Influence of Formulation Parameters on the Release of Diclofenac Sodium from Matrices with Manufacturing Formulation Ingredients

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ABSTRACT: *Effects of formulation parameters on the fractional release profile of diclofenac sodium from matrices having the manufacturing formulation ingredients are studied. As a content of cetyl alcohol (rate controlling agent) in the matrix increases, the fractional release decreases. The fractional release increases either by increasing sucrose content outside the granule or by decreasing sucrose content inside the granule. Results presented here indicate that as PVP content outside the granule or aerosil fraction inside or outside the granule in the matrix increases, the fractional release increases. The fractional release profiles of diclofenac sodium from matrices, when each ingredient is inside or outside, or half inside - half outside the granule, are compared.*

KEY WORDS: *Diclofenac sodium, Cetyl alcohol, Fractional release profile, Manufacturing formulation*

INTRODUCTION

Diclofenac sodium is a widely used nonsteroidal anti-inflammatory (NSAID) drug in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis [1] and it is also effective in the relief of pain [2]. It is used at the daily dosage of 75 to 150 mg given in two to four divided administrations [3]. In order to minimize the incidence of gastric mucosal damage resulting from the administration of diclofenac sodium and provide an effective blood level for a reasonably long period, it has been formulated as sustained release tablets [2,4]. Different methods including enteric-coating matrix as well as microencapsulation process have been utilized to prepare controlled release products [5-15]. Several retarding substances have been used in the controlled release formulation of diclofenac sodium including Eudragit RS100 [5], ethyl cellulose [5-7,] hydroxypropyl cellulose [8], hydroxypropyl methyl cellulose [9], hydrogenated vegetable oil and carboxypolymethylene [10], methacrylic acid copolymer and carnauba wax [11], ion-exchange resins [12], cetostearyl alcohol [9] and cetyl alcohol [13].

The matrix system is commonly used for manufacturing sustained-release dosage form because it facilitates the manufacturing process [14]. Cetyl alcohol, polyvinyl pyrrolidone K-30, sucrose, magnesium stearate and silicon dioxide (Aerosil-200) are inert ingredients in the manufacturing formulation [15].

In this study, effects of manufacturing method and formulations on the fractional release profile of diclofenac sodium from matrices having the manufacturing formulation ingredients, are investigated.

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Table 1: Formulations of the matrices evaluated

	Cetyl Alcohol (mg)	Sucrose (mg)		PVP (mg)		Aerosil (mg)		Magnesium-Stearate (mg)
		Inside	Outside	Inside	Outside	Inside	Outside	
A	40	100	-	30	-	-	3	4
B	60	100	-	30	-	-	3	4
C	60	80	-	4	-	-	3	4
D	60	120	-	4	-	-	3	4
E	60	-	80	4	-	-	3	4
F	60	-	120	4	-	-	3	4
G	60	60	60	4	-	-	3	4
H	60	100	-	15	-	-	3	4
I	60	100	-	30	-	-	3	4
J	60	100	-	-	4	-	3	4
K	60	100	-	-	20	-	3	4
L	60	100	-	-	15	-	3	4
M	60	100	-	7.5	7.5	-	3	4
N	60	100	-	4	-	4	-	3
O	60	100	-	4	-	15	-	3
P	60	100	-	4	-	-	4	3
Q	60	100	-	4	-	-	15	3
R	60	100	-	4	-	9	-	3
S	60	100	-	4	-	-	9	3
T	60	100	-	4	-	4.5	4.5	3

EXPERIMENTAL PROCEDURES

Materials

Diclofenac sodium (Ciba-Giegy, Switzerland), cetyl alcohol (Surfachem Limited LTD, UK), polyvinyl pyrrolidone K-30 (BASF, Germany), magnesium stearate (Faci Hacia, Italy), sucrose (Carlo Erba, Italy), Aerosil-200 (Degussa, Germany), were used for manufacturing different formulations.

Method

a) Tablet preparation: Formulations of evaluated matrices are shown in Table1.

Ingredients in the matrix are divided into two domains; inside and outside the granules. The melting method was used to prepare granules. The inside granule materials were mixed with 100 mg diclofenac sodium and cetyl alcohol. The mixtures were well blended and warmed to 60°C The granules were cooled and screened through a No. 18 mesh sieve. The granules were mixed with the outside granule materials. Then magnesium stearate was added as a lubricant. The blended mixtures were compressed on an eccentric compressing machine, Fette type EXI. The compressing force was regulated so that the hardness of tablets from all trails was 50-60 N. To obtain the effect of granulation method on the release profile, a wet granulation system also was utilized. To prepare the inner granules using 10% m/v PVP in chloroform as a binder and sucrose as a filler. The wet mass was passed through a no. 16 mesh screen and dried. Cetyl alcohol was added to the dried granules and well blended. Then they were warmed to 60°C to make the coated granules.

b) Release studies: Release of diclofenac sodium from the tablets was determined using

USP standard dissolution method 2 (with paddle)[16]. The dissolution medium was 900 ml of phosphate buffer (pH=7.4) at a temperature of 37 ± 0.5 °C and at rotational speed of 50 rpm. For each formulation, three tablets were tested. Samples were taken at one-hour intervals. The concentration of each sample was determined by measuring the optical density at maximum absorbance,wavelength, 276nm, using a Hewlett Packard model 8452A UV-Visible spectrophotometer.

RESULTS AND DISCUSSIONS

The fractional release profiles of diclofenac sodium versus time over 12 hours for two matrices with different contents of cetyl alcohol [A and B in Table 1] are shown in Fig.1. Since cetyl alcohol is the rate-controlling agent, an increase in the content of cetyl alcohol in the matrix causes a decrease in the fractional release .

The effects of sucrose content inside and outside the granule on fractional release profile of diclofenac sodium are shown in Figures 2a and 2b, respectively. Two different contents of sucrose inside and outside the granule (C, D, E and F in Table 1) have been studied. Since sucrose outside the granule acts as a disintegrator, the increase in the sucrose content outside the granule, the fractional release increases. However, when sucrose is trapped inside the granule, it is encapsulated, by cetyl alcohol. Since cetyl alcohol is a hydrophobic material, sucrose absorbs water by means of osmosis through the surrounding polymer. Therefore, sucrose inside the granule of cetyl alcohol cannot act as a disintegrator. On the other hand, as the sucrose content in a tablet increases, compressibility and hardness of the tablet increases. Therefore, as the content of sucrose inside the granule increases, the fractional release decreases. Fig. 3 shows the effects of sucrose location on the fractional release of diclofenac sodium. A specific quantity of sucrose, 41.2%, was inside or outside or half inside-half outside the granule (D,F and G in Table 1).The results are consistent with the expectation that as content of sucrose outside the granule increases, the fractional release increases.

Figures 4a and 4b show the fractional release profiles

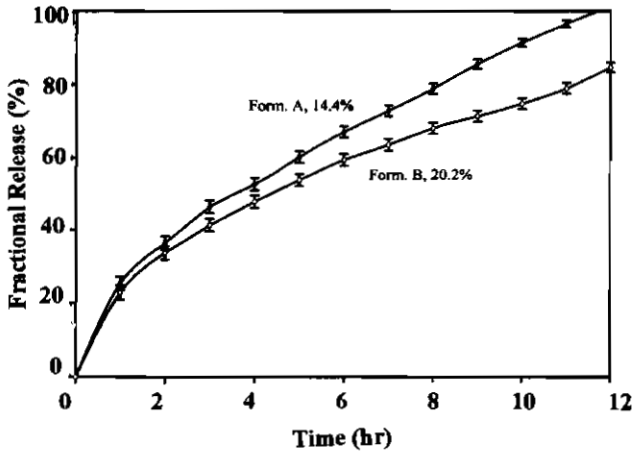

Fig.1: Effect of cetyl alcohol content in the matrix on the fractional release profile of diclofenac sodium (n=3, error bars represent standard deviations)

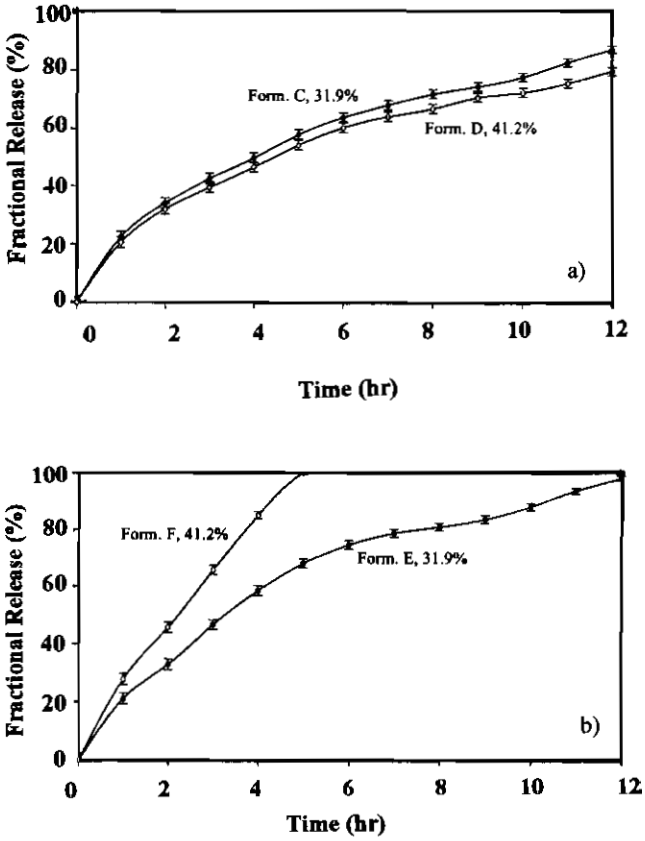

Fig.2: Effect of sucrose content in the matrix on the fractional release profile of diclofenac sodium
a) Sucrose is inside the granules
b) Sucrose is outside the granules (n=3, error bars represent standard deviations

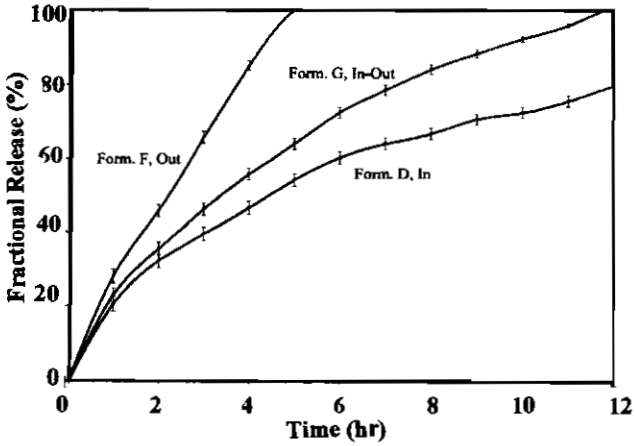

Fig.3: Effect of sucrose location in the matrix on the fractional release profile of diclofenac sodium (n=3, error bars represent standard deviations)

of diclofenac sodium from matrices with different fractions of the PVP inside and outside the granule (H, I, J and K in Table 1). The results presented here indicate that as the PVP content outside the granule increases, the fractional release increases. Similar to the sucrose role outside the granule, PVP acts as a disintegrator. The PVP content inside the granule does not affect the fractional release. When PVP is trapped inside the granule, it cannot act as a disintegrator. The effect of the PVP location on the fractional release of diclofenac sodium is shown in Fig. 5. The PVP fraction was 5.3% being located inside or outside or half inside-half outside the granule (H, L and M in Table 1). Comparing between inside and outside the granule, the release rate would be faster when PVP is located outside the granule. The minimum release rate may be achieved when PVP is distributed inside and outside the granules. Dry and wet granulation systems are compared in Fig.6. 10% w/v PVP in chloroform was used as a binder in the wet granulation system. The PVP fraction was 5.3% that was located inside the granules (H

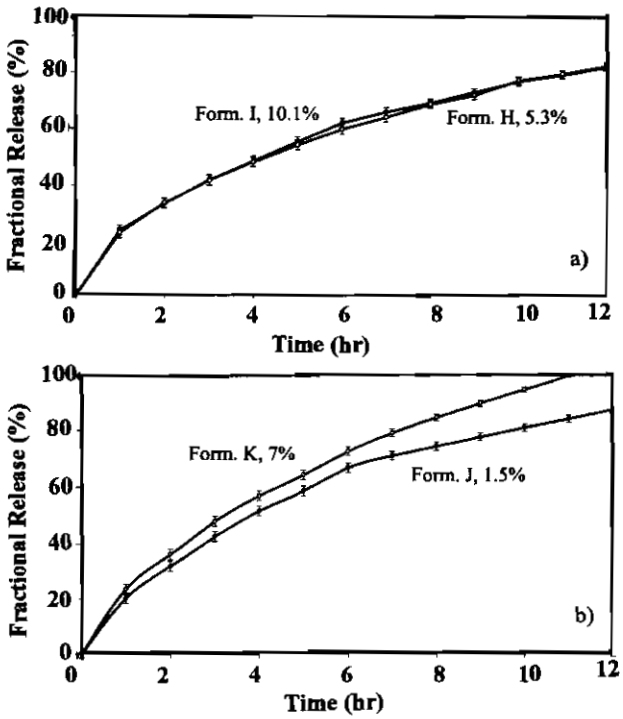

Fig.4: Effect of the PVP content in the matrix on the fractional release profile of diclofenac sodium
a) PVP is inside the granules
b) PVP is outside the granules (n=3, error bars represent standard deviations)

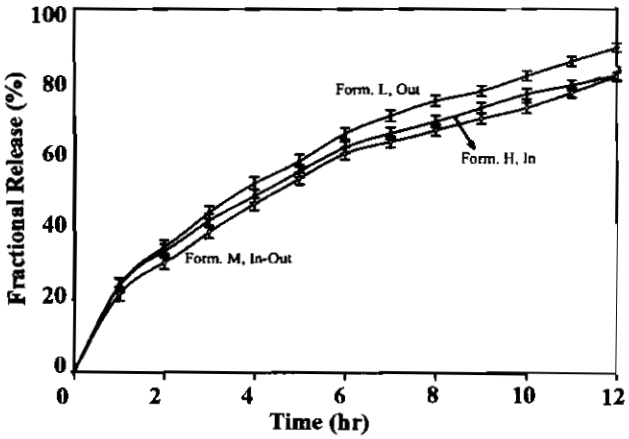

Fig.5: Effect of the PVP location in the matrix on the fractional release profile of diclofenac sodium (n=3, error bars represent standard deviations)

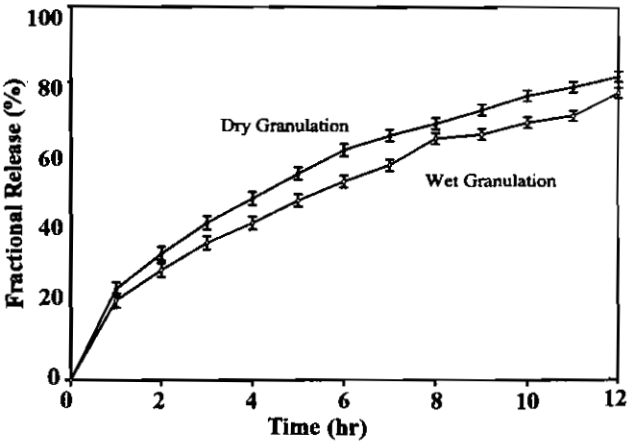

Fig.6: Comparison between dry and wet granulation systems. 10% w/v PVP inchloroform was used as a binder in the wet granulation system (n=3, error bars represent standard deviations)

in Table 1). The release rate is faster for the dry granulation system.

Fractional release profiles of diclofenac sodium from matrices with different contents of aerosil inside and outside the granule are shown in Figures 7a and 7b (N, O, P and Q in Table 1). Since aerosil is a hydrophilic agent, increasing the aerosil content in the matrix, the fractional release increases. Aerosil fraction outside the granule is more effective on the release rate. Fig.8 shows the effect of aerosil location on the fractional release. Aerosil fraction was 3.3% (R,S and T in Table 1). Aerosil in the granule has a minimum effect on the release rate. The maxi-

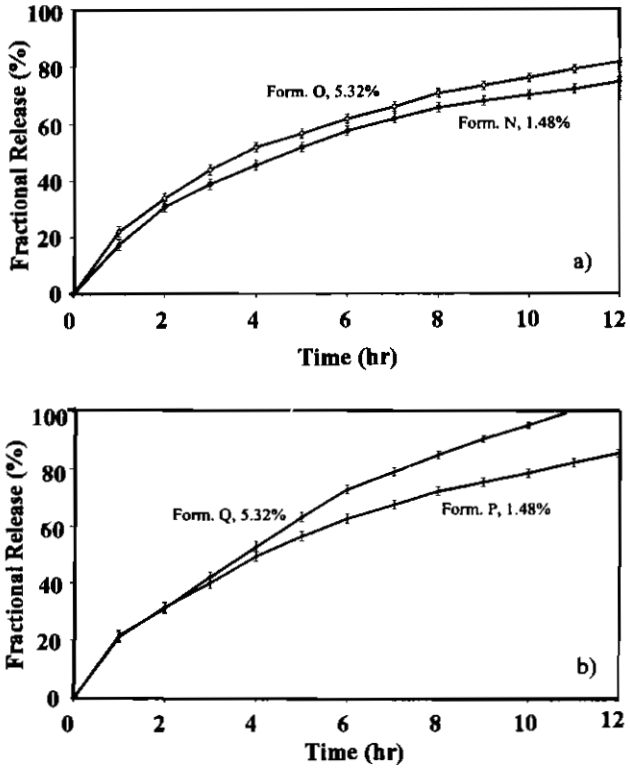

Fig.7: Effect of aerosil content in the matrix on the fractional release profile of diclofenac sodium a) Aerosil is inside the granules
b) Aerosil is outside the granules (n=3, error bars represent standard deviations)

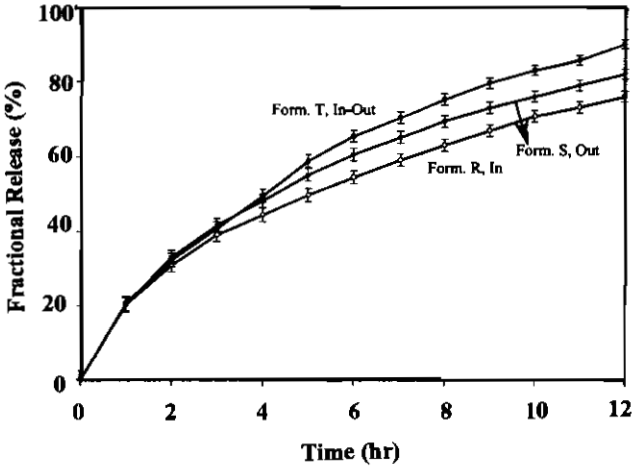

Fig.8: Effect of aerosil location in the matrix on the fractional release profile of diclofenac sodium (n=3, error bars represent standard deviations)

mum release rate may be achieved when aerosil is distributed inside and outside the granules.

CONCLUSIONS

Different fractional release profiles of diclofenac sodium from matrices with the manufacturing formulation ingredients could be achieved by choosing different compositions and various locations for the ingredients. As cetyl alcohol fraction in the matrix increases, the fractional release decreases. By increasing sucrose or PVP or aerosil content outside the granule, the release rate increases. The fractional release increases either by increasing aerosil content inside the granule, or by decreasing sucrose content inside the granule. A comparison between different locations of each ingredient, inside or outside or half inside-half outside the granules, indicates that: a) moderate release rate may be achieved when sucrose is distributed inside and outside the granule b) minimum release profile could be obtained with distribution of PVP c) maximum release rate may be achieved when aerosil is distributed.

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