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Application of Evangel® as Drug Release Retardant in Aminophylline Floating Tablet Formulations

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ABSTRACT

Evangel®, a pregelatinized starch was used in the formulation of aminophylline floating tablets and evaluated by *in vitro* methods to verify its usefulness as drug release retardant. Varying concentrations of the polymer were used alongside sodium bicarbonate and citric acid as carbon dioxide generating agents to prepare tablets by wet granulation technique. The floating tablets obtained were evaluated for density, *in-vitro* buoyancy and general tablet properties. Results showed that the tablet properties were satisfactory except batch Bthat had drug contents below the pharmacopeial standard.Combinations of Evangel® (in the range of 50 – 100 mg), sodium bicarbonate (100 - 150 mg) and citric acid (50 mg) was found to achieve optimum *in-vitro* buoyancy. The release of aminophylline from the floating tablet formulation followed a zero order kinetic model and is independent of drug concentration.

KEYWORDS: Evangel, drug release, retardant, aminophylline, floating tablet.

INTRODUCTION

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance, flexibility in formulation, etc. In the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate [1]. Gastric emptying of dosage forms is an extremely variable process and the ability to prolong and control emptying time is a valuable attribute of dosage forms which are intended to reside in the stomach for a longer period of time than conventional dosage forms. Such variability in controlling drug release arises from difficulties in confining the dosage form at the desired area of the gastrointestinal tract [2, 3]. To overcome this physiological problem, attempts are being made to develop controlled drug delivery systems that can provide therapeutically effective plasma levels of the drug for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration, as well as achieving steady state by delivering drug in a controlled and reproducible manner. Gastro-retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in high pH environments. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of muco-adhesion, floatation, sedimentation, expansion, etc. Based on these approaches, floating drug delivery systems seem to be the promising delivery systems for controlled release of drugs [4, 5].

Floating drug delivery systems (FDDS) or dynamically controlled systems (DCS) are low-density systems (LDS) that have sufficient buoyancy to float over the gastric contents (GC) and remain buoyant in the stomach without yielding to the gastric emptying mechanisms for a prolonged

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period of time. This results in an increased gastric retention time (GRT) and a better control of fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres [2]. The present study seeks to formulate and evaluate floating tablets of aminophylline using Evangel®, a pre-gelatinized starch and biodegradable polymer as the drug release retardant. Aminophylline is the ethylenediamine salt of theophylline which acts as a bronchodilator. It is rapidly absorbed from the upper part of the gastrointestinal tract (GIT). Retention of the drug in the stomach will be beneficial to patients who may need repeated administration of the bronchodilator at short intervals. The development of an optimal modified-release preparation is necessary to decrease the dosing frequency while maintaining stable plasma concentrations. Based on the mechanism of buoyancy, the effervescent approach was used in the development of floating tablets. The effervescent approach involves the use of gas generating agents, sodium bicarbonate and citric acid to produce carbon dioxide gas in an aqueous dissolution medium. The gas generated is trapped and protected within the gel formed by the hydration of the polymer, thereby decreasing the density of the tablet. Reduction of density of the system causes it to float in the fluid.

MATERIALS AND METHODS

Materials

The following materials were used as procured from their manufacturers: aminophylline, citric acid (Merck), sodium bicarbonate, lactose, talc, magnesium stearate (BDH), polyvinylpyrollidone, PVP (K-30) and Evangel® (Evans Pharmaceuticals).

Methods

Preparation of floating tablets of aminophylline

Tablets were prepared by the conventional wet granulation method according to the composition in Table 1. Aminophylline, Evangel®, sodium bicarbonate, citric acid and lactose were blended to uniformity. The mix was granulated with a solution of PVP in sufficient isopropyl alcohol as binder. The wet mass was passed through a 1.7 mm stainless steel sieve (Endecott, England). The wet granules were dried in a hot air oven (Memmert, England) at 60^{o}C for 1h. The dry mass of the respective batches were passed through 1.0 mm stainless steel sieve and later lubricated with talc and magnesium stearate and compressed into tablets at 20 N using F3 single punch tablet press (Manesty, England) for a targeted mean tablet weight of 500 mg.

Evaluation of tablet properties

The British Pharmacopeia method [6] was used for the determination of uniformity of tablet weight, crushing strength, friability and disintegration time.

Active content uniformity

Twenty tablets taken from each batch were weighed together; their mean was calculated and they were later pulverized together. An amount of the powder equivalent to the mean of the twenty tablets for each batch was dissolved in 0.1N HCl, shaken vigorously and made up to 100 ml. The mixture was filtered. A 1ml volume of the filtrate was made up to 100 ml. The absorbance was measured at 272 nm using a UV-spectrophotometer (Jenway, Europe). The amount of aminophylline in the sample was estimated from a standard curve for aminophylline.

Table 1: Composition of various batches of floating tablets of aminophylline

Ingredient	Amount (mg)		
	Batch A	Batch B	Batch C
Aminophylline	200.0	200.0	200.0
Evangel®	50.0	100.0	150.0
Sodium bicarbonate	150.0	100.0	50.0
Citric acid	50.0	50.0	50.0
Lactose	17.5	17.5	17.5
PVP (K-30)	25.0	25.0	25.0
Talc	5.0	5.0	5.0
Magnesium stearate	2.5	2.5	2.5
Total	500	500	500

Tablet thickness and diameter

The thickness as well as the diameter of ten tablets from each batch was determined using micrometer screw gauge. The mean values as well as the standard deviation were calculated for each batch of tablets.

Tablet density

Three tablets were selected at random from each batch and their densities were determined using the relationship:

Density = Mass / Volume……..…….. (1)

The weight of each tablet was determined. Their respective volumes were determined in 50 ml Sunola soya oilplaced in a graduated measuring cylinder. The initial volume of oil was noted as V_o. The respective tablets were carefully placed in the cylinder until the tablets were completely immersed in the oil. The new level of oil was noted as V_1. The volume of each tablet was calculated as $V_1 - V_o$. The weight of each tablet obtained was divided by its corresponding tablet volume to obtain the density of each tablet.

***In-vitro* buoyancy (floating test)**

This was carried out using the method described by Rosa *et al* [7]. Each tablet was in turn placed in a 100 ml beaker containing 100 ml 0.1N HCl. The time taken for the tablet to rise to the surface and float was noted as the floating lag time. The duration of time the dosage form constantly remained on the surface of the medium was taken as the total floating time.

***In - vitro* drug release studies**

The static basket magnetic stirrer assembly was used to carry out the *in-vitro* drug release studies. A 300ml dissolution medium of 0.1N HCl was maintained at 37^{o}C and constantly stirred at 50 rpm. The tablet was placed inside the dissolution vessel. At 5 min intervals, a 5 ml of sample was withdrawn. After each withdrawal, the volume of the dissolution medium was adjusted to 300 ml with fresh dissolution medium. Each withdrawn sample was filtered and diluted to a suitable concentration with 0.1N HCl. The absorbance of each diluted sample was measured at 272 nm using a UV-spectrophotometer (Jenway, Europe). The data obtained from the *in-vitro* release studies were also fitted to zero order [8, 9], Higuchi [10] and Korsmeyer-Peppas models [11] to determine the possible release mechanism of the drug from the floating tablet.

RESULTS AND DISCUSSION

Evaluation of tablet properties

Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, density, drug content uniformity, hardness and friability in the case of solid dosage forms [12]. The properties of the different batches of aminophyline tablets, based on the above parameters, are presented in Table 2. The British Pharmacopeia specifies acceptable absolute drug content limits of 90-110 %. This is equivalent to 180 – 220 mg of aminophylline in the current preparations. The aminophylline contents obtained from the tablets showed that batch B fell somewhat below the minimum acceptable limit. Considering tablet hardness or crushing strength, a value of 4 kg (about 39 N) is usually considered to be the minimum for satisfactory tablets. The results of this parameter for all the batches of aminophyline floating tablets tested were above the minimum value. The tablet friability is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping [13]. A friability of less than 1 % is considered acceptable especially for tablets produced by wet granulation. Tablets produced by direct compression can have values above unity [14]. From the results of this test, values below 1 % were obtained for all the batches of tablets evaluated. For most uncoated tablets, the British Pharmacopeia requires that the tablet disintegrate in 15 min while for coated tablets; up to 2 hours may be tolerated [6]. None of the batches of tablets studied disintegrated in less than 15 min (Table 3). Higher values of disintegration time were obtained using 0.1N HCl when compared to distilled water as disintegrating medium. These values, however, are acceptable since the tablets were designed to offer prolonged release. This effect is also expected, considering the high concentrations of the gelling polymer, Evangel®.

***In vitro* buoyancy (floating) test**

The results of this test are presented in Table 3. It showed that the floating lag time was in the range of 8.23 - 16.40 min while the total floating time was within 13.02 - 15.90 min. Floating lag time and total floating time decreased with increasing concentration of the release retardant (Figure 1). This indicates that lower concentrations of Evangel® may favour prolonged floatation of the tablet, thus prolonging the drug release. The density of the tablets was in the range of 1.10 - 1.21 g/cm^3. The tablet needs to have a density which is less than that of the gastric content (about 1.004g/cm^3) for it to float [12, 15]. Although the densities obtained for tablets formulated in this work seem a little above those of the natural gastric content, it is noted that the air trapped in the swollen polymer confers buoyancy to these dosage forms. However, it was obvious in this study that the density of the tablet reduced gradually with time until the tablet attained a density less than that of the dissolution medium and finally floated on the surface of the liquid. This is attributable to the gradual reactions

between sodium bicarbonate, citric acid and water leading to an accumulation of carbon dioxide entrapped within the matrix of the tablets. Evangel®, due to its gelling nature contributed substantially to the entrapment of the gas generated. This would invariably cause a drop in density of the tablets in the aqueous acid liquid.

In vitro release studies

The release profile of the drug is presented in Figure 2. Up to 50% (T_{50}) of aminophylline for all the batches dissolved in less than 20 min.Above 75% of the drug dissolved in 25 min for batches B and C. This conforms to the USP specification for uncoated or plain aminophylline tablet (16). The assessment of the release kinetics shows that the drug release from the different batches of the floating tablets was predominated by zero order kinetic model (Table 4) indicating that the release pattern was independent of the concentration of the drug. Mechanism of drug release was found to be anomalous for batches A and B while those of batch C followed a diffusion controlled mechanism (17).

CONCLUSION

The respective batches of preparations released up to 50% (T_{50}) of aminophylline in the release studies of floating tablets of aminophylline prepared with Evangel® as drug release retardant. The *in vitro* release kinetics followed zero order with anomalous release mechanism found for batches A and B and a diffusion controlled mechanism for batch C. An optimal *in vitro* buoyancy of this formulation may be achieved if Evangel® is used in concentrations lower than 100 mg alongside concentrations of sodium bicarbonate less than 150 mg and 50 mg or less of citric acid as carbon dioxidegenerating agents. When used in optimal concentrations, Evangel® will not only produce a drug release retarding effect, but will also enhance floatation in the presence of gas-generating excipients. This has been empirically demonstrated in the present study using aminophylline floating tablets.

Table 2: Physical properties of tablets of different batches

Tablet Batch	Tablet weight (mg)	Drug content (mg)	Hardness (kgf)	Friability (%)	Thickness (cm)	Diameter (cm)
A	491.1±0.01	185	5.2±0.16	0.22	0.41±0.01	1.31±0.01
B	489.0±0.02	136	5.8±0.14	0.16	0.40±0.01	1.31±0.01
C	487.6±0.02	192	5.4±0.21	0.77	0.40±0.01	1.31±0.01

Table 3: Floating properties for different batches of formulated tablets

Tablet batch	Density (g/cm^3)	Disintegration time (min)		Floating lag time (min)	Total floating time (min)
		0.1N HCl	Distilled water		
A	1.21	32.10	26.24	16.40	15.90
B	1.18	26.50	19.02	10.70	15.80
C	1.10	21.25	16.40	8.23	13.02

Table 4: Kinetic parameters for different batches of formulated tablets

Batch	Kinetic order	Slope (n)	Correlation (r^2)
A	Zero	4.7444	**0.9907**
	Higuchi	20.05	0.9058
	Korsmeyer-Peppas	0.63	0.9696
B	Zero	6.0724	**0.9951**
	Higuchi	25.48	0.8722
	Korsmeyer-Peppas	0.33	0.2555
C	Zero	5.5355	**0.9457**
	Higuchi	23.78	0.9362
	Korsmeyer-Peppas	0.52	0.8832

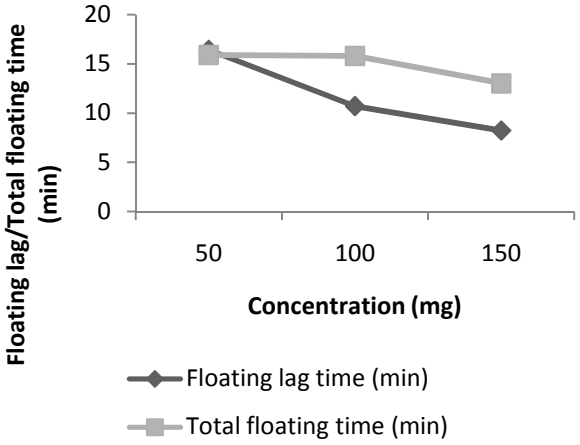

Figure 1: Effect of concentration of release retardant on the floating lag time and total floating time of tablets.

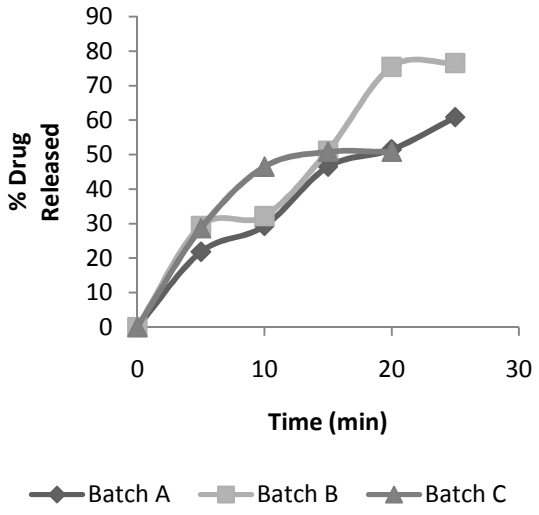

Figure 2: *In-vitro* release profile of aminophyline from different batches of floating tablets

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