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Formulation Variables Affecting Drug Release From Xanthan Gum Matrices at Laboratory Scale and Pilot Scale

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ABSTRACT The purpose of this research was to study processing variables at the laboratory and pilot scales that can affect hydration rates of xanthan gum matrices containing diclofenac sodium and the rate of drug release. Tablets from the laboratory scale and pilot scale proceedings were made by wet granulation. Swelling indices of xanthan gum formulations prepared with different amounts of water were measured in water under a magnifying lens. Granules were thermally treated in an oven at 60°C, 70 °C, and 80°C to studythe effects of elevated temperatures on drug release from xanthan gum matrices. Granules from the pilot scale formulations were bulkier compared to their laboratory scale counterparts, resulting in more porous, softer tablets. Drug release was linear from xanthan gum matrices prepared at the laboratory scale and pilot scales; however, release was faster from the pilot scales. Thermal treatment of the granules did not affect the swelling index and rate of drug release from tablets in both the pilot and laboratory scale proceedings. On the other hand, the release from both proceedings was affected by the amount of water used for granulation and the speed of the impeller during granulation. The data suggest that processing variables that affect the degree of wetness during granulation, such as increase in impeller speed and increase in amount of water used for granulation, also may affect the swelling index of xanthan gum matrices and therefore the rate of drug release.

KEYWORDS: Xanthan gum, Diclofenac sodium, Granulation, Hydration,Laboratory, Pilot scale.

INTRODUCTION

Hydrophilic matrices of hydroxy propyl methyl cellulose, polyvinyl alcohol, and polyethylene oxide have been studied to some detail for controlling drug release [1-3]. Drug release from these matrices usually is preceded by polymer erosion or hydration, or a combination of both processes,.depending on the drug/excipient or formulation variables [1]. Kinetics of drug release from these matrices are dependent on the relative magnitude of polymer hydration at the moving rubbery/glassy front within the tablet and the rate of polymer erosion at the swollen polymer/dissolution medium front [3]. Of particular interest is the process by which a uniform rate of drug release can be achieved. For this to be attained, synchronization between the rate of hydration with that of erosion is a prerequisite [4].

Xanthan gum is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending, and emulsifying water-based systems [5]. It appears to be gaining appreciation for the fabrication of matrices with uniform drug release characteristics [6-9]. Because drug release from xanthan gum matrices is preceded by polymer hydration, processing variables that might affect its hydration would also affect its performance as a controlled release dosage form. Thus, the purpose of this investigation was to study processing variables at the laboratory and pilot scales that can affect hydration rates of xanthan gum matrices containing diclofenac sodium and hence rate of drug release.

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MATERIALS AND METHODS

Materials

Xanthan gum [XG] Rhodigel 23 was obtained from Rhone-Poulenc, Paris, France; diclofenac sodium from Yung Zip Chemicals, Taiwan, ROC; microcrystalline cellulose Avicel PH101® from FMC Corporation, Philadelphia, PA; and magnesium stearate from Shanghai Medicines and Health Products, Shanghai, China.

Laboratory scale preparation of tablets

A 100-g batch was made for the laboratory scale (LS) preparation for lots 1 through 5 (**Table 1**).

Table 1: Composition for Laboratory Scale and Pilot Scale Proceedings

Lot Number	Diclofenac	Microcrystalline Cellulose	Xanthan Gum	Water
1	50	32.5	17.5	50
2	50	35	15	50
3	50	37.5	12.5	50
4	50	40	10	50
5	50	42.5	7.5	50

Before mixing, the powders were passed through a 0.716 mm aperture sieve and then mixed in a plastic bag. The powders were then mixed in planetary mixer (Kenwood Chef, Havant, UK) with half the portion of water for 3 minutes. The second portion of water was then added, and mixing continued for another 3 minutes, after which the granules were passed through a 2.0 mm sieve and dried in an oven at 60ºC for 5 hours. Two additional impeller speeds, one above and one below that used for granulation, were used to study the effect of different impeller speeds on rate of drug release from tablets at the LS using lot 2. The moisture content was about 2% in all the cases after the drying process. The granules were later screened through 1.4 mm sieve. Tablets of about 200 mg weight (100 mg of diclofenac sodium) were made from these granules after adding 1% magnesium stearate, using a rotary tableting machine (YY ZP19, Shanghai Tianhe Pharmaceutical Machinery Factory, Shanghai, China [3]) equipped with 8-mm flat-faced punches. The hardness of the tablets was determined using a hardness tester (Erweka, Heusenstamm, Germany), and the tensile strength calculated using the relationship

$$T = 2P/HD\,\pi \qquad (1)$$

where T is the tensile strength (N/m_2), H is the thickness of tablet (m), D the diameter (m), and P is the applied force (N). An average of 10 readings was made.

Pilot scale preparation of tablets

For the pilot scale (PS), tablets were prepared using the same manufacturing formula as lots 1 and 2, but at 40 times the batch size of the laboratory scale. Before mixing, the powders were passed through a 0.716 mm sieve and then mixed in a large plastic bag. The powders were then introduced into a high-shear mixer (M15, NR Industries Co. Limited, Bangkok, Thailand), which was run at an impeller speed of 1500 rpm. About one third of the amount of water was added, then mixing continued for 30 seconds each time until the final addition of the water. Adhered material on the walls of the mixer was scraped off between the mixing process. In addition, 2 additional speeds of 1700 and 1300 rpm were evaluated using lot 2 to access the effect of mixing speed on rate of drug release from these matrices. The wet mass was finally mixed for 1 minute and then sieved through a 2.0 mm perforated granulator(Pharmaceuticals and Medical Supply Limited, Bangkok, Thailand). Granules were dried on a fluidized-bed drier (NR Industries Co. Limited) with an inlet and outlet temperature of 65ºC and 50ºC, respectively, for 3 hours. This ensured moisture content of about 2%. The dried granules were sieved through an oscillating granulator with a 1.4 mm sieve (NR Industries Co. Limited). After adding 1% magnesium stearate to the granules, tablets were made with the same tableting machine used above. The machine was adjusted to produce tablets of approximately 200 mg weight with the same compression settings as in the preparation of the LS.

In-vitro dissolution studies

Drug release from the various tablets was determined using the paddle method of the USP 23 dissolution apparatus (Model AT7 CH 4008, Sotax, Basel, Switzerland). The test was conducted in 900 mL of distilled water maintained at 37.0 °C ± 0.5 °C at a paddle rotation speed of 100 rpm. Samples of 5 mL each were collected at predetermined intervals using an automated fraction collector (Model C613, Sotax) during a 12-hour period. The drug concentrations in the samples were analyzed using a UV/VIS.spectrophotometer (D2000, Hitachi, Tokyo, Japan) at 277 nm after 1:1 dilution with distilled water. The mean of 6 tablets was used to characterize each concentration.

Determination of bulk density and granule size range

The bulk densities of granules from lot 2 for the LS and PS were determined by pouring each of them slowly into a 10 mL volume glass cylinder and then leveling off the excess with a spatula. The density was then calculated by dividing the weight by the volume. A mean of 6 readings was taken. In addition, the granule size ranges were determined using a series of sieves of decreasing aperture, namely 1.4 mm, 1.0 mm, 0.3 mm, and a base arranged on top of one another with the largest aperture on top. About 100 g of granules were then placed on the top-most sieve and the series subjected to mechanical vibration for 10 minutes. The amount of granules within the 1.0-1.4 mm, 0.3-1.0 mm, and < 0.3 mm size ranges was then calculated as percentages of the total amount of the granules.

Preparation of tablets with different size distribution

The different granule size ranges (1.0-1.4 mm, 0.3-1.0 mm, or < 0.3 mm) from the PS formula were compressed into 200 mg tablets after lubrication with 1% magnesium stearate to study the rate of drug release from these different granule size ranges in comparison to the rate of drug release from LS. The granules were compressed into tablets using the same tableting machine and settings described earlier; hardness of tablets was determined with the same apparatus as above.

Effect of thermal treatment of granules and volume of water used for granulation

The effect of temperature rise during the PS granulation was investigated at LS using lot 2. Immediately after addition of the water during the granulation, the granules were divided into 3 portions and each one placed in the oven at 60ºC, 70º C, or 80ºC for 10 minutes. These were then cooled to room temperature and subjected to the rest of the procedure described under LS preparation of tablets. Effect of the amount of water used for granulation on rate of drug release from tablets was conducted at the LS and PS using lot 2. The percentages of water used for both proceedings were 30%, 50%, and 70% of batch.

Measurement of swelling index

Measurement of hydration rates of XG-containing matrices were carried out to relate the observed phenomena of drug release with the rates of.polymer hydration. Therefore, a larger tablet diameter was used to distinguish and clearly measure the hydrated boundary. Each of the granules from lot 2 (LS) obtained after preparation with different quantities of water, and granules thermally treated described therein were compressed into 400-mg thin discs of 14 mm diameter using a hydraulic press (Beckman Press, Glenrothes, Scotland, UK) at 8000 kg load. Although the tablets produced with the hydraulic press were different in diameter and thickness compared to those prepared from the tableting machine, this nevertheless provided a means for comparing the hydration rates between the LS and PS. Similarly, granules that had been subjected to temperature treatment described above were compressed with the hydraulic press. Square polyethylene sheets of about 3 x 3 cm were attached onto the 2 flat faces of the discs using a small amount of distilled water. These were then lowered into petri dishes containing distilled water. At predetermined intervals, the petri dishes were placed under a magnifying lens (Kyowa Optical, Tokyo, Japan) and the diametric increase was measured with a ruler graduated in millimeters. Consequently, the swelling index expressed as a percentage (SI%) was calculated using the expression

$$\frac{X_1 - X_0}{X_0} \times 100 \qquad (2)$$

where x_0 was the initial diameter and x_t, the diameter after time t.

RESULTS AND DISCUSSION

Drug release from LS tablets

Diclofenac sodium release from tablets made from lots 1-5 are shown in **Figure 1.** It can be observed from the figure that as the XG concentration was increased, diclofenac sodium release became slower, as observed by other authors who used XG as a matrix forming material [7, 10]. Drug release was generally linear, especially 1-4 hours after initial release for all the formulae. Such linear drug release from hydrophilic matrices has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer [4]. During the dissolution studies, the outer layer of all the tablets appeared to be hydrated after being placed in the dissolution medium. There was a progressive increase in the size of this hydrated layer, followed by a gradual loss in integrity resulting from the hydrodynamic stress induced by the dissolution apparatus, up to a point [11]. Thereafter, it remained more or less unchanged until the final stages of the dissolution test, where the inner dry core became wetted until the entire tablet disappeared. At 7.5% and 12.5% XG concentration, rapid erosion of the hydrated layer was readily noticeable. On the other hand, above 15% XG concentration, the hydrated layer persisted for a considerable part of the dissolution process. This could be attributed to an increase in the viscosity of the hydrated layer with the increase in XG concentration, which thus improved its resistance to erosion [10].

Relating drug release from LS and PS prepared tablets

Drug release from LS and PS tablets prepared using the same manufacturing formulae are shown in **Figure 2.**

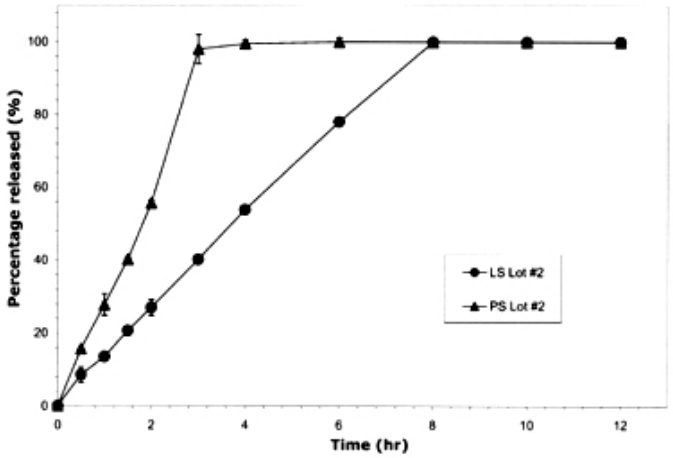

Figure 2. Diclofenac sodium release from LS and PS scale prepared tablets (lot 2).

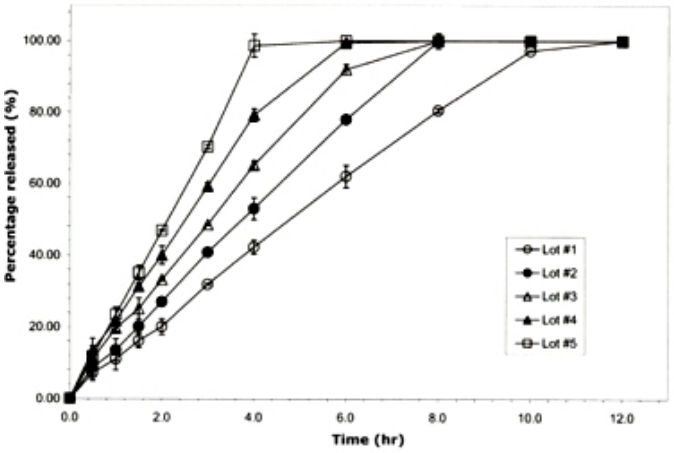

Figure 1. Diclofenac sodium release from LS tablets (lots 1 to 5).

The drug release was slower from the LS tablets compared to the PS tablets where about 100% of drug released within 3-4 hours. This was probably because of a better hydration in the LS tablets, which slowed down the rate of drug release. Common to both LS and PS prepared tablets, however, was that drug release was linear, suggesting that the mechanism of drug release from the XG matrices was not affected by either method of manufacture. Generally, granules obtained from the PS were coarse and more rounded in shape compared to those obtained from the LS. **Table 2** shows the size distribution and bulk densities of granules obtained from the LS and PS proceedings. There was a higher proportion of the larger size range of granules (1.0-1.4 mm) in the PS. Also, the bulk density of the granules from the PS was significantly

higher ($P < 10^{-6}$) compared to those from LS. This might be because in the PS, the components of the mix were subjected to a more intimate mixing due to the high shear, which led to an efficient distribution of the water in the mix. Consequently, more air spaces were displaced, resulting in the formation of more dense granules [8]. Because granule size enlargement by agglomeration in high-shear mixing is governed by the mechanisms of nucleation and coalescence [12], it is apparent that this phenomenon would be favored in the above circumstances because of the cohesive nature of XG, leading to more of the larger granules being formed.

Table 2: Properties of Granules from Laboratory and Pilot Scale

Proceedings	Granule Size Range (mm)			Bulk Density (mg/mL)
	< 0.3	0.3-1.0	1.0-1.4	
Laboratory Scale	50.40%	32.81%	16.77%	0.35
Pilot Scale	5.66%	23.62%	70.68%	0.49

Using lot 2 for comparison, tablets from the PS appeared to be softer (tensile strength = 13.8 x 10^5 N/m^2) with numerous pinholes, suggesting that consolidation of the granules at the PS was poorer compared to the LS (18.1 x 10^5 N/m^2). This could be attributed to the granule size distribution and higher bulk density of the granules from the PS because a higher bulk density means that a smaller volume is being occupied at the same weight. Therefore, at the same compression settings, granules from the PS were subjected to a lower force distribution compared to the LS.

Drug release from PS lot 2 tablets with different granule size ranges

Drug releases from the different granule size ranges made from PS are shown in **Figure 3**. The rate of drug release from the tablets was fastest for the <0.3 mm range followed by the 1.0-1.4 mm and then 0.3-1.0 mm.

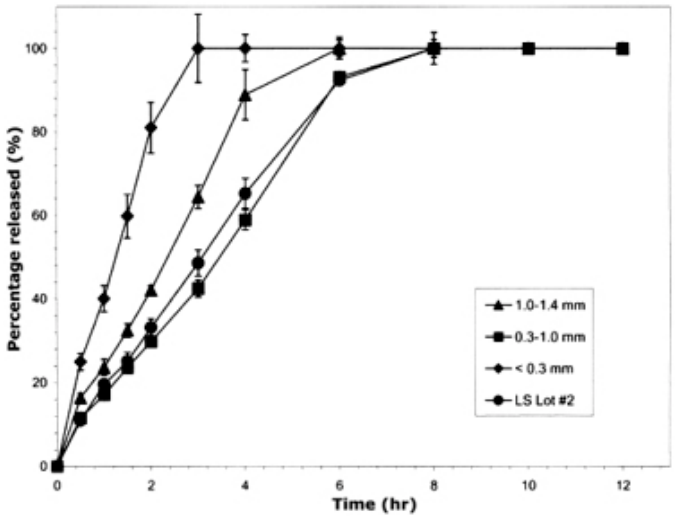

Figure 3. Diclofenac sodium release from tablets compressed from different granule size ranges (PS lot 2) and from LS lot 2.

However, there appeared to be no direct relationship between the rate of drug release from the tablets and the different granule size ranges. The tablets made from granules of <0.3 mm fraction appeared to disintegrate rapidly with no sign of hydration during the dissolution process (hardness = 11.6 x 10^5 N/m^2). On the other hand, tablets from the 1.0-0.3 mm and 1.0-1.4 mm fraction appeared to be hydrated although those from the 1.0-0.3 mm granules (hardness = 15.9 x10^5 N/m^2) appeared to persist for a longer period compared to those from 1.0- 1.4 mm (hardness = 14.7 x 10^5 N/m^2) fraction. The bulk densities of the different granule size ranges used to prepare the tablets were 0.54 g/cc for < 0.3 mm, 0.49 g/cc for 0.3-1.0 mm, and 0.47 g/cc for 1.0-1.4 mm. A higher bulk density for the < 0.3 mm fraction may be attributed to closer packing, resulting in a smaller volume. On the other hand, in view of the fairly close bulk density values of the 0.3-1.0 and 1.0-1.4 mm fractions, it can be considered that under the same compression, the force distribution would be used to a fairly similar extent. However, stronger consolidation can be expected with a smaller granule size range because of closer and more intimate packing and an increase in area of contact area [13]. This is supported by the earlier observation that tablets from the 0.3-1.0 mm granule size range persisted for a longer period during the dissolution process compared to those

from the 1.0-1.4 mm. Penetration of dissolution medium into a better consolidated matrix and subsequent disintegration may thus be expected to be slower. Additionally, the hydrated outer layer may persist longer under these circumstances. The above explanation may account for the faster rate of drug release from tablets made from 1-1.4 mm size range compared to those from made from the 0.3-1.0 mm size. Except for the 0.3-1.0 mm size range, where release rate was comparable to that of LS lot 2, the rates of drug release from the tablets that were made from the different size ranges in PS were higher than drug release from lot 2 in the LS. In addition, the bulk density of the 0.3- 1.0 mm range was 0.55 g/cc, being higher than the bulk density of LS lot 2 (0.35 g/cc). Therefore, it is unlikely that the difference in size ranges of the granules between the two proceedings was accountable for the observed difference in rates of drug release between LS and PS.

Effects of thermal treatment of the granules and amount of water for granulation on drug release

The drug release profiles of tablets prepared from granules that were thermally treated at 60ºC, 70ºC, and 80ºC were essentially the same, suggesting that the above treatment had no effect on the polymer matrix. Thermal treatment of polymers to high temperatures may induce structural changes in the polymer structural configuration, which can later affect the rate of drug release. In the present study, the temperature of the mix in the PS was as high as 60ºC; however, results of thermal treatment of granules from LS.showed that no such effect took place. This may be attributable to the stiff polymer chains and high melting point of XG (270ºC) [14].

Granules prepared in the PS with the same formula as in lot 2 appeared to be overly wetted during preparation. Therefore, the amount of water used for the granulation was reduced to 30% of the batch. **Figure 4** shows the release profiles of the tablets prepared from the granules before and after reducing the amount of water used for granulation.

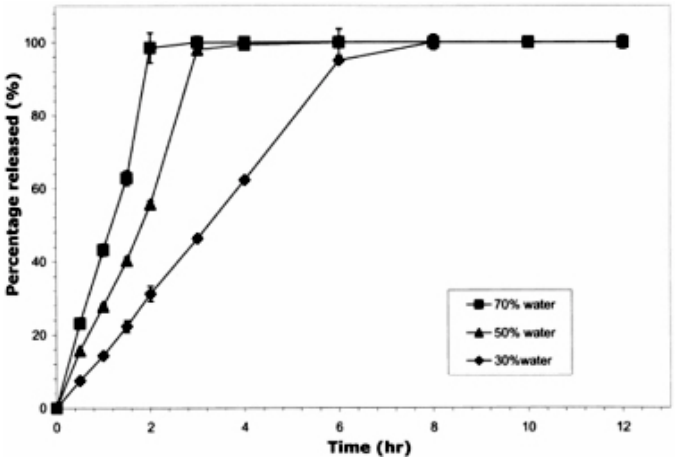

Figure 4. Diclofenac sodium release from PS tablets (lot 2) prepared with different percentages of water.

The rate of drug release was appreciably reduced with a reduction in the amount of water used for granulation. Also, increasing the amount of water to 70% caused an increase in the rate of drug release as shown in the figure. Similarly, in the case of the LS batch (lot 2), changing the amount of water for granulation also showed a similar effect. When the amount of water for granulation in the PS was decreased to 30% and increased to 70%, there was a corresponding decrease and increase in the rate of drug released respectively as shown in **Figure 5**. Thus it appeared that the amount of water in which the XG was exposed to during granulation could affect the rate of drug release form the tablets.

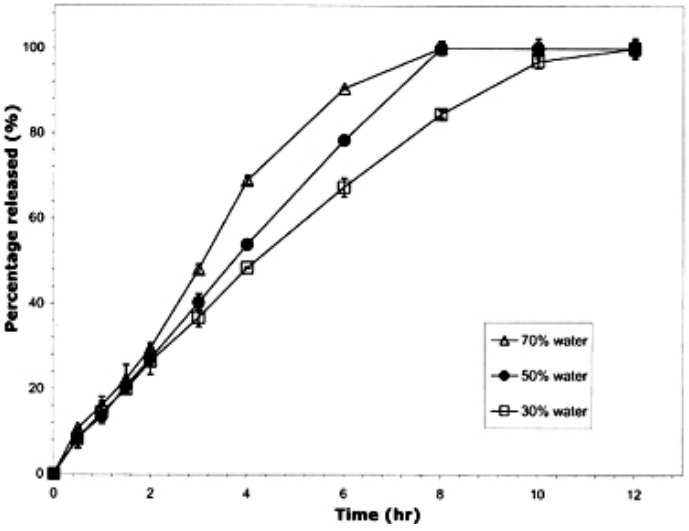

Figure 5. Diclofenac sodium release from LS tablets (lot 2) prepared with different percentages of water.

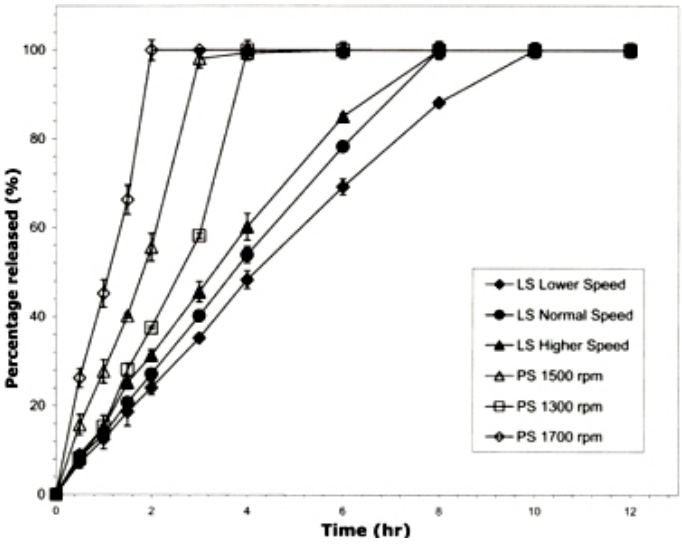

Figure 6. Diclofenac sodium release from LS and PS tablets (lot 2) prepared with different impeller speeds.

Effects of impeller speeds on drug release at LS and PS

Figure 6 shows the effect of impeller speeds during granulation on rate of drug release at the LS and PS. It can be seen that there was an increase in the rate of drug release with increase in impeller speed in both proceedings. This was the result of more efficient mixing with increased impeller speeds, resulting in better distribution of the water and better hydration. On re-exposure of the matrix to water, the ability of the matrix to rehydrate was thus reduced.

Swelling index of the XG containing discs

There was no change in the SI% of discs made from granules that had been subjected to 60°C, 70°C, or 80°

C confirming the earlier observation that the rate of drug release remained unchanged after the thermal treatment of the granules. The SI%, however, were different for the discs that had been made from granules prepared with different percentages of water namely, no water, 30%, 50%, and 70% of batch size (LS, lot 2), being fastest with the formulation containing no water and slowest for the 70% prepared (**Figure 7**). SI% studies were not performed on the PS formulations because the results at LS in this circumstance were applicable to the PS as well. In addition, **Figure 8** shows the SI% for discs made from granules with different impeller speeds at LS (lot 2).

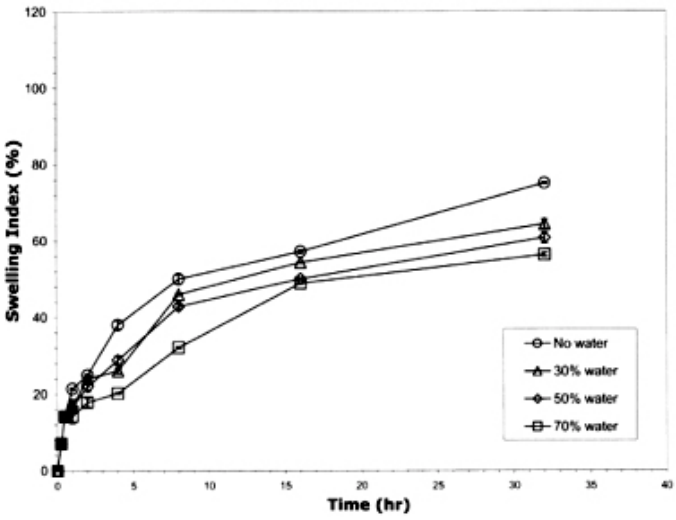

Figure 7. Swelling indices of discs (LS lot 2) prepared with different percentages of water.

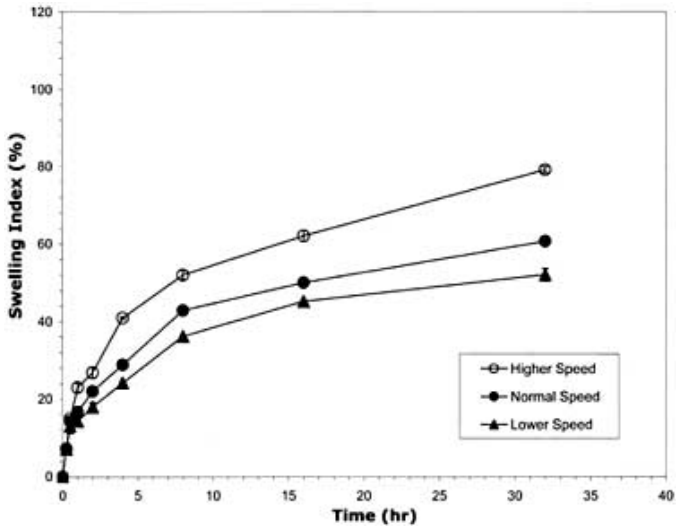

Figure 8. Swelling indices of discs (LS lot 2) prepared with different impeller speeds.

The above results tend to suggest that not only pre-exposure of the XG polymer to water may reduce its ability to fully hydrate on further exposure, but also the degree of exposure is important. Any process that may facilitate proper wetting of the polymer, such as high-shear mixing or the addition of a higher amount of water, can potentially reduce the rate of rehydration of the XG matrix and therefore increase the rate of drug release..This may explain the different release profiles obtained with LS and PS batches of tablets made using the same manufacturing compositions as shown in **Figure 2**. By virtue of better and more efficient mixing in the PS production procedure, there was better

wetting, which resulted in a reduced rate of hydration of the matrix with consequent faster rate of drug release.

CONCLUSION

Diclofenac sodium release from the LS and PS formulations studied was generally linear. Thermal treatment did not appear to have any effect on the rate of drug release; however, hydration of xanthan gum seemed to be affected by the wetness of the powder mass during granulation. Because drug release from xanthan gum matrices proceeds via hydration of the matrix structure, it is important that wetness be properly controlled to avoid variations in rate of drug release among production batches.

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