

DEVELOPMENT OF THEOPHYLLINE SUSTAINED RELEASE DOSAGE FORM BASED ON KOLLIDON SR

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ABSTRACT

Sustained release theophylline matrix tablets constituting Kollidon SR (Polyvinyl acetate and povidone based matrix retarding polymer) were developed in this study in an attempt to design a dosage form that manifests desirable release profile and thorough adherence to official monographs. Four matrix tablet formulations were prepared by dry blending and direct compression of Kollidon SR and HPMC-15cps (hydroxypropylmethylcellulose) in varying proportion with fixed percentage of theophylline. Tablets containing only Kollidon SR with the active ingredient demonstrated a rapid rate of drug release with an initial burst effect. Incorporation of HPMC-15cps in the matrix tablet prolonged the release of drug with subsequent minimization of burst effect as confirmed by mean dissolution time, T_{50} and Higuchi release rate data. Among the batches containing HPMC-15 cps, a direct relationship was obtained between release rate and the percentage of HPMC used. A suitable controlled release profile was obtained with the matrix tablets containing 20% Kollidon SR and 30% HPMC-15cps. The formulation showed close resemblance to commercial products and compliance with USP specification. The results were explored and explained by the difference of physico-chemical property and hydration characteristics of the polymers. In addition to this result, the exponential model was applied to characterize the drug release behaviour from polymeric systems. It was found that, Fickian release is predominant in tablets containing Kollidon SR alone and non-Fickian mechanism plays an important role in the release of drug from HPMC containing tablets with a trend towards zero-order or case II release. *In vitro* release profile of two commercial brands were also undertaken for comparison and modulation of the experimental batches.

INTRODUCTION

In the last several decades, many different types of controlled-release dosage forms have been developed to improve clinical efficacy of drug and patient compliance (Merkus, 1986; Jantzen, 1996). Xanthine drugs especially theophylline and related substances are thought to be the most useful bronchodilators for moderate to severe reversible bronchospasm (Goodman and Gilman, 1996). The *in vitro* release profile from sustained release theophylline tablet formulation with a matrix base has been reported earlier (Shora *et al.*, 1980). Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for the manufacture of sustained release dosage forms. Plastic matrix systems, due to their chemical inertness and drug-embedding ability, have been widely used for sustaining the release of drugs (Lordi *et al.*, 1990). Kollidon SR is one of the recently developed matrix forming agents with plastic behaviour. Chemically, Kollidon SR is polyvinyl acetate and polyvinyl pyrrolidone based matrix retarding agent particularly suitable for

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the manufacture of pH independent sustained release matrix tablets. Polyvinyl acetate is a very plastic material that produces a coherent mass even under low compression force. When the tablets prepared with Kollidon SR are introduced into gastric or intestinal fluid, the water soluble polyvinylpyrrolidone is leached out to form pores through which the active ingredients slowly diffuses outwards in a controlled and pre-determined fashion. Kollidon SR contains no ionic groups which render them inert to the drug molecule. Its high flowability, low reposition angle and excellent compressibility characteristics endows the tablets with desired hardness and low friability while simultaneously reducing the process variables and processing cost (BASF, 1999). This experiment is aimed to develop sustained release theophylline tablets with suitable release profile using Kollidon SR as a matrix former that also complies with pharmacopoeial specifications. Fixed amount of theophylline were used in all the experimental batches while the amount of Kollidon SR was decreased gradually and the reduced amount of Kollidon SR was replaced by HPMC-15cps to modulate the drug release pattern. HPMC-15cps is a class of hydrophilic matrix system. It was incorporated into the matrix formulation due to its claim as a fast gel formation to control initial release, and formation of strong, viscous gels to control drug release (The Dow Chemical Company, 1987). When such a system is exposed to an aqueous medium it does not disintegrate, but immediately after hydration it develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the centre of the matrix system (Talukdar *et al.*, 1996). The use of HPMC-15 cps as matrix material in direct compression process has been reported earlier (Bain *et al.*, 1991).

Along with the experimental batches, dissolution profile of Asmany 300 SR ® of Square Pharmaceuticals Ltd. Bangladesh and Spophyllin Retard® of Slovakofarma were also investigated for comparison and modulation purpose of the proposed formulations. The objective of the present study was to investigate the possible use of Kollidon SR in combination with a second polymer as release-retardant matrix forming agent in directly compressed matrix tablets. Drug release kinetics has also been studied in this experiment to investigate the release characteristics of theophylline from Kollidon SR matrix tablets with the help of exponential model.

MATERIAL AND METHODS

Materials:

Theophylline was a kind gift from Square Pharmaceuticals Ltd. Bangladesh. Kollidon SR was used as received from BASF Bangladesh Ltd. Hydroxypropyl methylcellulose-15cps was obtained from Shin-Etsu chemical Co. Ltd., Japan. Aerosil (Silicon di oxide) and Magnesium stearate was from Hanau Chemicals Ltd. Japan. Monobasic potassium phosphate, sodium hydroxide and hydrochloric acid were purchased from BDH, UK. Asmany 300 SR ® of Square Pharmaceuticals Ltd. Bangladesh and Spophyllin Retard ® of Slovakofarma were purchased from local market.

Preparation of matrix tablets:

For tablet preparation, method of dry blending of the active ingredients with release retarding agents, release rate modifiers, lubricants and flow promoters followed by direct compression was adopted. Table 1 shows the formulations of Kollidon SR matrix tablets. Formulation T1 contains only theophylline and Kollidon-SR while formulations T2 to T4 contain theophylline along with Kollidon SR and HPMC-15cps. The amount of Kollidon SR was gradually reduced from formulation T2 to T4 and the reduced amount of Kollidon SR was replaced by HPMC-15cps. Ten tablets were prepared for each formulation. Properly weighed Kollidon SR, HPMC-15cps, Magnesium stearate, Aerosil and Theophylline were blended in a laboratory mixture for 10 minutes. Particular attention has been given to ensure thorough mixing and phase homogenization.

The appropriate amounts of the mixture were then compressed using a Perkin-Elmer laboratory hydraulic press equipped with a 13 mm flat faced punch and die set. The compression force and compression time were 5 ton and 30 seconds respectively. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study.

Dissolution studies:

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 12 hours using a six station USP XXII type 1 apparatus at $37 \pm 0.5^\circ\text{C}$ and 50 rpm speed. The dissolution studies were carried out in triplicate for 12 hours (initial 2 hours in simulated gastric fluid and rest 10 hours in phosphate buffer of pH 6.8). At every 1-hour interval, samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed for theophylline by an UV spectrophotometer at 271 nm (Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from theophylline reference standard. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

Data treatment:

The dissolution data were also fitted according to the well-known exponential Eq. (1) which is often used to describe the drug release behaviour from polymeric systems:

$$\frac{M_t}{M_\infty} = Kt^n \dots\dots\dots(1)$$

Where M_t/M_∞ is the fractional (0.1-0.7) drug release at time t ; K is a constant incorporating the properties of the macromolecular polymeric systems and the drug and n is a kinetic constant which depends on and is used to characterize the transport mechanism. The value of n for a tablet, $n = 0.45$ for Fickian (Case I) release, >0.45 but <0.89 for non-Fickian (Anomalous) release and 0.89 for Case II (Zero order) release and >0.89 for super case II type of release (Ritger and Peppas, 1987). Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain and anomalous transport (Non Fickian) refers to the summation of both diffusion and dissolution controlled drug release. From the above equation the n values for different formulations have been calculated to identify the drug release mechanism. Talukder *et al.* (1996) applied this equation to evaluate the drug release mechanism from xanthan gum matrix tablets. Although the constant K used in Eq. (1) is one of the measures of the drug release rate, it should not be used for comparison because there are different kinetics in different test conditions (Talukder *et al.*, 1996). Therefore to characterize the drug release rate in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold (1993) using Eq. (2)

$$\text{MDT} = \frac{n}{n+1} k^{-\frac{1}{n}} \dots\dots\dots(2)$$

The values of release exponent (n) and mean dissolution time (MDT) calculated according to Eq. (1) and (2) respectively are presented in Table 2.

RESULTS AND DISCUSSION

The serum half-life of theophylline in a healthy, nonsmoking asthmatic adult is 7 to 9 hours. Theophylline has been shown to be well absorbed throughout the length of the gastrointestinal tract and produce peak plasma concentration within 2 hours. The use of rapid release oral theophylline preparation have been declined due to the higher incidence of side effects resulting from rapid absorption. Theophylline has a short elimination half-life, which also encourages the drug to be formulated in sustained release dosage form. Due to its rapid elimination and narrow therapeutic index, this drug is indeed a suitable candidate to be formulated into sustained release dosage forms.

Effect of Kollidon SR on release rate of drug:

The *in vitro* release profiles of theophylline from Kollidon SR matrix tablets are presented in Fig.1. From the figure it is observed that, tablets of batch T1, composed of equal percentage of theophylline and Kollidon SR, released 91.61% of drug after 12 hours of dissolution period. About 42.28% of the active ingredient was released within the first two hours. It is important to mention that, this initial rapid release of drug from the matrix system is often therapeutically undesirable because the total amount of drug released is remarkably influenced by this initial control of release from the dosage form (Talukder *et al.*, 1996). Generally, if the polymer does not hydrate quickly, the surface barrier cannot be formed immediately, which may cause a large portion of drug to be released during the fast initial phase of release profile.

Effect of HPMC-15cps on release rate of drug:

In an attempt to control this initial burst effect, HPMC-15 cps was incorporated into the formulations. Batch T2, T3 and T4 contains 10, 20 and 30% of HPMC-15cps respectively along with kollidon SR. HPMC-15 cps is a class of hydrophilic matrix system. When such system comes in contact with liquid dissolution medium, the solvent penetrates into the free spaces

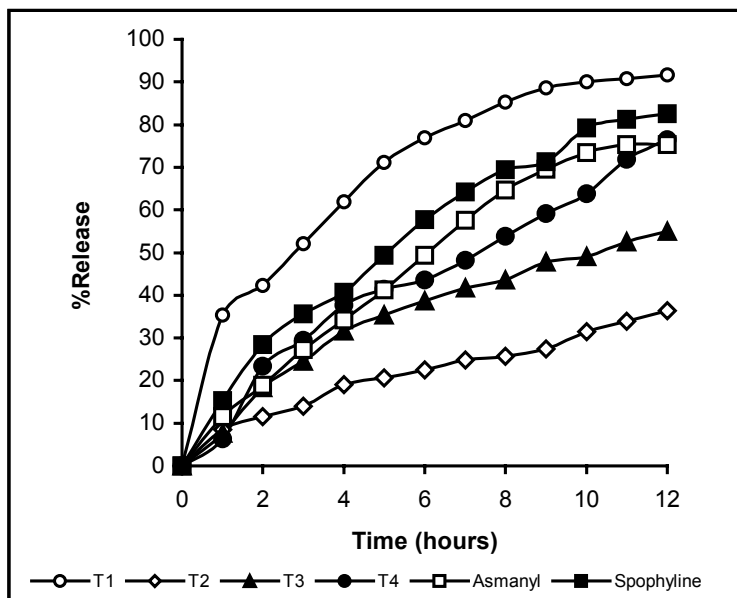


Fig.1. Release profile of theophylline from Kollidon SR matrix tablets

between macromolecular chains. After solvation of the polymer chains, the dimensions of the polymer molecule increase due to the polymer relaxation by the stress of the penetrated solvent. This phenomenon is defined as swelling and it is characterized by the formation of a gel-like network surrounding the tablet (Alderman, 1984). Batch T2, containing 40% Kollidon SR and 10% HPMC-15 cps demonstrated slower release. Only 36.41% of drug was released in 12 hours with no evidence of burst release (11.50% theophylline released in first 2 hours). Further increment of HPMC-15cps in the formulations clearly increased the percentage of drug release. With 20% of HPMC-15cps (Batch T3), 55.02 % theophylline was released after 12 hours. The best sustained release profile was obtained with Batch T4 containing 30% of HPMC-15cps and 20% of Kollidon SR. Tablets of this batch released 76.52% theophylline after 12 hours of dissolution period with no evidence of initial burst release. According to USP specification, for controlled release drug delivery system (Tablet/capsule), at time equal to 0.25D, 20-50% drug will be dissolved, at time equal to 0.5D, 45-75% dissolved and thereafter at any time up until 1.0D, not less than 75% of drug will be dissolved where D is the labeled usual dosing frequency or interval (Banaker, 1991). With this objective in view, it is observed that only T4 alone shows drug release according to USP specification. Moreover, release profile of this formulation is more congruous with those of commercial brands i.e. Asmany 300 SR ® (Square Pharmaceuticals Ltd., Bangladesh) and Spophyllin Retard ® (Slovakofarma). Asmany released 75.32% whereas Spophylline released 82.56% of theophylline after 12-hour dissolution period. Both the commercial brands were within USP limit and show significant similarity with batch T4 in terms of cumulative percent of release.

The values of release exponent (n), mean dissolution time (MDT), Higuchi release rate and time for 50% drug release (T_{50}) for different formulations are depicted in Table 2. The graphical representation of these release parameters are illustrated in figure 2. For T1 matrix system, the value of the release exponent, $n=0.45$ which is typical for case I or Fickian diffusion. This can be attributed to the presence of water-soluble polyvinyl pyrrolidone in the Kollidon SR matrix system. Kollidon SR is composed of 80% polyvinyl acetate and 19% povidone (BASF, 1999). When the tablets are introduced into aqueous environment, the water-soluble povidone is leached

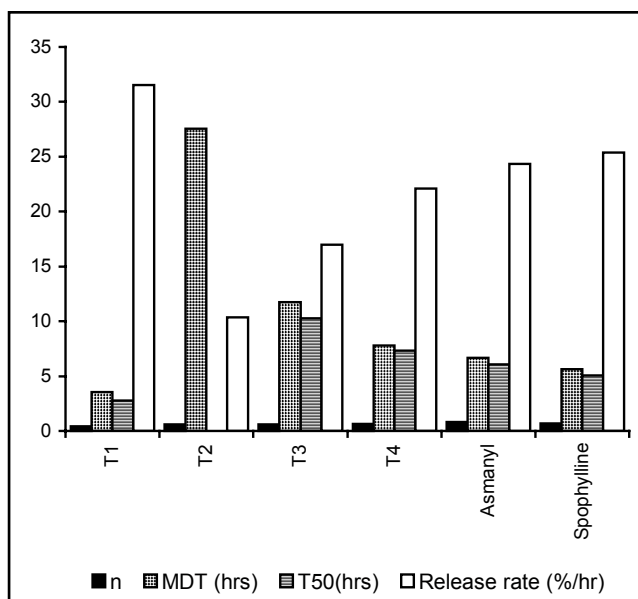


Fig.2. Drug release parameters of different formulations

out slowly from the matrix generating numerous pores and channels through which the drug is released by diffusion process. Moreover, theophylline is a highly water-soluble drug with pKa value 8.6 (The Pharmaceutical Codex, 1994). Being a water-soluble drug, theophylline is released from the Kollidon SR matrix system by the mechanism of diffusion (Alderman, 1984). The pore formation and consequent structural changes proceed rapidly at the beginning of the dissolution period, as the concentration of povidone remains high initially. Due to poor swelling property of Kollidon SR, a burst release was evident at this point of dissolution as observed from figure 1. The T_{50} of this batch is only 2.78 hours with a very high value of Higuchi release rate ($31.52\%/ \sqrt{\text{time}}$). Incorporation of HPMC-15cps in the matrix system in an increasing percentage caused the active ingredients to be released in non-Fickian or anomalous fashion with a trend towards case II or zero order release (relaxation controlled or swelling controlled) as evident from table 2. The cumulative percentage of release and Higuchi release rate of theophylline from tablets of batch T2 to T4 were considerably lower than those of batch T1. T4 matrix tablets composed of 19.73% kollidon SR and 29.60% of HPMC-15 cps demonstrated better sustained release efficacy. The Higuchi release rate for this formulation was $22.06\% / \sqrt{\text{time}}$ and the T_{50} value was found to be 7.32 hours. This phenomenon can generally be attributed to structural changes induced in the polymer by the penetrant (Peterlin 1979, 1980). HPMC-15 cps, being a class of hydrophilic matrix former, swells in the presence of liquid solvent due to polymer relaxation and is characterized by the formation of a gel-like network surrounding the tablet. The more the matrix swells, the longer the diffusion pathlength required for the drug to come out, which results in decrease in release rate. The mechanical properties of the surface-hydrated gelatinous barrier play an important role in overall drug release rate (Talukder *et al.*, 1996). The release rate and T_{50} values of these batches can be considered as a function of the percentage of HPMC-15cps used in the formulations.

Table 1
Formulation of theophylline loaded Kollidon SR based matrix tablets

Code	Wt. of TH/ Tablet (mg)	Wt. of Kollidon SR/ Tablet (mg)	Wt. of HPMC- 15cps/ Tablet (mg)	Wt. of Aerosil/ Tablet (mg)	Wt. of Mg- stearate/ Tab. (mg)	Total Wt. (mg)
T1	300	300	0	4	2	606
T2	300	240	60	4	2	606
T3	300	180	120	4	2	606
T4	300	120	180	4	2	606

The differences in release rate and T_{50} values among the experimental batches are confirmed from their mean dissolution time (MDT) data presented in Table 2. MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability and vice-versa. From table 2, the lowest MDT value (3.56 hrs) was found with batch T1 which also showed a low value of T_{50} (2.78 hrs) and a high value of Higuchi release rate ($31.52\%/ \sqrt{\text{time}}$). On the other hand all the batches containing HPMC-15cps exhibited a higher value of MDT than that of batch T1 indicating the higher drug-retarding ability of these formulations. An inverse relationship was found between the percentage of HPMC-15 cps in the formulations and the MDT values of the dosage form. The MDT value was found to decrease as the amount of HPMC was increased in the formulations (Table 2).

Table 2
Drug release parameters of the matrix tablets

Formulations	n	MDT (hrs)	T ₅₀ (hrs)	Release rate (%/√hr)
T1	0.4508	3.56	2.78	31.52
T2	0.5868	27.54	>12	10.36
T3	0.5909	11.76	10.27	16.96
T4	0.6425	7.79	7.32	22.07
Asmanyl	0.8016	6.67	6.08	24.34
Spophylline	0.6984	5.61	5.08	25.4

However Quadir (2001) carried out similar work with HPMC-15 cps, where HPMC was used alone as the rate-retarding polymer for theophylline as the model drug. The amount of HPMC-15 cps was decreased gradually and the reduced amount of HPMC was replaced with inert filler. The study showed that, drug release was decreased with an increase in the percentage of HPMC-15 cps. In our present study drug release was increased with increase in the proportion of HPMC-15 cps in the formulation. This can be explained by the fact that the drug release was governed mainly by Kollidon SR while HPMC-15 cps was incorporated as a release rate modifier. HPMC-15 cps in 10% concentration was able to form a gelatinous layer, which augmented the sustaining effect of Kollidon SR. However further increase of HPMC percentage in the formulation virtually reduced the amount of Kollidon SR thus decreasing the overall retarding capacity of the matrix system.

Among the prepared tablets, batch T4 showed the MDT value of 7.79 hours, which is close to those of commercial brands (6.67 hours for Asmanyl and 5.61 hours for Spophylline). The Higuchi release rate and T₅₀ values of formulation T4 are quite similar to these commercial brands. Taking into account of all the observed values of cumulative percentage of release, Higuchi release rate, T₅₀ values and MDT data, it is observed that, the formulation T4 resembles best with the commercial tablets and showed compliance to legislative references.

CONCLUSIONS

The approach of the present study was to develop a sustain release theophylline matrix tablet with kollidon SR. Considering all the parameters, it can be inferred from pharmacokinetic viewpoint that, Kollidon SR alone cannot be used to sustain the release of theophylline as per the USP specifications. The study also reveals that, it is possible to design theophylline loaded Kollidon SR sustained release matrix tablets with desirable release characteristics by judicious and critical combination of Kollidon SR with other hydrophilic materials. Commercial availability of Kollidon SR and its direct compression characteristics will reduce the unit cost of product by decreasing processing steps; the presence of HPMC in the matrix will modulate the drug release to an acceptable pharmacokinetic profile. The MDT values along with Higuchi release rate and T₅₀ data, clearly manifests the necessity of combining a hydrophilic matrix system with Kollidon SR. However, further studies in this context should be carried out to evaluate stability and reproducibility of this dosage form. *In vitro-In vivo* correlation should also be performed to assess the efficacy of Kollidon SR based matrix tablets in *in vivo* environment.

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