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FORMULATION AND EVALUATION OF CONTROLLED RELEASE AMINOPHYLLINE MATRIX TABLETS

Ahmed Shaker Ali*, Adel Mohamed Ali** and Fergany Abd El-Hameed Mohammed*

**Department of Pharmaceutics, Faculty of Pharmacy Assiut University, Assiut-Egypt*
***Faculty of Pharmacy Al-Isra University, Amman-Jordan*

تم فى هذا البحث استخدام ثلاث مواد لتحضير اقراص منضبطة الإنطلاق تحتوى على ٢٠٠ مجم امينوفللين وهذه المواد هى: هيدروكسى بروبيل ميثيل السليولوز وكاربوكسى ميثيل سليولوز الصوديوم وزلال البيض. وقد تم تقويم هذه الأقراص من حيث خواصها الطبيعية وسرعة انطلاق الدواء منها. ومن نتائج هذا البحث تبين أن جميع الأقراص المحضرة لها صفات فيزيائية مقبولة. وقد وجد أن سرعة انطلاق الدواء تختلف حسب تركيب كل قرص. واتضح من النتائج أيضا أنه لا يوجد اختلاف واضح بين سرعة انطلاق الدواء من الأقراص التى تحتوى على هيدروكسى بروبيل ميثيل اللسليولوز وتلك التى تحتوى على زلال البيض ، وأن أبطأ انطلاق للدواء كان من الأقراص التى حضرت بواسطة كربوكسى ميثيل سليولوز الصوديوم سواء بمفرده أو مع أى من هيدروكسى بروبيل ميثيل السليولوز أو زلال البيض. وأيضا اتضح أن ميكانيكية انطلاق الدواء من الأقراص المحضرة تتبع معادلة "هيجوشى" للانتشار.

Three matrix excipients namely: Hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl cellulose (NaCMC) and egg albumin (EA) were utilized for the preparation of controlled release matrix tablets containing 200 mg of aminophylline. The prepared tablets were evaluated with respect to physical parameters and dissolution rate. All formulations showed acceptable physical parameters. The release rate was variable depending on the composition of the matrix tablet. There was no significant difference between the dissolution rates of the matrix tablets prepared with HPMC or EA. The slowest release rate was observed in case of the matrix tablets prepared using NaCMC either alone or in combination with either HPMC or EA. The dissolution data of the drug from most matrix tablets formulation were fitted to Higuchi diffusion model.

INTRODUCTION

The principle of drug diffusion through a matrix has been widely applied to the preparation of sustained release tablets.[1-15] Two types of materials are used for the matrix carrier: a hydrophobic material such as wax or ethylcellulose for an insoluble matrix carrier, and a water soluble hydrophilic material such as cellulose derivative for a gel-forming matrix carrier. Hydroxypropylmethyl-cellulose and carboxymethy-cellulose are the most commonly used cellulose polymers for this purpose.[16-21] Preparation of matrix tablets by direct compression has been gaining increased attention because of the simple and low-cost manufacturing process.[22] Egg albumin is a biodegradable drug carrier which has been used in solid dispersion and microencapsulation processes.[23,24] It has been also recently used for the preparation of controlled matrix tablets[25] The aim of the present work was to study the utility of using egg albumin either alone or in combination with other known hydrophilic polymers for the formulation of controlled release aminophylline matrix tablets.

EXPERIMENTAL

Materials

- Hydroxypropylmethyl cellulose [HPMC] (Methocel K100 M, Ltd., Orpington, UK).

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- Sodium carboxymethylcellulose [Na CMC] (BDH chemicals Ltd., Poole, UK).
- Egg albumin [EA] (Ovalbumin, Ovosec, Spain).
- Microcrystalline cellulose, mean particle size 98 μm (Avicil PH 102, FMC Corporation, USA).
- Aminophylline B.P. (a gift from the United Pharmaceutical Manufacturing, Amman, Jordan).
- All other materials were of analytical grade.

Methods

Preparation of tablets

The tablet formulations of aminophylline are listed in Table 1. All materials were passed through 125 μm sieve and retained on 90 μm sieve. The powders were mixed together for 10 min. in a high speed mixer (Erweka Turbula system S27, Germany). The tablets were prepared by direct compression using single flat-faced punch (13 mm diameter) [Erweka - AR 400 E, Germany]. The machine was adjusted to produce tablets of 100-120 N hardness.

Evaluation of the prepared tablets

- Uniformity of weight and drug content were determined according to USP/NF 23 procedures
- Hardness and friability were determined using Erweka hardness tester (TBH 30) and Erweka friabilator (TAR) respectively.
- Tablet disintegration was performed at 37°C in simulated gastric fluid without enzyme using a Pharma Test (PTZ -Italy) disintegration tester.

Dissolution studies

The dissolution rate of the drug from different matrix tablets were determined according to USP paddle method using Hanson dissolution test station (Hanson Research Co. USA). The dissolution medium was 900 ml of pH 1.2 HCl solution or phosphate buffer pH 6.8 maintained at 37°C and the stirring rate was 100 rpm. Samples of 5 ml were periodically withdrawn and replaced with an equal volume of the dissolution medium equilibrated at 37°C. The drug concentration in each filtered sample (0.45 μm Millipore filter) was determined by measuring the absorbance at 271 nm using a (Shimadzu UV/Vis 1205). None of the excipients interfered with the determination. Dissolution tests were carried out on six tablets and mean values were reported.

RESULTS AND DISCUSSION

Physical properties

Table 2 shows the physical properties of the prepared aminophylline matrix tablets. It could

Table 1: Formulation of different matrix tablets of aminophylline.

Formula appriviation	Composition of each tablet (mg)					
	Amino-phylline	HPMC	egg albumin	NaCMC	Avicel PH101	Talc
HPMC	200	150	-	-	46	4
EA	200	-	150	-	46	4
NaCMC	200	-	-	150	46	4
HPMC+EA	200	75	75	-	46	4
HPMC+NaCMC	200	75	-	75	46	4
EA+NaCMC	200	-	75	75	46	4

Table 2: Physical characteristics of aminophylline matrix tablets.

Formulation	Weight (mg) mean (C.V.%)	Drug content mg mean (C.V.%)	Hardness kg mean (C.V.%)	Disintegration time	Friability %
HPMC	401 (1.81)	199.6 (1.96)	12.19 (4.23)	>12 hr	0.437
EA	398 (2.16)	201.4 (1.74)	9.54 (2.64)	>12 hr	0.413
NaCMC	402 (2.67)	200.3 (1.51)	10.83 (2.84)	>12 hr	0.685
HPMC+EA	403 (1.93)	198.9 (2.15)	10.03 (2.74)	>12 hr	0.611
HPMC+NaCMC	398 (2.42)	200.7 (1.85)	11.44 (3.52)	>12 hr	0.563
EA+NaCMC	399 (2.06)	199.3 (2.23)	10.12 (2.06)	>12 hr	0.250

be observed that all the prepared tablets fulfill the USP/NF 23 requirements for uniformity of weight, drug content and friability. These tablets showed acceptable hardness and uniformity of thickness and diameter values. Tablets containing HPMC showed better crushing strength than those including NaCMC or EA. The disintegration time values for all tested formulations exceeds 12 hr.

Release characteristics

The process of release of drugs from a hydrophilic polymer-drug matrix is a complex one. This involves water penetration into the dry matrix, hydration and gel formation of the polymer, diffusion of the dissolved drug in the resultant gel and erosion of the resultant gel layer. The modeling of these processes is further complicated by the swelling of the system. The mechanism of drug release from compressed polymer-drug matrix could be represented as follows

$$\text{Drug-polymer matrix} \xrightarrow{\text{dissolution medium}} \text{Swollen gel} + \text{Gel - erosion}$$

Swollen gel reduces drug release; Gel - erosion increases drug release

Thus the rate of formation of the gel layer, the thickness of this layer and the rate of erosion would influence the drug release pattern.[26]

Figure 1 shows the dissolution profiles of aminophylline from different matrix tablets at pH 1.2 dissolution medium. It was observed that the release of aminophylline from the matrix tablets of EA, HPMC or combination of EA+HPMC followed a biphasic pattern i.e: an initial relatively fast dissolution phase followed by a slower dissolution phase. Concerning the initial phase, the dissolution of the drug from the matrix tablets of either EA or EA+HPMC proceeded faster than that from HPMC matrix tablets. This may be due to the slower swelling nature of EA compared to HPMC {visually observed}. The biphasic dissolution pattern could be explained in view of the depletion of the outer layer of the matrix from the drug and hence increase of the diffusion layer thickness.

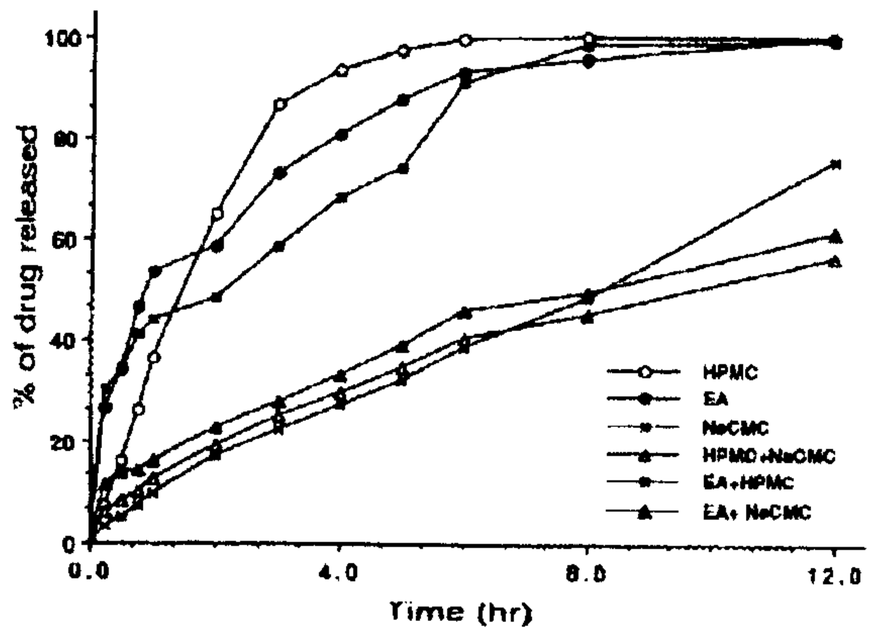

Fig. 1: Dissolution profiles of aminophylline from different matrix tablets in pH 1.2 solution.

It could be also noted that the matrix tablets prepared with NaCMC or combination of NaCMC with either EA or HMPC gave a significantly slower dissolution rate of aminophylline. This can be explained as follows: when the matrix tablets comes into contact with water it swells and forms a porous gel barrier. The pores near the surface of matrix are filled with water and the drug release is initially controlled by the dissolution of the drug in the water filled pores and then by diffusion.[27,28]

Dissolution of NaCMC resulted in formation of a highly viscous solution in the pores which in turn slowed down the drug release by formation of an additional gel-like barrier.

The dissolution profiles of aminophylline from different matrix tablets at pH 6.8 are presented in Figure 2. The dissolution profiles of the drug from the different matrix formulation is quite similar to those observed in the case of dissolution in acidic medium. However, the dissolution rate of the drug at pH 6.8 in case of the matrix tablets prepared with NaCMC or NaCMC with either EA or HMPC was relatively faster than that at pH 1.2. This may be due to the slower erosion of NaCMC gel-layer barrier in acidic medium.

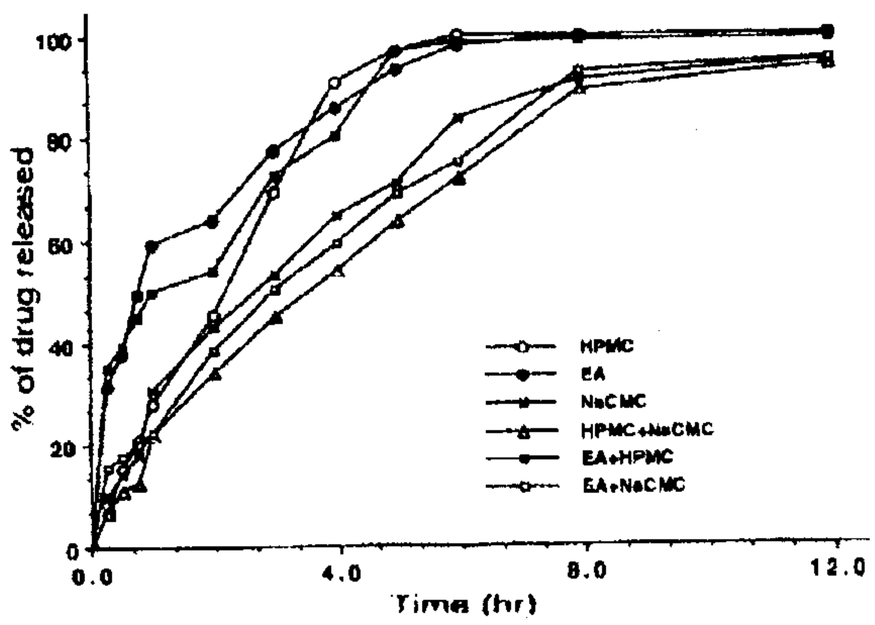

Fig. 2: Dissolution profiles of aminophylline from different matrix tablets in pH 6.8 phosphate buffer.

Kinetic of drug release

The equation originally derived by Higuchi[29] and modified by Takenaka *et al.*[30] was used to predict the release of aminophylline from matrix tablets. The equation may be simply written as:

$$Q = K_H t^{1/2}$$

where Q is the percent of drug released after time "t". Zero order as well as first order models were also applied. The release data were fitted to these models according to least square regression analysis by using P. C program {Cricket-graph Ver 1.2, Apple MaC}. The results of analysis are presented in Tables 3 and 4. It was noted that the release of aminophylline from matrix tablets prepared with NaCMC at pH 1.2 followed zero order kinetic. The release data of the drug from all other formulations were best fitted to Higuchi diffusion model as indicated by the highest regression coefficient "r". These results are in agreement with those reported by Abdel-Rahman *et al.*[31] A biphasic pattern was confirmed with some formulations.

Table 3: Release kinetics of aminophylline from differetn matrix tablet formulations at pH 1.2.

Formulation	Zero order		Higuchi diffusion model				First order	
			1st stage		2nd stage			
	r	k %/h	r	K_H %/√h	r	K_H %/√h	r	Khr^{-1} x10
HPMC	0.959	9.87	0.991	7.55	0.997	1.72	-0.988	7.71
EA	0.929	5.89	0.979	5.28	0.972	2.18	-0.953	3.69
NaCMC	0.998	5.98	0.991	2.02	0.983	4.15	-0.973	1.06
HPMC+EA	0.951	6.71	0.992	3.94	--	--	-0.915	3.18
HPMC+NaCMC	0.983	5.37	0.991	2.51	--	--	-0.984	0.66
EA+NaCMC	0.921	7.20	0.971	2.27	--	--	-0.942	2.86

Table 4: Release kinetics of aminophylline from differetn matrix tablet formulations at pH 6.8.

Formulation	Zero order		Higuchi diffusion model				First order	
			1st stage		2nd stage			
	r	k %/h	r	K_H %/√h	r	K_H %/√h	r	Khr^{-1} x10
HPMC	0.946	22.44	0.965	5.22	0.966	7.17	-0.961	5.56
EA	0.861	20.56	0.972	5.28	0.999	3.25	-0.933	3.39
NaCMC	0.980	13.50	0.982	4.24	---	---	-0.967	2.16
HPMC+EA	0.844	17.53	0.958	4.76	0.968	6.299	-0.943	4.21
HPMC+NaCMC	0.985	11.76	0.988	4.03	0.890	2.620	0.946	2.74
EA+NaCMC	0.982	11.71	0.993	4.06	0.910	2.840	-0.989	3.36

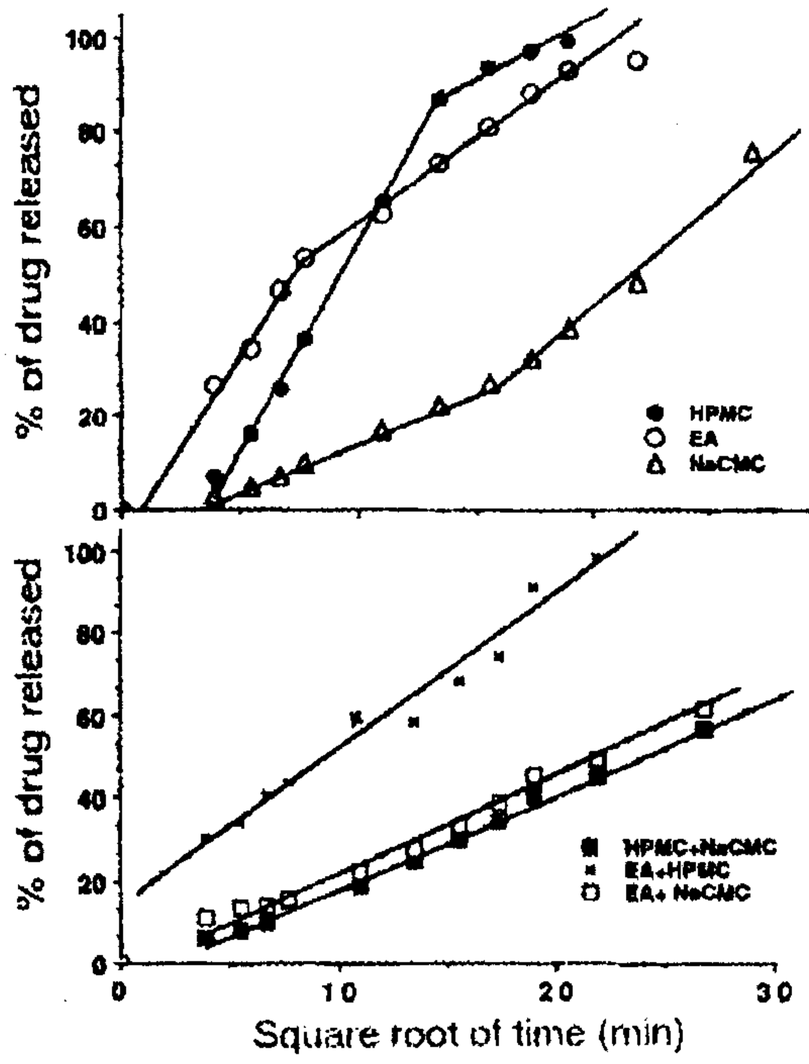

Fig. 3: Higuchi plot of aminophylline release data from the matrix tablets in pH 1.2 solution.

The Higuchi plot of aminophylline release data from different matrix tablets are shown in Figure 3. The release of the drug from the matrix tablets prepared with either HPMC or EA yielded two intersected lines. The release of the drug in the second phase proceeded at a rate which was slower than that of the first phase. This behavior was explained earlier. These results are in agreement with those reported by Aly and Megawa.[32] In the case of the matrix tablet of NaCMC a biphasic pattern was obtained. The drug release was faster in the second phase compared to the first phase. This may be due to erosion of the NaCMC gel-layer barrier. The initial retarding effect (lag time of about 2 hr) which can be observed in case of NaCMC containing formulations before reaching the steady state may be attributed to the slow erosion of gel barrier.

Conclusion

Controlled release matrix tablets of aminophylline were successfully prepared using EA, HPMC and NaCMC. The prepared tablets showed acceptable physical parameters according to USP/NF 23. All formulations showed controlled release profiles of the drug. There was no significant difference between HPMC and EA matrix tablets with respect to drug release rates. Incorporation of NaCMC in the matrix tablets significantly slowed down the drug release rate. The drug release kinetics was according to Higuchi diffusion model from all formulations except that of NaCMC where the drug release followed zero-order diffusion model.

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