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The influence of granulating solvents on drug release from tablets containing grewia gum

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Abstract

The influence of granulating solvents on release of indomethacin from tablets containing grewia gum was evaluated. The tablets were prepared by either wet granulation or direct compression. The experimental design was based on a 3x5 factorial design. The drug/gum ratio was varied at three levels, 2:1, 1:1 and 1:2. At each of these levels, the solvent effects were examined at five levels namely, 100% water, 75% water and 25% ethanol, 50% each of water and ethanol, 25% water and 75%. These were compared with a fifth level which is a matrix tablet prepared by direct compression without any solvent. The dissolution rates of the tablets were determined using a rotating paddle dissolution apparatus. The cumulative percent of drug dissolved from the three matrix tablets are not significantly different ($p>0.05$). Although no rank correlation was observed among the tablets prepared with 100%, 75% and 50% water, drug release from the tablets prepared with 25% water are significantly lower than the other wet granulated tablets, but higher than the matrix tablets. The granulating solvent influenced the release of drug which increased with increase in the water content.

Keywords: Grewia gum: Granulating solvents; Release mechanisms.

Introduction

Plant polymers with gummy or mucilaginous characteristics and their derivatives have been used in the formulation of controlled release dosage forms (Chukwu, 1994; Ofoefule and Chukwu 1994, Talukdar and Kinget 1995, Sujja - areevath *et al.,* 1996, Chukwu *et al.,* 1997, Adikwu, *et al.,* 1997). The mechanism by which they control drug release include their ability to rapidly form a gel layer at the matrix periphery exposed to aqueous fluid (Woodford and Hsieh 1988). Drugs are released from these matrices by a combination of diffusion through and erosion of the gel (Huber *et al.,* 1966, Korsmeyer *et al.,* 1983, Tahara *et al.,* 1995). When the polymer is introduced into an aqueous solvent, it becomes swollen as the solvent molecules diffuse into it. The volume of the polymer phase increases as solvent is imbibed, but few polymer molecules enter the solvent phase because of their lower diffusion. The active substance then dissolves and diffuses out through the gel.

The drug diffusion through the polymer matrix depends on the water solubility of the drug (Ford *et al.,* 1987). Formulation factors such as excipients, presence of surfactant, the viscosity of the polymer as well as the type and nature of

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polymer modify drug release from these polymers (Mitchell *et al.*, 1990; Daly *et al.*, 1984; Cheong *et al.*, 1992; Kellaway and Najib, 1983). Talukdar and Kinget (1995) showed that the swelling behaviour of xanthan gum is influenced by the ionic strength and buffer concentration. In a study of the release of diclofenac sodium from encapsulated natural gum formulations, it was shown that the amount of gum present played the dominant role in determining the drug release rate (Sujja - areevath *et al.*, 1996). An inverse relationship was found between the drug release rate and matrix swelling rate (Wan *et al.*, 1993). The two important parameters for the release of drug from tablet matrices are the infiltration rate of medium into the matrix for drugs with reasonable aqueous solubility, and the erosion rate of the matrix system, for drugs with poor aqueous solubility (Tahara *et al.*, 1995).

The drug release through a matrix can be characterised mathematically using the equation (Korsmeyer *et al.*, 1983).

$$M_t/M_\infty = kt^n \quad \text{.....(1)}$$

where M_t/M_∞ is the fractional release of the drug in time t, k is the kinetic constant, and n is the diffusional exponent for drug release. The value of n indicates the drug release mechanism. It is 0.5 for Fickian diffusion and 1 for Case II diffusion. A value of n greater than 0.5 but less than 1 indicates a non - Fickian or anomalous diffusion, which is a mixture of Fickian and Case II diffusion. When n is greater than 1, the drug release occurs through the Super Case II diffusion (Korsmeyer *et al.*, 1983, Mandal 1995).

Grewia gum is a polysaccharide derived from the inner stem bark of the edible plant *Grewia mollis*, Juss, (Family Tiliaceae). The physicochemical and rheological properties of the gum, and the water vapour permeability of the gum film have been reported (Okafor *et al* 2001, Okafor 2001a, Okafor and Chukwu 2003a). The binding property of the gum in sodium salicylate tablets has also been reported (Okafor and Chukwu 2003b). The gum has been used in the formulation of sustained release theophylline hydrate and chlorpheniramine maleate tablets (Okafor 2001b). The objectives of the present study were to evaluate the influence of granulating solvents on the release of indomethacin from tablets containing grewia gum, and to characterise the release mechanisms.

Experimental

Materials. The following materials were used: indomethacin U.S.P (Spectrum Chemical Manufacturing Co. U.S.A.), varying proportions of ethanol, 95% (Sigma Chemical Co. U.S.A.) and grewia gum which was processed in our laboratory according to the method of Okafor *et al.*, 2001a.

Experimental design. Table 1 shows the batch formulae for the tablets. The experimental design was based on a 3x5 factorial design. The drug/gum ratio was varied at three levels, 2:1, 1:1 and 1:2. At each of these levels, the solvent effects were evaluated at five levels. Within these five levels, four different combinations of water and ethanol (100:0, 3:1, 1:1 and 1:3) were compared with the fifth level which is a matrix tablet prepared by direct compression without any solvent. The solvents were selected on the basis of the ability or inability of the gum to swell in them. Grewia gum swells in water whereas ethanol precipitates it. The drug/gum and water/ethanol ratios were carefully chosen to study their effect on drug release as they increase or decrease. The significance of the present study is to determine the influence of solvent on release of drug from grewia gum irrespective of the drug/gum ratio.

Preparation of tablets. The batches containing solvents were prepared by wet granulation. The drug, gum and lactose were thoroughly mixed in a mortar for 10 minutes. The mixtures were moistened thoroughly with

the appropriate volume of solvent. The wet mass was screened through a 1.7 mm stainless steel sieve and dried at 60°C in a hot air oven (Gallenkamp) for 2h. The dried granules were screened through a 1.00 mm sieve. The batches containing no solvent were prepared by mixing the drug, gum and lactose thoroughly in a mortar for 10 minutes. The granules and the powder mixes for direct compression were in each case mixed for 5 minutes with 1% lubritab which served as the lubricant.

A 125mg quantity of the mixture was fed manually into the die cavity of a single punch tabletting machine (Eagle Scientific, England), fitted with 7.5mm flat-faced punches. The tablets were compressed at 5 striches pressure setting according to the calibration on the machine.

Dissolution study. The dissolution profiles of the tablets were monitored using an Erweka D.T.D. apparatus. The dissolution medium consisted of 1000ml of distilled water at a temperature of 37± 1°C. The U.S.P. II rotating paddle dissolution method was used at a rotation speed of 50 r.p.m. 5ml samples were withdrawn for analysis at predetermined time intervals using a filter pipette.

The amount of indomethacin dissolved at the time intervals was measured in an SP6 - 450 UV - Vis spectrophotometer (Pye Unicam, United Kingdom) at a wavelength of 318nm. The mean of six determinations for each batch was used to generate a dissolution curve. The dissolution data obtained between 5 and 120 minutes were fitted to equation 1 and the best fit parameters (k and n) were calculated.

Results and Discussion

The dissolution profiles of the various batches of tablets are shown in Figures 1-3. The tablets prepared with 100% water showed higher release rates than the others. Hydrophilic polymeric gums are known to swell in the presence of water resulting to increased release rate of drugs due to increased swelling rate (Mandal 1995). The cumulative percent of drug dissolved at 2h are presented in Table 2. The cumulative percent of drug dissolved from the three directly compressed matrix tablets (A_1, B_1 and C_1) are not significantly different ($p > 0.05$). This shows that when no solvent is used in preparing the tablets, the amount of indomethacin released is independent of the drug/gum ratio. Similar results on the release of indomethacin from hydroxypropylmethylcellulose tablets have been reported (Mandal, 1995; Ford *et al.*, 1985).

The cumulative percent of drug dissolved at 2h from the various tablets prepared by wet granulation are significantly different ($p < 0.05$). This suggests that the use of granulating solvents can significantly influence the release of drug from tablets containing grewia gum. Similar observation was made for HPMC tablets (Mandal 1995). Drug release seems to increase as the water content of the granulating solvent increased. Drug release from tablets containing 25% water are significantly lower than the others but higher than the directly compressed matrix tablets containing no water. This observation suggests that increase in water content of granulating solvent, in the presence of lactose enhanced the dissolution rate of tablets prepared by wet granulation. The differences in the drug release between tablets prepared by wet granulation and those directly compressed can be attributed to the release mechanism. Polymeric gums are known to swell in the presence of water to form a gel layer surrounding the tablets (Woodford and Hsieh 1988). Drug release occurs by diffusion and erosion of the gel layer (Huber *et al.* 1966). The degree of swelling and the gel forming ability of gums are influenced by the presence of water during the preparation of tablets (Talukdar and

Kinget 1995, Wan *et al.* 1993, Rizk *et al.* 1994). Kawashima *et al.* (1993) reported that the presence of organic solvent (a non-solvent) reduced the gel forming ability of water soluble cellulose derivatives to a degree dependent on the nature of the organic solvent used during the granulation process.

Values of the best fit parameters and the coefficient of determination (R^2) obtained from equation 1 are presented in Table 3. The values obtained for R^2 suggest good correlation for the dissolution data. The kinetic constant, K, decreased with increasing amount of gum in the tablets, but no particular rank order correlation was observed. In general, K values increased with increase in the amount of water used in the wet granulation. The parameter n, which indicates the release mechanism, was significantly affected by the presence of water. Drug release from tablets of formulation A followed non-Fickian or anomalous diffusion in the absence of any solvent. This mechanism operated as long as the amount of water is low. When the amount of water used in granulation is 50% or more, the drug release mechanism changed to simple Fickian diffusion.

Table 1: Batch formula for indomethacin tablets containing grewia gum.

Formulations	Indomethacin (mg)	Grewia gum (mg)	Lactose (mg)	Drug/ gum	Solvent water:ethanol
A1	40	20	65	2:1	None
A2	40	20	65	2:1	100:0
A3	40	20	65	2:1	3:1
A4	40	20	65	2:1	1:1
A5	40	20	65	2:1	1:3
B1	40	40	45	1:1	None
B2	40	40	45	1:1	100:0
B3	40	40	45	1:1	3:1
B4	40	40	45	1:1	1:1
B5	40	40	45	1:1	1:3
C1	40	80	5	1:2	None
C2	40	80	5	1:2	100:0
C3	40	80	5	1:2	3:1
C4	40	80	5	1:2	1:1
C5	40	80	5	1:2	1:3

Table 2: Average cumulative percent of indomethacin dissolved at 2 hour

Formulations	Mean $\pm$ % C.V.(n = 6)	t-test*
A1	18.0 $\pm$ 0.4	A2>A4>A3>A5>A1
A2	35 $\pm$ 0.8	
A3	30.5 $\pm$ 0.6	
A4	33.1 $\pm$ 0.4	
A5	21.2 $\pm$ 0.6	
B1	18.4 $\pm$ 0.7	B3=B2>B4>B5>B1
B2	28.0 $\pm$ 0.3	
B3	29.1 $\pm$ 0.2	
B4	25.0 $\pm$ 0.8	
B5	20.4 $\pm$ 0.9	
C1	17.8 $\pm$ 0.9	C3>C2=C4>C5>C1
C2	23.0 $\pm$ 0.5	
C3	25.0 $\pm$ 0.6	
C4	23.4 $\pm$ 0.6	
C5	19.2 $\pm$ 0.2	

* student t-test at $p<0.05$

Table 3: Best fit parameters, k and n, based on the equation: $M_t/M_\infty = kt^n$

Formulations	Kinetic constant (k) (Mean ± % C.V.; n = 6)	Diffusional exponent (n) (Mean ± % C.V.; n = 6)	Correlayion coefficient (R^2)
A1	0.71 ± 0.40*	0.69 ± 0.40*	0.99
A2	5.33 ± 0.20	0.48 ± 0.10	0.95
A3	2.71 ± 0.20	0.58 ± 0.30	0.97
A4	0.60 ± 0.40	0.54 ± 0.30	0.98
A5	1.37 ± 0.50	0.67 ± 0.10	0.99
B1	0.25 ± 0.30	0.93 ± 0.10	0.97
B2	2.08 ± 0.70	0.63 ± 0.70	0.99
B3	1.91 ± 0.70	0.65 ± 0.30	0.99
B4	1.59 ± 0.30	0.66 ± 0.40	0.99
B5	0.38 ± 0.10	0.89 ± 0.20	0.99
C1	0.18 ± 0.80	0.98 ± 0.50	0.98
C2	1.07 ± 0.50	0.71 ± 0.20	0.98
C3	1.55 ± 0.80	0.68 ± 0.10	0.99
C4	0.65 ± 0.20	0.80 ± 0.60	0.99
C5	0.17 ± 0.50	1.02 ± 0.40	0.99

*coefficient of variation

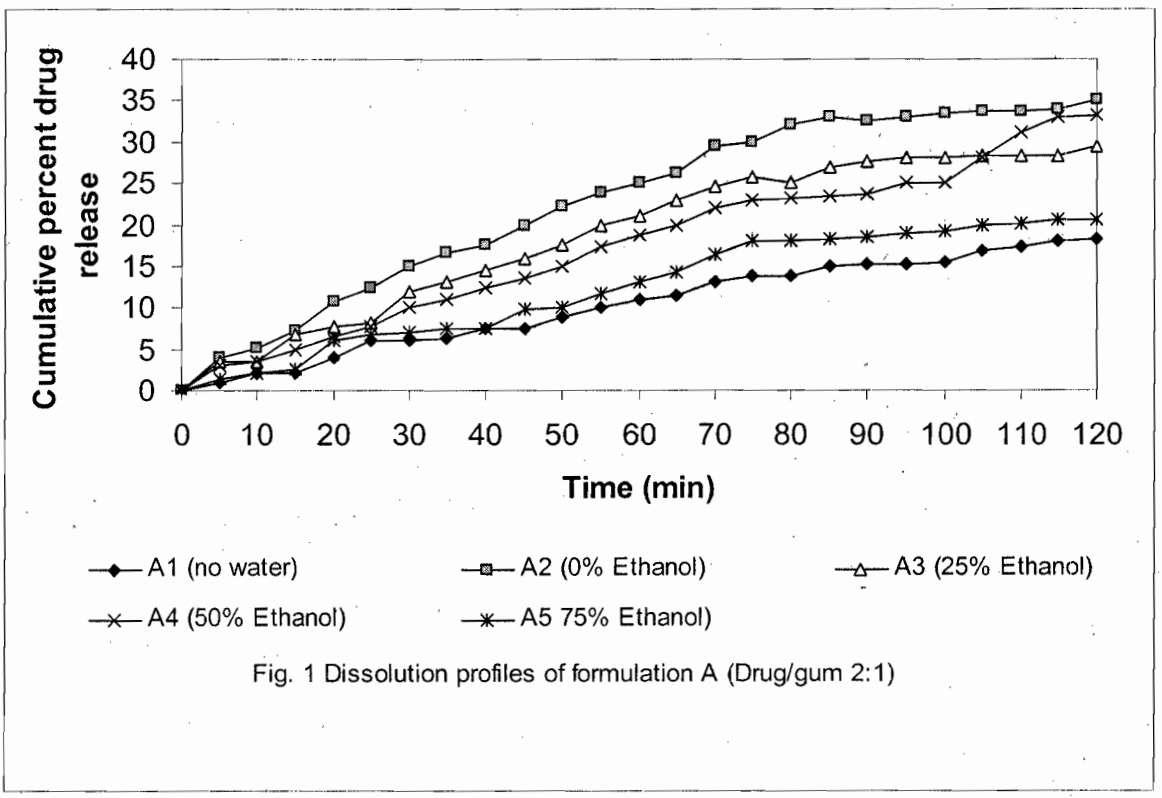

Fig. 1 Dissolution profiles of formulation A (Drug/gum 2:1)

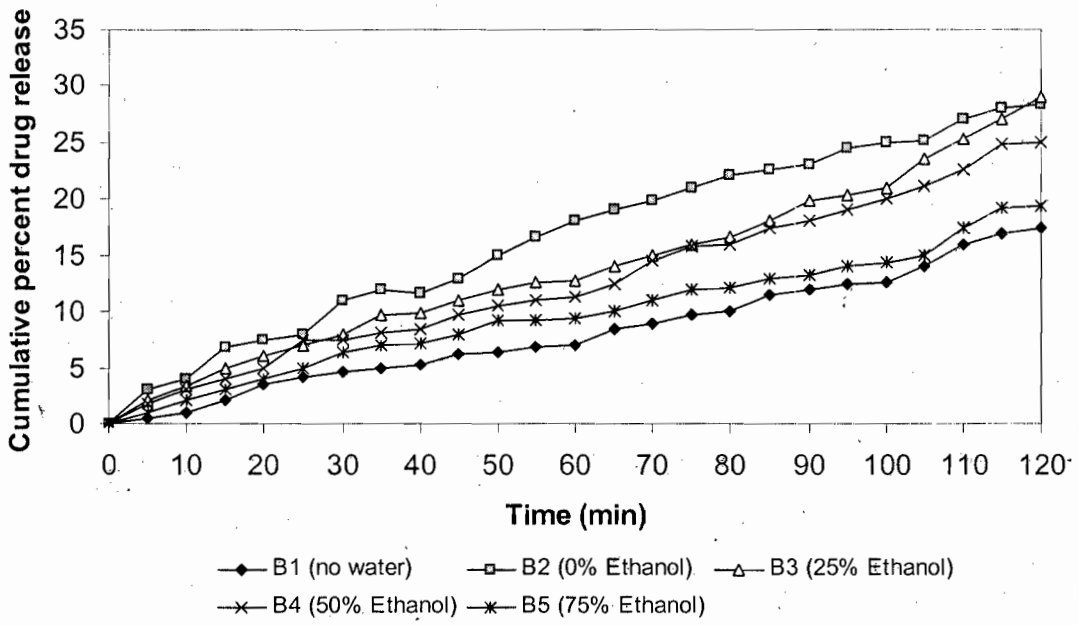

Fig. 2 Dissolution profiles of formulation B (Drug/gum = 1:1).

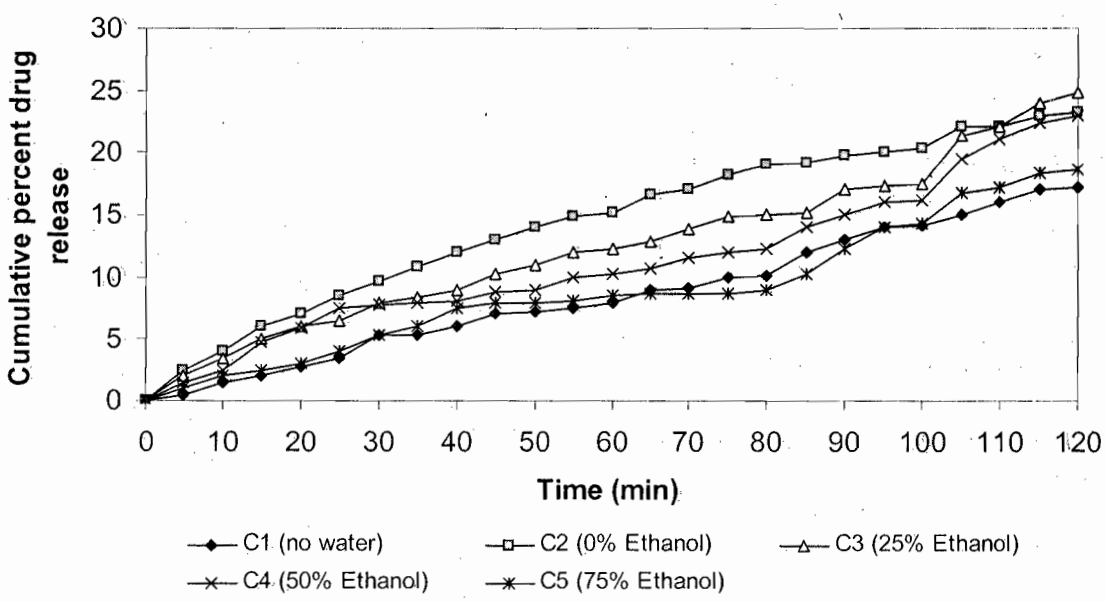

Fig. 3 Dissolution profiles of formulation C (Drug/gum = 1:2).

The drug release from the other tablet batches (B_1 and C_1) followed anomalous and case II diffusion respectively with the increase in grewia gum content. The release of drug from formulations B and C tended towards the anomalous diffusion as the amount of water used in the preparation of tablets increased.

In conclusion, the granulating solvents used in the formulation of indomethacin containing grewia gum significantly influenced the drug release, with drug release increasing with increase in water content. The presence of solvents influenced the mechanism of drug release from the tablets. The relative proportions of water and ethanol played a significant role in the release mechanism. The drug/gum ratio also influenced the release mechanism. Formulations A_1, B_1 and C_1 represents formulations containing no solvent, but having drug/gum ratios of 2:1, 1:1 and 1:2 respectively. The release mechanisms for these formulations changed from non-Fickian or anomalous diffusion (A_1) to anomalous (B_1) and case II diffusion (C_1).

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