EFFECT OF CHANNELING AGENTS ON THE RELEASE PATTERN OF THEOPHYLLINE FROM KOLLIDON SR BASED MATRIX TABLETS

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ABSTRACT

The purpose of the present study was to investigate the effect of channeling agent on the release profile of theophylline from Kollidon SR based matrix systems. Matrix tablets of theophylline using Kollidon SR which is plastic in nature were prepared by direct compression process. NaCl and PEG 1500 were used as channeling agents. Drug release study was evaluated for eight hours using USP 22 paddle-type dissolution apparatus using distilled water as the dissolution medium. The release mechanisms were explored and explained with zero order, Higuchi, first order and Korsmeyer equations. The release rate, extent and mechanisms were found to be governed by the type and content of the channeling agents. Increased rate and extent of the drug release were found by using higher content of channeling agent (42.49%) in the matrix due to increased porosity when compared with the formulation having no channeling agents. On the other hand decreased rate and extent of drug release were observed in the formulation having lower channeling agent content (19.76%). PEG 1500 ensures maximum release of drug from Kollidon SR than NaCl when other parameters were kept unchanged. It was found that type and amount of channeling agent significantly affect the time required for 50% of drug release ($T_{50\%}$), percentage drug release at 8 hours, release rate constant (K) and diffusion exponent (n). Kinetic modeling of dissolution profiles revealed drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport, which was mainly dependent on the type and amount of channeling agents. These studies indicate that the proper balance between a matrix forming agent and a channeling agent can produce a drug dissolution profile similar to a desired dissolution profile.

Keywords: Channeling agent, theophylline, release profile, Kollidon SR

INTRODUCTION

Delivering the biologically active compound in a controlled fashion is one of the critical challenges in pharmaceutics. In the last two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance (Merkus, 1986). There have been numerous developments in polymeric carriers and sustained release systems such as Monolithic Devices (Singh *et al.*, 1988), the drug in the polymeric Reservoir Devices (Nakagami *et al.*, 1991), polymeric colloidal particles or microencapsulates i.e. Microspheres or Nanoparticles (Giddings *et al.*, 1975), enteric coatings (Gregoriadis *et al.*, 1986), soluble polymers with covalently attached 'Pendant' Drug molecules (Poznansky and Juliano, 1984), Osmotic Pump (O'Donnell and McGinity, 1997) etc. The matrix system is commonly used for manufacturing sustained release dosage form because it makes such manufacturing easy (Cardinal, 1984). Various synthetic as well as natural polymers have been examined in sustained drug delivery application. Most of them are synthetic hydrophilic as well as some are plastic in nature. Polymer has its own ability to retard the release of drug from the matrix. Some times channeling agents are used to control drug release over the polymer (Gonzalez-Rodriguez *et al.*, 2001). Previously we investigated the effect of NaCl and PEG 1500 as channeling agent on theophylline release from METHOCEL K4M, a hydrophilic polymer, based matrix tablets (Razzak *et al.*, 2008). The objective of the present study was to observe such effect of NaCl and PEG 1500 on theophylline release from Kollidon SR, a plastic polymer.

MATERIALS AND METHODS

Theophylline was gift sample from Square Pharmaceuticals Bangladesh Limited. Kollidon SR and PEG 1500 were received from BASF Bangladesh Ltd. NaCl was obtained from Loba Cheme Pvt. Ltd., India. Aerosil 200 and Magnesium stearate were procured from Degussa, Germany and Wilfrid Smith Ltd., UK respectively.

Preparation of matrix tablets of Theophylline

Before tablet preparation both the channeling agents (NaCl and PEG 1500) were analysed by sieves of different mesh size. After thorough analysis substantial amount of particles were retained in a 40/50 sieve gradation. The particles were passed through 40 mesh and retained on 50 mesh sieve which gave the particle size in a range of 297μm - 420 μm (Russell and Lantz, 1981).

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During tablet preparation, method of dry blending of the active ingredients with polymer, filler, lubricant and glidant was adopted for direct compression. Required amount of active ingredient and other excipients weighted accurately for thirty tablets according to the formulations (table 1) and blended in a laboratory designed small drum blender for 30 minutes. Particular attention has been given to ensure thorough mixing and phase homogenization. The appropriate amounts of the mixture were accurately weighted in an electronic balance for the preparation of each tablet and finally compressed using a Perkin-Elmer laboratory hydraulic press equipped with an 11.7 mm flat faced punch and die set. The compression force and compression time were 5 ton and 30 seconds respectively. All the preparations were stored in airtight containers at room temperature for further study.

In vitro release studies of theophylline

Theophylline release from matrix tablets was determined by using Dissolution Tester USP XXII. The dissolution test was performed using 900 ml distilled water at 37°C ± 0.5°C and r.p.m. was set at 50. At every 1 hour interval samples of 10 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered through a Whatmaan filter paper (Copley instruments, England) and diluted to a suitable concentration with distilled water. The absorbance of the solutions was measured at 271 nm by using a Shimadzu UV-1201 UV/Vis double beam spectrophotometer (Shimadzu, Japan). Percentage of drug released was calculated using an equation obtained from the standard curve. The dissolution study was continued for 8 hours to get a simulated picture of the drug release in the *in vivo* condition and drug dissolved at specified time periods was plotted against time (hours). This drug release profiles were fitted into several mathematical models to get an idea about the release mechanism of theophylline from the matrix tablets.

Kinetic modeling of drug release

After completing *in vitro* dissolution of all the batches for eight hours, the data was treated with zero order (Mockel and Lippold, 1993), Higuchi (Higuchi, 1963) and First order (Wagner, 1969) equations (equation 1-3 respectively).

$$M_t = M_0 + k_0 t \quad (1)$$

$$M_t = M_0 - k_H t^{1/2} \quad (2)$$

$$\ln M_t = \ln M_0 - k_1 t \quad (3)$$

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M_0 is the dose of the drug incorporated in the delivery system. k_0, k_H and k_1 are rate constants for zero order, Higuchi and first order model respectively. These models fail to explain drug

Table 1: Composition of different formulations of matrix tablets (in mg)

Formulation Code	Theophylline	Kollidon SR	NaCl	PEG 1500	Aerosil 200	Mg-stearate
F-1	300	100	-	-	4	2
F-2	300	100	100	-	4	2
F-3	300	100	200	-	4	2
F-4	300	100	300	-	4	2
F-5	300	100	-	100	4	2
F-6	300	100	-	200	4	2
F-7	300	100	-	300	4	2

Table 2: Release rate constants and R-squared values for different release kinetics as well as successive fractional dissolution time of seven formulations of theophylline matrix tablets

Formulation Code	Zero Order		Highuchi		First Order		Korsmeyer		Fractional dissolution time
	K_o	R^2	K_h	R^2	K_1	R^2	n	R^2	$T_{50\%}$
F-1	5.02	0.975	15.34	0.981	-0.029	0.993	0.664	0.998	10.4
F-2	7.96	0.968	24.47	0.984	-0.060	0.994	0.619	0.991	5.0
F-3	9.26	0.954	28.76	0.990	-0.081	0.998	0.616	0.996	3.7
F-4	9.61	0.917	30.57	0.999	-0.100	0.991	0.509	0.998	2.7
F-5	8.72	0.955	27.08	0.990	-0.073	0.994	0.573	0.988	4.0
F-6	9.53	0.936	29.97	0.996	-0.093	0.996	0.541	0.994	3.1
F-7	9.75	0.908	31.18	0.999	-0.107	0.991	0.489	0.997	2.5

release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data were also fitted to well-known Korsmeyer (Korsmeyer *et al.*, 1983) kinetic equation to ascertain the mechanism of drug release.

$$\log (M_t/M_\infty) = \log k + n \log t \qquad (4)$$

Where, M_∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablet; and n is the diffusional exponent or release exponent; indicative of the mechanism of drug release. For those tablets having cylindrical shape, when n is bellow 0.45, the Fickian diffusion phenomenon dominates, and n between 0.45 and 0.89 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the n value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero-order release. In this case, the drug release is dominated by the erosion and swelling of the polymer (Pappas, 1985; Chueh *et al.*, 1995). Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and Lippold, 1993):

$$MDT = \left(\frac{n}{n+1}\right) k^{-1/n}$$

RESULTS AND DISCUSSION

The investigation was undertaken to observe the effect of channeling agents (NaCl, PEG 1500) on theophylline release from Kollidon SR based seven formulations (table 1). From table 2 we observed that F-1 prominently fitted with Korsmeyer (R^2 = 0.998) kinetic model of drug release. The value of release exponent (n) was 0.664 which indicated that the release pattern of theophylline from F-1 was followed anomalous transport mechanism, which appears to indicate a coupling of the diffusion and erosion mechanism (Korsmeyer *et al.*, 1983). Meanwhile the release profile of F-2 and F-3 matched best with first order kinetic model (R^2 = 0.994 and R^2 = 0.998).Their values of diffusional exponent (n) obtained from Korsmeyer release were 0.619 and 0.616. The values of the n indicated that the drug was released from both formulations by anomalous transport, also known as non-Fickian release mechanism which refers to a combination of both diffusion and erosion controlled drug release (Kuksal *et al.*, 2006). Whereas the release profile of F-4 matched best with Higuchian (R^2 = 0.999) release pattern. Lowest fitting of F-4 with zero order release profile indicated a rapid release of drug at the initial moments of dissolution. The n value obtained from Korsmeyer kinetic model was 0.509 for F-4 which indicated that the drug was released by diffusion and erosion mechanisms. In the same manner F-5 followed first order model (R^2 = 0.994) and F-6 followed first order and Higuchian release pattern to the same extent (R^2 = 0.996) whereas F-7 was best fitted with Higuchian model (R^2 = 0.999) predominantly. The values of n for F-5, F-6 and F-7 were obtained 0.573, 0.541 and 0.489 respectively that indicated an anomalous transport of drug release. For each channeling agent the values of diffusion exponent (n) was reduced with the increased amount of channeling agent that indicated the shifting of release mechanism from non- Fickian transport towards Fickian transport. This effect was due to the formation of channels on the surface of the matrix that facillated the diffusion mechanism.

From the table 2, it was also clear that $T_{50\%}$ (MDT) values were changed due to the change of the amount of channeling agents in the matrix tablets. In all these formulations the values of $T_{50\%}$ (MDT) were larger for those formulations which contained smaller quantities or absence of channeling agents. For example $T_{50\%}$ (MDT) values for F-1, F-2, F-3 and F-4 were 10.4 hours, 5.0 hours, 3.7 hours and 2.7 hours respectively. This reduction of the magnitude of $T_{50\%}$ (MDT) indicated that the increment of NaCl increased the channeling effect to facillate the drug release. Similar pattern was also observed in case of F-5, F-6 and F-7 where PEG 1500 used as channeling agent.

Qualitative effect of NaCl and PEG 1500 as channeling agent on drug release

Formulation F-2 and F-5 were compared to investigate the effect of the channeling agent (NaCl and PEG 1500) on Kollidon SR based theophylline matrix tablets. Both the formulations contained 100 mg of NaCl and PEG 1500 respectively keeping other parameters unchanged. The amount of channeling agents was 19.76%. From the zero order release profile it was observed that the total percent release of theophylline at the end of the eight hour from F-2 and F-5 were 69.0% and 75.8% respectively (fig. 1).

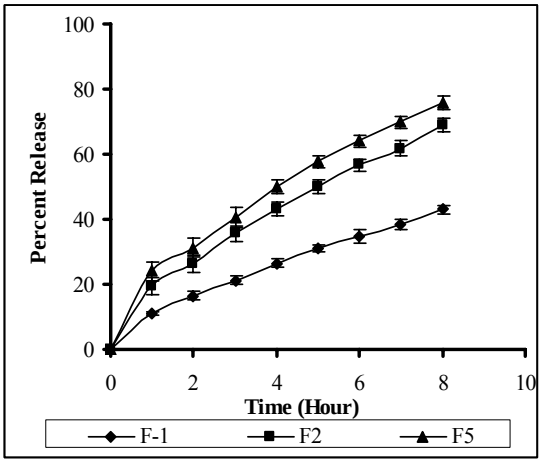


Fig. 1: Qualitative effect of channeling agents on drug release profile (NaCl-100mg, PEG 1500-100mg); F1 was used as control with no channeling agents

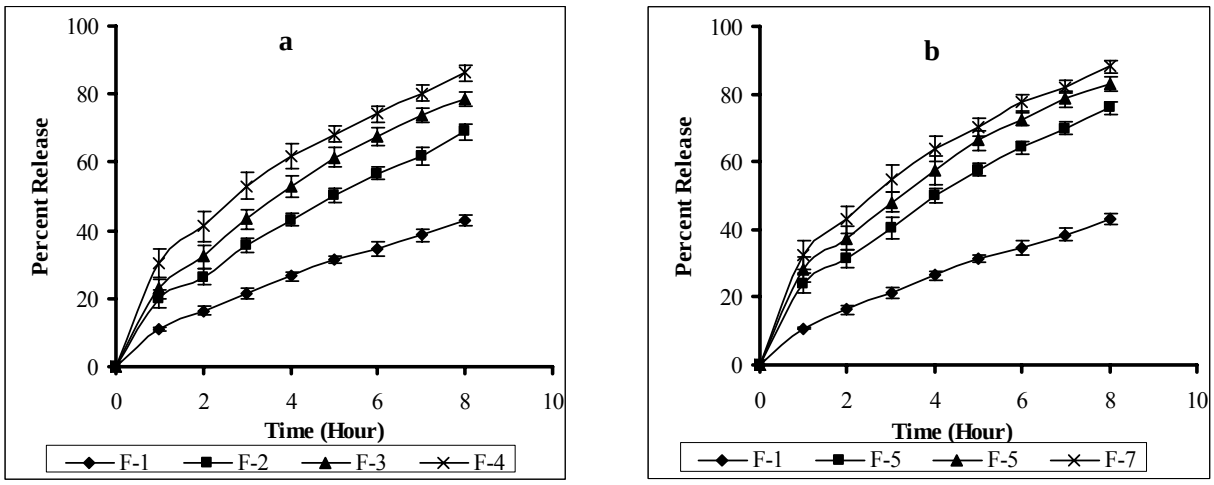
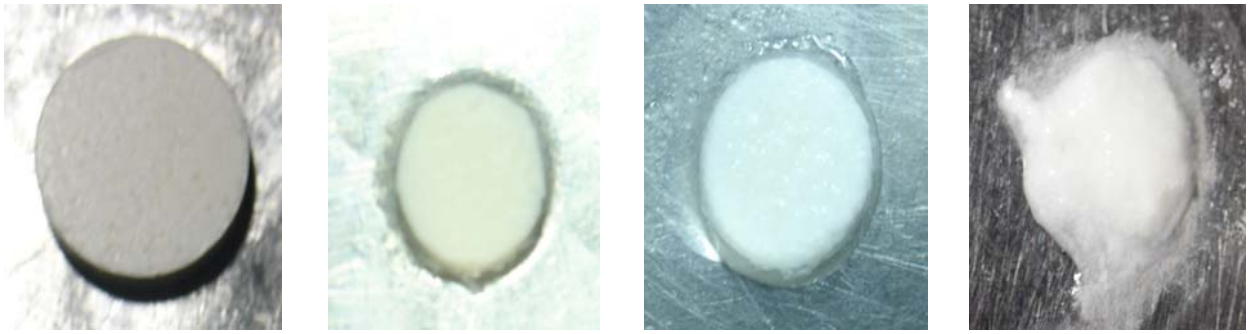


Fig. 2: Quantitative effect of channeling agents on drug release profile from Kollidon SR (a) NaCl, (b) PEG 1500.



a) intact tablet (Before dissolution) b) one hour after dissolution c) four hours after dissolution d) eight hours after dissolution

Fig. 3: Surface texture of theophylline matrix tablet of F-3. The photograph was taken by Sony DSC V3 fitted with Carl Zeiss Vario-Sonnar (2.8- 4 / 7- 28 mm) lens.

From the fig. 1, it was found that the release rate of theophylline governed by NaCl and PEG 1500 was more or less same but the extent of release of drug was significantly more in case of PEG 1500 than NaCl (after one way ANOVA, the p value was 0.00000002 that was less than 0.05 for F2 and F5). From Kollidon SR, all formulations followed anomalous transport for release of theophylline from matrices.

Quantitative effect of channeling agents (NaCl, PEG 1500) on drug release

From the zero order release profile it was observed that the total percent release of theophylline from F-1, F-2, F-3, F-4 were 42.9%, 69.0%, 78.5%, 86.2% and from F-5, F-6, F-7 were 75.8%, 83.0% and 88.1% respectively at the end of eight hour (fig. 2). From the figure 2, it was also observed that without channeling agent, drug release from the formulation F-1 was slow. This effect was due to the characteristic property of Kollidon SR to form insoluble or skeleton network around the matrix system. The rate and extent of theophylline release from the matrices increased significantly with the increment of the amount NaCl in the formulation F-2, F-3 and F-4 (after one way ANOVA, the p value was less than 0.05 i.e. 0.00000000 for F1-F4) (fig. 2a). Similar phenomenon was also observed for PEG 1500 in the formulation F-5, F-6 and F-7 (p value was 0.00000000 for F1, F5, F6 and F7) (fig. 2b). The addition of channeling agents deviated the formulations to follow zero order kinetic model (table 2).

In all these cases the increase of the amount of NaCl and PEG 1500 caused a gradual increase of drug release in dissolution media which was supported by the values of $T_{50\%}$. From the fig. 2 another observation was that when the amount of channeling agent was increased, the control of the polymer upon the release profile was lost to some extent which was demonstrated by the standard error bars parallel to Y-axis. Conversely it can be said that at relatively higher polymer contents (considering polymer to NaCl ratio) the drug release pattern became slow but steady. From the above formulations it can be concluded that a suitable combination of Kollidon SR and channeling agents (NaCl and PEG 1500) can give us matrix system with desirable drug release.

CONCLUSION

Channeling agents variation both qualitative and quantitative significantly affected drug release kinetics from prepared matrix tablets in our study. Higher amount of channeling agent increased drug release rate and extent. Most of the formulations fitted better with first order kinetic model and some with Korsmeyer equation which defined drug release rate and mechanism. With the increase of channeling agent content, maximum formulations deviated to follow zero order release kinetics. In all cases the increase of the channeling agent content caused a lowering of the magnitude of release exponent (n) which indicates the shifting of release mechanism from non-Fickian to Fickian direction. In case of release rate NaCl and PEG 1500 exert almost same effect but PEG 1500 offered greater release than NaCl from plastic polymer Kollidon SR. We have taken different photographs of F-3 at different time interval to observe the surface texture of the tablet (fig. 3). If the facility of scanning electron micrograph (SEM) is available then it will be possible for us to take the picture of the pores formed by channeling agents. In future we have a plan to observe such effects with some other plastic release retarding polymers.

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