMC distribution, amount of water for granulation, and tablet hardness on drug-release characteristics. Each formulation was tested for $Q_{1\,hr}$ (% drug released at 1 hr during dissolution) and $t_{50\%}$ (time in which 50% drug is released). Statistical analysis was performed using two-sample equal-variance t-test. Similarity factor, f_2, was also determined to compare the dissolution profiles against that of the reference product.

MATERIALS AND METHODS

The Active Pharmaceutical Ingredient (API) and Magnesium Stearate NF were provided by Mallinckrodt, Inc., St. Louis, MO. Hydroxypropyl Methylcellulose 2208 USP (Methocel®, K15M, Premium) was purchased from Dow Chemicals, Midland, MI. Spray-dried Lactose Monohydrate NF (Lactose 315) and Fast-Flo® Lactose Monohydrate NF (Lactose 316) were obtained from Foremost Farms USA, Rothschild, WI. Colloidal Silicon Dioxide NF (Syloid® 244FP) was purchased from W.R. Grace and Company, Columbia, MD.

Tablet Formulation

The formulation composition used in this study was as follows:

API (Active Pharmaceutical Ingredient)	10%
HPMC K15M	32%
Lactose 315	20%
Lactose 316	36%
Lubricant/Glidant	2%

The API used in this study was salt of a weakly alkaline drug that has low molecular weight and high water solubility. The formulation listed above was made by both dry-blend–direct-compression and wet-granulation methods. The same lot of HPMC K15M

was used throughout the entire study. In the wet-granulation method, 20% of lactose was added to the wet granulation intragranularly whereas the remaining 36% lactose was mixed later with the dried granules in a dry-blending step. This external addition of lactose provided better compressibility to the formulation based on our previous studies.

Experimental Design

A multilevel factorial design was employed using the software StatGraphics Plus, Version 5.0 (Manugistics, Inc., Rockville, Maryland) to determine the effect of the three factors: tablet hardness, amount of water added in the wet-granulation step, and the intra-:intergranular distribution of HPMC within the tablet matrix on drug-release characteristics. Each factor was tested at either two or three levels designated as −1, 0, and +1 as follows: hardness—3.3 kp (−1) and 6.0 kp (+1), amount of water added in the wet-granulation—0.51 g of water per gram of HPMC (−1) and 0.86 g of water per gram of HPMC (+1), intragranular:intergranular HPMC distribution—32%:0% (−1), 28%:4% (0), and 24%:8% (+1). Based on multilevel Design of Experiments (D.O.E), 12 types of tablets (F_1 to F_{12}) were made as shown in Table 1. A randomized table (Table 2) was generated using StatGraphics Plus. The tablets made from dry-blend approach were designated as the reference tablets (F_{ref}). For each formulation, response variables studied were $Q_{1\,hr}$ (% drug released in first hour during dissolution) and $t_{50\%}$ (time in which 50% drug is released).

Preparation of Dry Blend

All the ingredients listed in the formulation chart were blended together by shaking for 5 min in a glass bottle. Blend uniformity was checked to assure that a homogeneous blend was achieved before tableting by direct compression.

Preparation of Wet-Granulation Blend

Wet granulations were made in a VG-25 High Shear Granulator (Glatt Air Technologies, Inc. Ramsey, NJ). The API (10%), HPMC (32% for formulation 1, 28% for formulation 2, and 24% for formulation 3) and 20% lactose 315 were first preblended for 5 min in the granulator followed by

Table 2. Randomized study design.

Test tablets	Amount of water for granulation	Tablet hardness	Intra-:Intergranular HPMC distribution
F_{12}	1	1	1
F_4	1	1	−1
F_{11}	1	−1	1
F_6	−1	1	0
F_9	−1	−1	1
F_7	1	−1	0
F_2	−1	1	−1
F_3	1	−1	−1
F_{10}	−1	1	1
F_5	−1	−1	0
F_1	−1	−1	−1
F_8	1	1	0

Table 1. Design of experiments.

	Reference formulation	Formulation 1		Formulation 2		Formulation 3	
Granulation method	Dry blend, Direct compression	Wet granulation		Wet granulation		Wet granulation	
Intragranular HPMC	NA	32%		28%		24%	
Intergranular HPMC		0%		4%		8%	
Granulation end-point	NA	Normal granulation	Over granulation	Normal granulation	Over granulation	Normal granulation	Over granulation
Hardness ~ 3.3 kp	—	F_1	F_3	F_5	F_7	F_9	F_{11}
Hardness ~ 6 kp	F_{ref}	F_2	F_4	F_6	F_8	F_{10}	F_{12}

addition of water at a spray rate of 140 g/min. Wet granulation was carried out at two levels of water addition for each formulation: 0.51 g of water per gram of HPMC (−1) and 0.86 g of water per gram of HPMC (+1). End-point of granulation was determined using qualitative judgment based on visual inspection and hand evaluation of granules. The wet granules obtained at (−1) level were designated as ''normal'' granules which contained the minimum amount of water necessary to form coherent granules that could easily pass through a 4-mesh screen. The granules obtained at the (+1) level were designated as ''overgranulated'' granules. The amount of water added at this step was such that it allowed satisfactory movement of the mass through a 4-mesh screen by hand milling. The wet granules were dried in the GPCG-1 Fluid Bed Dryer (Glatt Air technologies, Inc. Ramsey, NJ). The drying end point was controlled by monitoring the Loss on Drying (LOD) values. The LOD value of the pre-blend, prior to water addition, was used as a reference. Drying was stopped when the LOD value of post-drying sample was within ± 1% to the pre-blend sample. These dry granules were then milled through a 20-mesh screen (The Fitzpatrick Company, Elmhurst, IL) prior to blending and lubrication. Thirty-six percent of lactose 316 was added in the blending step followed by lubrication with magnesium stearate and silicon dioxide. The blending and lubrication times were 10 min and 3 min, respectively.

Tableting

For formulations made from both dry-blend and wet-granulation approaches, tablets were prepared on a Korsch PH 106 tablet press (Berlin, Germany) using a 9/32 inch (7.14 mm) deep-cup concave tooling. The target weight for all tablets was 150 mg and the target hardness levels were 3.3 and 6.0 kp. The weight and hardness of the tablets were measured using standard techniques.

Dissolution Studies

Drug-release profiles were determined using USP I (basket) apparatus at 50 rpm and with 900 mL distilled water as media maintained at 37°C (±0.5°C). Three to six tablets were used for each test. Ten-milliliter samples were collected at 1, 2, 4, and 8 hr without replacement with fresh media. Samples were analyzed by HPLC and the percent drug dissolved at each sampling time was calculated after correction for the cumulative amount removed in previous samples.

Release-Profile Analysis

The Higuchi square-root equation (Eq. (1))[22] gives the drug release from a planar surface of an insoluble, heterogeneous matrix by diffusion through the intergranular openings created by the porosity of the matrix.

$$Q = [D \in C_s t(2A - \in C_s)/\tau]^{1/2} \quad (1)$$

where Q is the cumulative amount of drug released per unit area at time t, D is the diffusion coefficient of the drug in the dissolution medium, $\in$ is the porosity of the matrix, C_s is the solubility of the drug in the dissolution medium, τ is the tortuosity of the matrix, and A is the drug concentration in the tablet. The equation predicts a straight-line relationship if Q is plotted versus $t^{1/2}$.

It is clear that some of the assumptions in the derivation of the classic Higuchi equation are not valid for the HPMC-based matrix system prepared in this study. However, due to the simplicity of this equation, it is often used to analyze experimental drug-release data to get a rough idea of the underlying release mechanism.[26,27]

In the present work, release data was subjected to a simple Higuchi-type equation (Eq. (2)).

$$Q = (K_H \times t^{1/2}) + c \quad (2)$$

where Q is the % cumulative drug released in time t, K_H is Higuchi-type release rate, and c is the y-intercept. Regression coefficient (r^2) was obtained for each plot. In this study, two parameters that can be used to describe dissolution profiles, $t_{50\%}$ and $Q_{1\,hr}$ were used to compare the various types of tablets. A summary of the mean values of K_H, c, r^2, $t_{50\%}$ and $Q_{1\,hr}$ are given in Table 3.

Statistical Analysis

Data obtained from the 12 types of tablets were analyzed using StatGraphics Plus that was used to

Table 3. Summary of mean values of dissolution parameters for each type of tablet.

Test tablets	K_H (%/hr$^{1/2}$)	y-Intercept, c (%)	r^2 [a]	$Q_{1\,hr}$ (%)	$t_{50\%}$ (hr)	Similarity factor, f_2
F_1	40.3	1.14	0.993	40.3	1.47	63
F_2	41.4	−3.77	0.994	36.6	1.68	77
F_3	40.6	7.27	0.989	46.4	1.11	48
F_4	42.8	−2.71	0.995	39.0	1.52	65
F_5	41.2	−5.3	0.993	35.0	1.80	80
F_6	42.6	−5.45	0.997	36.3	1.70	80
F_7	39.0	3.03	0.990	40.7	1.45	61
F_8	39.5	−1.79	0.997	37.0	1.72	76
F_9	40.5	−5.52	0.997	34.2	1.88	81
F_{10}	40.9	−7.6	0.998	32.7	1.98	76
F_{11}	41.8	−7.8	0.999	33.5	1.91	81
F_{12}	43.6	−8.14	0.998	34.8	1.78	90
[b]F_{ref}	42.5	−7.73	0.999	34.5	1.85	100

[a]r^2: Regression coefficient for % drug released vs. square-root of time plot.
[b]F_{ref} was used as the reference product for calculation of f_2 values.

Table 4. t-Test results (based on p-values obtained).[a]

	$Q_{1\,hr}$ (%)		$t_{50\%}$ (hr)	
Test tablets	[b]Comparison with F_{ref}	[c]Comparison between 3.3 and 6.0 kp tablets	[b]Comparison with F_{ref}	[c]Comparison between 3.3 and 6.0 kp tablets
F_1	S	S	S	S
F_2	NS		S	
F_3	S	S	S	S
F_4	S		S	
F_5	NS	NS	NS	NS
F_6	NS		NS	
F_7	S	S	S	S
F_8	NS		NS	
F_9	NS	NS	NS	NS
F_{10}	NS		NS	
F_{11}	NS	NS	NS	NS
F_{12}	NS		NS	

[a]p-Value ≤ 0.05: Significant Result (S); p-Value > 0.05: Not Significant (NS).
[b]Q_{1hr} and $t_{50\%}$ values of each formulation were compared with those of F_{ref} formulation.
[c]Q_{1hr} and $t_{50\%}$ values of 3.3 kp tablets were compared with those of 6.0 kp tablets within same group.

generate the study design and the response surface plots. A two-sample equal-variance Student's t-test was performed (i) to compare the $t_{50\%}$ and $Q_{1\,hr}$ values of tablets made by wet-granulation method vs. those of tablets made by dry-blend–direct-compression method, and (ii) to compare the $t_{50\%}$ and $Q_{1\,hr}$ values of tablets having 3.3 kp vs. those having 6.0 kp hardness levels with the levels of HPMC distribution and water for granulation remaining constant. Results are given in Table 4. A p-value of less than or equal to 0.05 was considered as statistically significant.

Similarity factor, f_2, was also calculated to compare the various dissolution profiles using Eq. (3).

$$f_2 = 50\mathrm{Log}\left\{\left[1+1/n\sum_{t=1}^{n}(R_t-T_t)^2\right]^{-0.5}\times 100\right\} \quad (3)$$

where Log = logarithm to base 10, n = number of sampling time points, Σ = summation over all time points, R_t = dissolution at time point t of the reference product, and T_t = dissolution at time point t of the test product. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.[23] Tablets made from dry-blend approach (F_{ref}) were used as the reference product and f_2 values were calculated for dissolution profiles of all other formulations in comparison with the dissolution profile of F_{ref} (Table 3).

RESULTS AND DISCUSSION

The test tablets in this study can be separated into three groups as follows: Group 1, consisting of F_1, F_2, F_3, and F_4 made from formulation 1 having an intra-:intergranular HPMC distribution of 32%:0%, Group 2, consisting of F_5, F_6, F_7, and F_8 made from formulation 2 having an intra-:intergranular HPMC distribution of 28%:4%, and Group 3, consisting of F_9, F_{10}, F_{11}, and F_{12} made from formulation 3 having an intra-:intergranular HPMC distribution of 24%:8%.

Results from dissolution profiles indicated that most of the test tablets followed the Higuchi model for diffusional release of drug for up to 4 hr or approximately until 75% of drug was released. The dissolution parameters were determined from the linear portions of the percent cumulative drug released vs. square-root of time plots. This is in accordance with the findings of Ford et al.[9] It can be seen from Table 3 that the r^2 values of most of the test tablets show a good fit to the Higuchi-type equation, indicating that diffusion should be the predominant mechanism involved in drug release. But tablets made from overgranulation batches and having the lower hardness level of 3.3 kp (F_3 and F_7) show poor fit, indicating that other mechanisms of drug release such as erosion of tablet matrix and polymer dissolution may be equally important in these cases. Similar results have been reported before by other studies[9,19] showing that goodness of fit of the Higuchi model is likely to be reduced when attrition has a significant effect on dissolution kinetics. These tablets, along with F_1 tablets, also showed burst-release of drug. This was indicated by their positive y-intercepts as reported by other studies[9,18] and relatively high $Q_{1\,hr}$ values. Overall, the tablets in Group 1 do not show a very good fit. The F_6 and F_8 tablets in Group 2 having hardness 6.0 kp show a good fit. All tablets from Group 3 show a good fit.

By comparing the similarity factor values (f_2), it is found that only F_3 tablets have an f_2 value below 50, indicating that their dissolution profile is dissimilar as compared to that of F_{ref}. All other test tablets have an f_2 value above 50. However, tablets like F_1, F_4, and F_7 have relatively lower f_2 values (≤ 65) and hence, show some degree of dissimilarity with respect to F_{ref} tablets. This is further elucidated by the t-test results (Table 4) which show that these tablets have significantly different $Q_{1\,hr}$ and $t_{50\%}$ values as compared to those of F_{ref}. This suggests that just getting an f_2 value above 50 should not be considered as having good similarity with the reference profile unless supported by other statistical analysis results. Hence, it can be proposed that for an extended-release product, an f_2 value should not be used as the sole response factor when comparing two dissolution profiles.

The t-test results given in Table 4 are based on comparison of $Q_{1\,hr}$ and $t_{50\%}$ values of each test tablet with those of F_{ref}, respectively, and also comparison between 3.3 kp and 6.0 kp tablets within each group. These results along with the f_2 values effectively bring out the impact of the three factors—intra-:intergranular HPMC distribution, water for granulation, and hardness levels of tablets on the drug-release characteristics of the test tablets. A comparison of the dissolution profiles of all tablets with that of F_{ref} is shown in Figs. 1, 2, 3, and 4.

In Group 1, all tablets show statistically different values than F_{ref} (Table 4). But from the f_2 values (Table 3), it appears that the tablets made from normal granulation would show the desired dissolution profile if the tablets are made harder. But upon overgranulation, neither 3.3 kp nor 6.0 kp tablets

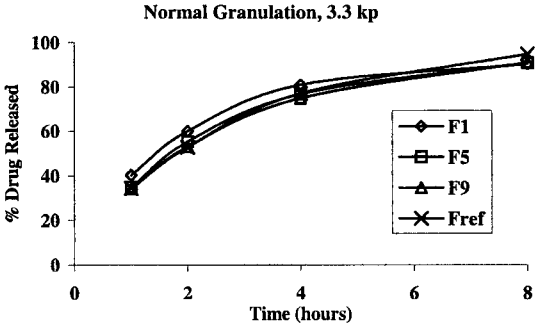

Figure 1. Effect of normal granulation and intra-:intergranular HPMC distribution on drug release (at 3.3 kp).

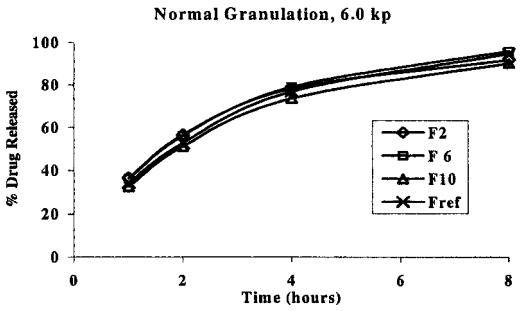

Figure 2. Effect of normal granulation and intra-:intergranular HPMC distribution on drug release (at 6.0 kp).

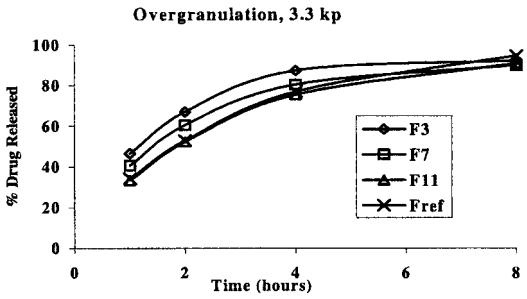

Figure 3. Effect of overgranulation and intra-:intergranular HPMC distribution on drug release (at 3.3 kp).

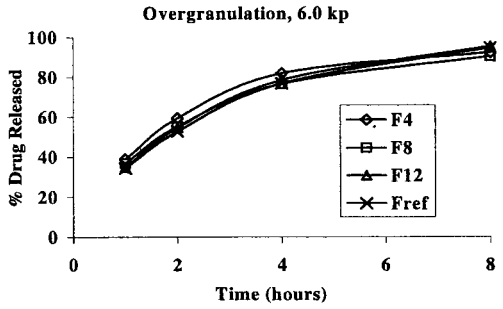

Figure 4. Effect of overgranulation and intra-:intergranular HPMC distribution on drug release (at 6.0 kp).

(F_3 and F_4 respectively) possess the desired characteristics as shown in Figs. 3 and 4.

In Group 2, 4% HPMC was added in the dry-blending step so that it was present in the intergranular matrix region of the tablet. The *t*-test as well as f_2 values indicate that for this group, normal granulation produces tablets (F_5 and F_6) possessing the desired release characteristics irrespective of the hardness level. But upon overgranulation, the tablets having 3.3 kp hardness (F_7) show faster release and, hence, have to be made harder ~6.0 kp (F_8) to get the desired results.

Group 3 contained 8% HPMC in the intergranular matrix region of the tablet. In this group, all tablets showed release characteristics similar to each other and to those of F_{ref}. Thus, neither hardness nor overgranulation seems to have any major impact on the release profile of these tablets as can be seen from Figs. 1, 2, 3, and 4.

These results indicate that presence of partial amount of HPMC in the intergranular region of the matrix makes the tablets less sensitive to the effect of tablet hardness on drug release. Also, increasing the amount of intergranular HPMC in the tablet matrix reduces the effect of overgranulation on drug-release profile irrespective of tablet hardness.

It should be mentioned here that during tableting, as expected, the blends made from overgranulated batches were found to be slightly less compressible than those made from normal granulation. But the flowability of the granules was comparable for all formulations.

The overall effects of the three factors—intra-:intergranular HPMC distribution, water for granulation, and hardness levels of tablets on the response variables like $Q_{1\,hr}$ and $t_{50\%}$ of the test tablets can be seen in the response surface plots shown in Figs. 5 and 6. These graphs illustrate that response variables, $Q_{1\,hr}$ and $t_{50\%}$, are much less process-dependent at the intra-:intergranular HPMC distribution of 24%:8% (Level +1). These response variables were modeled by the following quadratic equations (Eqs. (4) and (5)). They can also be used to predict $Q_{1\,hr}$ and $t_{50\%}$ in case a change in any of the three factors is required. It can be seen from the coefficient values in these equations that the intra-:intergranular HPMC distribution has the maximum impact on the response variables.

$$\begin{aligned} Q_{1\,hr} = {} & 37.25 + 1.35833 * \text{Amount of Water} \\ & - 1.14167 * \text{Hardness Level} \\ & - 3.3875 * \text{HPMC Distribution Level} \\ & - 0.491667 * \text{Amount of Water} \\ & \times \text{Hardness Level} \\ & - 0.8875\ \text{Amount of Water} \\ & \times \text{HPMC Distribution Level} \\ & + 1.3625 * \text{Hardness Level} \\ & \times \text{HPMC Distribution Level} - 0.0625 \\ & \times (\text{HPMC Distribution Level})^2 \end{aligned} \quad (4)$$

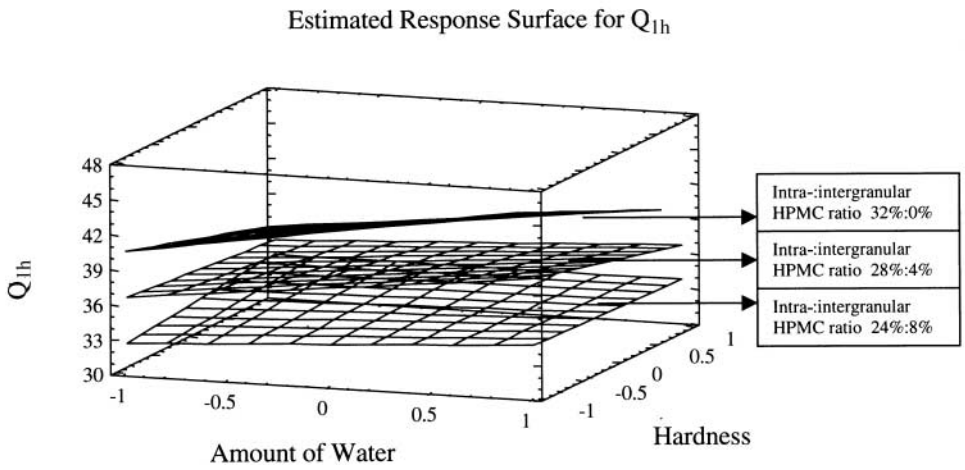

Figure 5. Response surface plot for $Q_{1\,hr}$ (%).

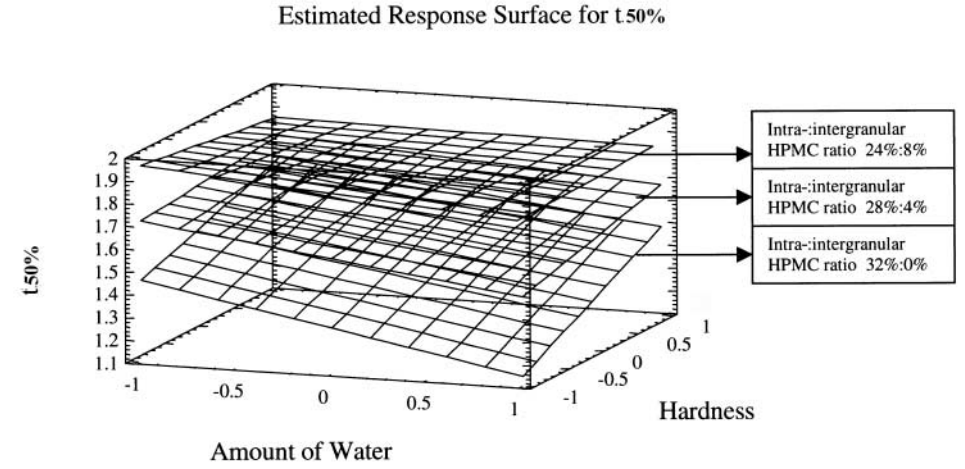

Figure 6. Response surface plot for $t_{50\%}$ (hours).

$$
\begin{aligned}
t_{50\%} = {} & 1.6675 - 0.085 * \text{Amount of Water} \\
& + 0.0633 * \text{Hardness Level} \\
& + 0.22125 * \text{HPMC Distribution Level} \\
& + 0.02833 * \text{Amount of Water} \\
& \times \text{Hardness Level} + 0.04375 \\
& \times \text{Amount of Water} \\
& \times \text{HPMC Distribution Level} - 0.08125 \\
& \times \text{Hardness Level} \\
& \times \text{HPMC Distribution Level} \\
& - 0.00125 * (\text{HPMC Distribution Level})^2
\end{aligned} \tag{5}
$$

In the present study, it was observed that the drug-release curves of tablets made from direct-compression and wet-granulation methods are often dissimilar unless some amount of HPMC is present in the matrix intergranularly. Also, changes in tablet hardness and amount of water added during granulation were found to have a significant effect on the drug-release profile. Contrary to this, in a study by Sheskey and Williams,[7] the drug release was not influenced by the method of tablet manufacture. They reported that both direct compression and wet granulation, using varying amounts of water for granulation, gave similar results for drug release. There are several possible explanations for the difference in findings. First, the formulation used in their

study was a simple one consisting of only a high dose of very water-soluble drug, HPMC, and lubricant. In the present study, the formulation contains a relatively low dose of very water-soluble drug with lactose present in a very high proportion and it is present both intra- and intergranularly. This could be a major contributor to the observed results. Secondly, the tablet hardness used in their study could be higher than the one used in the present study. Also, the amounts of water used in their study are different than the ones used in the present study. This indicates that depending on the specific formulation studied and the process used for manufacturing, there could be differences in conclusions drawn in relation to drug-release characteristics. Also, in other studies,[8,9,11] it was found that tablet hardness did not have any influence on the drug-release rate of HPMC matrix tablets prepared by either direct compression, roller compaction, or nonaqueous wet granulation. This is similar to the earlier findings by this group[24] where hardness did not have a significant effect on drug release for HPMC matrix tablets prepared by dry-blend–direct-compression method.

In the present work, although changes in the three factors studied did not alter the dissolution rate (Higuchi-type release rate) as can be seen from Table 3, they did alter the overall dissolution profile depending on the intra-:intergranular HPMC distribution. This may be due to changes in the pore structure and pore size distribution within the tablet. It has been shown by some studies[7,10] that granule densification occurs with increasing amounts of water addition during granulation. A coarse-structured tablet can be made if coarse, strong granules are used. In the study by Selkirk and Ganderton,[10] slightly higher air permeability was observed for tablets made from granules massed with 25% water than those massed with 13% water. Also, both wet-granulated tablets showed higher permeability than tablets made by direct compression. Similar results were obtained by Espinosa et al.[25] where amount of liquid used in wet granulation significantly affected the dissolution process of tablets. However, addition of a partial amount of HPMC to the granules in the dry-blend step may help in the formation of a more dense and compact tablet. It may reduce the permeability of tablets leading to a drug-release profile that is less process-dependent. Hence, no significant influence on drug release was observed for Group 3 tablets irrespective of tablet hardness or the amount of water added during granulation.

CONCLUSIONS

It can be concluded from this study that manufacturing process has a significant impact in determining the dissolution characteristics of HPMC matrix tablets. When HPMC K15M matrix tablets were prepared by wet-granulation approach, the tablet hardness, distribution of HPMC within the tablet (intergranular and intragranular), and the amount of water added in the wet granulation step all have a significant impact on dissolution. By incorporating partial amount of HPMC intergranularly in the dry-blend step, drug-release profiles could be made much less sensitive to the manufacturing process. From the three intra-:intergranular HPMC levels investigated, a 24%:8% distribution was found to give a robust product having good reproducibility.

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