ORIGINAL ARTICLE

Low level maize starch and sodium lauryl sulphate as release modifiers in Carbopol 941 capsule matrix

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The effects of maize starch, a widely used tablet/granule disintegrator, and sodium lauryl sulphate, a surfactant, on the *in vitro* release of theophylline embedded in a polyacrylic acid polymer (carbopol 941) matrix were investigated. The presence of maize starch (MS) and sodium lauryl sulphate (SLS) led to about two-fold increase in the maximum cumulative (Cmax) amount of theophylline released within 8 hours in both simulated gastric and intestinal fluids (SGF and SIF respectively) without enzymes. The release of theophylline was generally faster in SIF and MS performed better than SLS as release enhancer. The overall result demonstrates that drug release was found to be pH dependent, swelling–controlled and the presence of MS and SLS though affected drug release, they did not affect release kinetics from the carbopol matrix.

Key words: Carbopol 941, maize starch, sodium lauryl sulphate, theophylline, release modifiers

INTRODUCTION

For many reasons, oral drug delivery continues to be the preferred route of drug administration, and the use of hydrophilic matrices in achieving this is increasingly becoming important especially in controlling the release rate of drugs from solid dosage forms[1-5]. These systems are attractive approaches from economic as well as process development view of point[6-9]. A sustained release matrix tablet consists of a compressed compact containing a mixture of one or more bioactive agent (s) with one or more matrix former (s), which retards drug release.[8] Hydrophilic swellable polymers have widely been used to control the release of drugs from matrix tablet formulations in the last three decades[4,10,11]. Historically, carbopol polyacrylic acid polymers have demonstrated many useful performance properties in tablet applications [12-14]. They are useful at low levels (1–3%) as binders and at higher levels (5–30%), they achieve modified or even zero order-controlled release of bioactives. Carbopol 941 is one member of the carbopol family of polymers that is suitable for use in oral dosage forms.[15] Due to their extremely efficient thickening and gelling characteristics, carbopol resins have been widely used in various pharmaceutical applications, including beads, gels, and ointments.[14] Their equilibrium swelling capacity, solute permeability, and their *in vitro* performance characteristics make them valuable in drug delivery applications. Its uses as sustained release matrix and as bioadhesives in drug delivery have been studied extensively.[17-20] The use of carbopols in drug delivery, especially in sustained release formulations may sometimes require drug release enhancers or channelling agents on account of high drug release retardant effect encountered with the polymer.[19] These release enhancers are capable of causing the break up of tablets or granules or improve wettability, thereby facilitating the release of the incorporated active drug.[5,17] The presence of release enhancers in a suitable amount can lead to controlledrelease of active drug in tablets or granules.[21-23] In the present study, we assess the influence of maize starch (MS), a known tablet disintegrant, and sodium lauryl sulphate (SLS), a surfactant, on the rate and mechanisms of release of theophylline from carbopol 941 hydrophilic matrices.

MATERIALS AND METHOD

Materials

The following materials were used as procured from their manufacturers without further purification: anhydrous theophylline, sodium chloride, potassium di-hydrogen monophosphate, lactose (Merck, Germany), carbopol 941 (GF Goodrich, OH, USA), hydrochloric acid (May and Baker, England), MS and SLS (Sigma Chem. Company, USA).

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Method

Preparation of theophylline granules

The batches of theophylline granules were prepared according to the formula presented in Table 1. Weighed quantities of theophylline and other additives excluding carbopol 941 were placed in a mortar, triturated with a pestle to obtain a homogenous mixture and blended with a dispersion of carbopol 941 in 26 ml of double distilled water. The damp mass obtained was screened through a 1.7-mm stainless steel sieve and dried in a hot air oven (Gallenkamp, England) at 60°C for 3 hours. Dried granules were screened manually filled into 250 mg capacity hard gelatine capsule shells. Ninety capsules were filled per batch and each capsule contained quantity of granules equivalent to 100 mg of anhydrous theophylline. Filled capsules were stored in amber-coloured airtight specimen bottles.

Evaluation of Capsule Properties

Weight uniformity

Twenty capsules selected randomly from each batch were weighed individually and collectively on an electronic balance (Metler P 167, electronic weighing balance). The mean weights and coefficient of variations were calculated.

Drug content determination

The total drug content of each capsule was determined according to the BP 2001 method using 0.1N HCl. Three replicate determinations were made for each batch.

In vitro drug release study

Drug release study was carried out according to the USP 23 basket method. The basket apparatus was used in order to reduce the variability due to the hydrodynamic conditions of the test and to overcome the problem due to possible sticking of the gelled matrix on the wall of the dissolution vessel. The study was performed using an Erweka DT 8 – 1 dissolution rate tester (Erweka, Germany) at a speed of 100 rpm. A 500 ml volume of SGF (pH 1.2) and SIF (pH 7.5) maintained at 37 ± 0.1°C were used as dissolution media. Aliquots of the dissolution medium (4 ml) were withdrawn at hourly intervals up to 8 hours. The withdrawn amount was replaced with an equal volume of fresh dissolution medium kept at 37 ± 0.1°C. The withdrawn samples were analysed for drug content at 272 nm using a Shimadzu UV 160 A Spectrophotometer (Shimadzu, Japan). The data presented are for triplicate determinations.

Table 1: Composition of matrix granules

	Batch I	Batch II	Batch III
Theophylline (mg)	100.0	100.0	100.0
Carbopol 941 (%)	10.0	10.0	10.0
Maize starch (%)	-	2.5	-
Sodium lauryl sulphate (%)	-	-	2.5
Lactose qs (mg) to	250	250	250

In vitro drug release kinetics

In order to investigate the mode of release from capsules, the release data was analysed using the Korsemeyer–Peppa's[16] release model;

$$M_t / M_\infty = k^{tn}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinite time, K is the kinetic constant incorporating structural and geometric characteristics of the dosage form, and n is the diffusion exponent indicative of the release mechanism. Values of n = 0.5 represents Fickian diffusion, 0.5<n<1.0 represents non-Fickian, case II transport if n = 1.0 and super case II transport if n >1.0 [16]. The time required for release of 50% and 70% of the drug (t50 and t70) was selected as a measure of drug release rate.

Statistics

The data were expressed as mean ± S.D. The significance of the drug release results was assessed by an analysis of variance (ANOVA). A *P* value of <0.01 was considered significant.

RESULTS AND DISCUSSION

The results of the weight uniformity and total drug content of the capsules are shown in Table 2. The percentage drug content of the capsules ranged from 91.06 to 95.05%, while the coefficient of weight variation ranged from 3.80 to 3.38%. The drug release profile of the capsules in SGF and SIF are shown in Figures 1 and 2, while the time taken for 50 and 70% of theophylline to be released (T_{50} and T_{70}, respectively) is shown in Table 2. Figures 1 and 2 and Table 2 show poor release of theophylline from the carbopol 941 matrix in both SGF and SIF with <50% of the drug released within the study period of 8 hours. In the presence of MS and SLS, the release of theophylline improved significantly (*P* <0.01) in both SGF and SIF. MS, however, performed better than SLS in enhancing drug release in both dissolution media.

The coefficient of weight variations [Table 2] indicate that hand filling of capsules when properly carried out may

Table 2: *In vitro* release parameters of theophylline from matrix capsules

Batch	SGF		SIF		Drug content (%)	Weight uniformity (mg)
	T_{50}	T_{70}	T_{50}	T_{70}		
CP	-	-	-	-	92.50	272 ± 3.38
CP + SLS	-	-	8.0	-	91.66	276 ± 4.89
CP + MS	6.5	-	4.8	-	91.96	274 ± 3.08

X ± standard deviation; n = 3, 10 and 20 (dissolution, drug content and weight uniformity respectively)

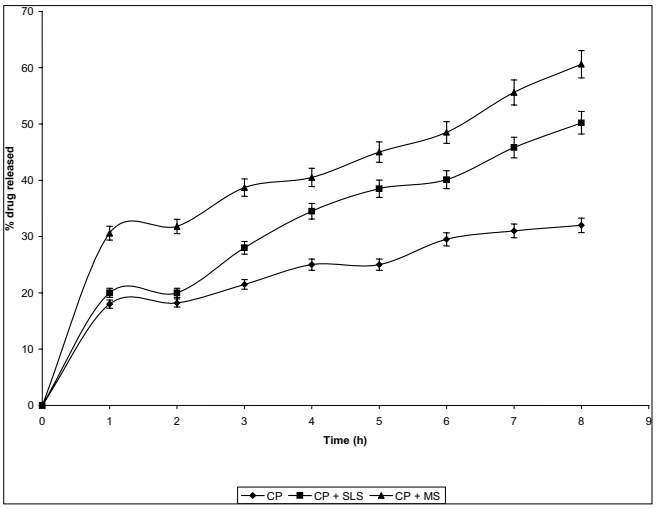

Figure 1: Dissolution profile of theophylline in SGF

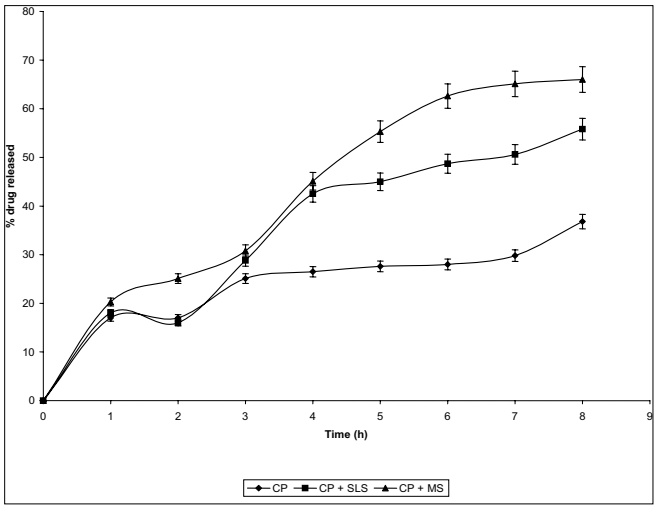

Figure 2: Dissolution profile of theophylline in SIF

produce capsules of good and acceptable weight uniformity. The results of the total drug content however did not show excellent content of active ingredient. In capsule control tests, weight uniformity (especially in hand filled capsules) may not be the rate-limiting step to *in vivo* bioavailability. As a result, weight uniformity and total drug content of hand filled capsules do not always reflect the actual flow and consolidation of granules in actual capsule filling operations. The presence of MS and SLS led to an almost 2-fold increase in the maximum cumulative percentage of theophylline released within 8 hours in both SGF and SIF [Figures 1 and 2]. There was a slight increase in theophylline (Cmax) release from the CP941 matrix in SIF and this may be due to the increase swelling of carbopols in the alkaline medium of SIF.[9] It is evident from Figures 1 and 2 that MS performed better than SLS as a drug release enhancer in both media. MS is known to enhance drug release primarily by acting as a disintegrator in tablets/capsules. These additives may also function as channeling agents creating pores through which dissolved drug can leach out of a tablet or the capsule matrix.[5] In this regard, MS and SLS[5] have been separately employed as channeling agents. Surfactants such as SLS enhance drug release by improving solubility and dissolution due to solubilization and/or wetting effects. The rate-determining step in tablet or capsule disintegration according to Levy[24] is the penetration of media through the pores of the tablets or capsules. An equation which has been found applicable to tablets and capsules was derived to explain the role of surfactants in drug release:

$$\iota^2 = \eta\gamma \cos \theta t = Kt \quad (1)$$

where ι is the length penetrated at time t, k is the coefficient of penetration, r is the average radius of the void space, θ is the contact angle, and η and γ are the surface tension and viscosity of the dissolution medium, respectively. Equation (1) indicates that a surfactant has two effects on the penetration of liquid into tablet or granule.[22] Addition of a surfactant lowers the surface tension and decreases the contact angle, consequently, increased penetration of fluid into the tablet or the granule matrix leading to enhanced disintegration. Reports on the usefulness of surfactants in enhancing drug release, however, have been conflicting.[5,22] Below the critical micelle concentration (cmc), release of drug may be enhanced due to better contact of drug with the dissolution medium *in vitro* or the absorbing membrane *in vivo*.[22] Above the cmc, a portion of the drug may be entrapped in the micelles and, as such, the drug will be unavailable for absorption *in vivo*. Variable effects of SLS on drug release reported in the literature include the works by Ofoefule and Chukwu,[22] Levy,[24] Ganderton *et al.*,[25] and Emeje *et al*.[5] Following these variable results, it has been suggested that the use of SLS as a drug release enhancer should be undertaken only after preformulation studies have revealed its compatibility with the drug and/or the polymers.[7, 22]

Release Kinetics

Table 3 indicates that drug release from the matrix capsules was dependent on the type of dissolution medium. Drug release from matrix capsules in SGF was diffusion controlled (Fickian release mechanism) irrespective of the presence of MS and SLS. The values of n for these formulations were

Table 3: Effect of additives on the release mechanism of theophylline from capsule matrices

Batch	SGF		SIF	
	n	R^2	n	R^2
CP	0.31	0.91	0.36	0.88
CP + SLS	0.48	0.93	0.65	0.87
CP + MS	0.33	0.90	0.65	0.95

< 0.5. However, drug release from capsule formulations containing MS and SLS followed the non-Fickian release mechanism (n > 0.5 < 1.0). The high insolubility of carbopol 941 in acidic pH of the SGF and its high swelling and stability in the alkaline pH of the SIF may be responsible for the diffusion/ dissolution mechanism of these formulations. Overall, the observed behavior may be due to a complex interaction between the carbopol, drug and the additives.[4]

CONCLUSIONS

The use of a disintegrant such as MS and a surfactant such as SLS in matrix granules or tablets can improve drug release especially from a gel-forming polymeric material such as the polyacrylic acid polymers. MS was found to perform better than SLS as a drug release enhancer from the carbopol 941 capsule matrix.

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