FORMULATION OF SUSTAINED - RELEASE THEOPHYLLINE TABLETS USING MUCUNA GUM AS A HYDROPHILIC RETARDANT

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ABSTRACT

Sustained-release theophylline tablets were prepared using mucuna gum as a hydrophilic polymer. The gum was found to prolong drug release from the product.

The release rate was dependent on the gelation rate with resultant dissolution and diffusion of the active ingredient as was observed from the dissolution and liquid penetration tests carried out. The release rate was dependent on the concentration of the gum in the tablets.

Keywords: Sustained - release, theophylline, mucuna gum.

INTRODUCTION

Sustained action dosage forms are formulated to provide an initial dose of the medicament with subsequent doses released slowly to maintain a therapeutic response over a period of several hours, usually ten to twelve hours (1).

Various materials are available for the formulation of sustained - release dosage of products. Use has been made of hydrophilic polymers most of which are cellulose derivatives (2-4). Many tropical gums exist whose property approximates those of the cellulose derivatives. One of such gums is mucuna gum.

Mucuna gum is a polysaecharede obtained from the seeds of *Mucuna flagillepes* (Fam. Papilionaceae). The gum has been evaluated in the formulation of emulsions and suspensions (5) and as an excipent in wet processed tablet (6).

MATERIALS AND METHODS

1. Materials

The following materials were used as procured without further purification. Acetone, lactose, sodium hydroxide (May and Baker), magnesium stearate, calcium chloride, theophylline (Merck) and hydrochloric acid (BDH).

2. Methods

2.1 Preparation of mucuna gum

The tough, dry seed coats of the seeds from *Mucuna flagillepes* were removed and the cotyledons placed in Sorensen's plycine buffer (pH 3.6) and autoclaved at 121°C for 15 min. Such heat treatment is believed to inactivate some autoxidation enhancing enzymes usually present in seeds and which could lead to darkening of seed gums (5). The cotyledons were thereafter air dried and pulverised in a hammer mill and screened through a 0.250mm sieve. The powder material was dispersed in the Sorensen's glycine buffer up to a concentration of 10% w/v and allowed to hydrate for 24 h.

The resulting gelatinous material was passed through a muslin cloth to remove any incompletely hydrated masses. The water - soluble fraction retained in filtrate was precipitated with acetone and the resulting precipitate was collected on a Buchner funnel by means of suction from a vacuum pump. The cake was broken up and dried in vacuum desiccator for 2 weeks. The dried material was pulverised using an end runner mill, passed through a 0.075mm mesh sieve and stored in powder bottles until used.

2.2 Formulation of Sustained - Release Tablets

Tablets were prepared from lactose granules, theophylline and various quantities of the gum as shown in Table 1. Magnesium stearate was used as the lubricant.

Table 1. Quantities employed for production of sustained - release tablets

Substance	Quantities employed (%)		
	Batch I	Batch II	Batch III
Theophylline	20	20	20
Mucuna gum	30	40	50
Lactose granules	49	39	29
Magnesium stearate	1	1	1

The tablets were directly compressed using a single punch tabletting machine fitted with 0.95mm flat faced punches at a constant pressure setting marked 50 units on the machine (Model Fz, Manesty).

2.3 Control Tests on the Tablets

2.3.1 Uniformity of Weight

Twenty tablets were selected at random from each batch of tablets and weighed on a torsion balance (model 0/437216, White Electronic). The mean tablet weight was calculated. The tablets were then weighed individually and the weights recorded. Using this data the coefficient of variation and standard deviation were calculated.

2.3.2 Tablet Friability

Ten tablets were randomly selected from each batch and weighed. The tablets were then subjected to tumbling stress in a friabilator (model TAR, Erweka) set to rotate at 25 rpm for 4 min. The tablets were then removed from the friabilator, dedusted and reweighed. The mean less in weight and percentage friability were then calculated.

2.3.3 Tablet Hardness

Ten tablets were selected at random from each batch. The hardness of each tablet was determined using an automatic hardness tester (model TBH-28, Erweka).

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2.3.4 **Disintegration Time**

Five tablets were randomly picked from each batch and each tablet was placed in a disintegration chamber of a disintegration test assembly (model ZT4, Erweka). The time taken for each tablet to break down into particles and pass into the disintegration medium (0.IN HC1) was recorded. The mean time for five tablets was computed.

2.3.5 **Liquid Penetration Test**

Ten tablets were placed in a dissolution test unit. At thirty-minute intervals, one tablet was removed, the gelled part was scraped away using a spatula and the dry part crushed in order to determine the drug content. The powdered material was extracted with 10-ml aliquots of 0.IN HCl and each extraction passed through a filter paper (Whatman, No. 1). The filtrate was appropriately diluted and the absorbance determined using a spectrophotometer (model SP6-450 UV/vis, Pye Unicam). The same procedure was repeated for the remaining nine tablets at 30 min intervals.

2.3.5 **Dissolution Rate**

A USP dissolution rate test assembly was used. The dissolution chamber contained 1000-ml of dissolution medium (0.IN HCl) maintained at 37 ± 0.5°C. A basket made of stainless steel material was flitted to a rotor set to rotate at 100 r.p.m. and during each dissolution test run, a tablet was placed in the basket. At 30 min intervals 5ml of the dissolution medium was withdrawn and assayed for theophylline at 272mm in a spectrophotometer (model SP6-450 UV/vis). Each 5ml aliquot withdrawn was replaced with equivalent volume of dissolution medium maintained at the same temperature. Replicate tests were done and each point on the dissolution curve is a mean of these two values.

RESULTS AND DISCUSSION

Table II shows some of the physical properties of the tablets produced from mucuna gum as the retardant. Although sustained - release tablets do not have to fall within the limits of disintegration and dissolution times specified by official compendia, some determinants of dissolution from tablets such as hardness have to be carefully controlled.

Table II. Some physical properties of the sustained - release tablets formulated with mucuna gum.

Property	Gum Concentration					
	30% "/w		40% "/w		50% "/w	
Friability (%)	0.90		0.70		0.68	
SD	+0.003	±	0.06	±	0.004	
CV(%)	0.14		2.42		0.16	
Hardness (Kgf)	4.18		4.58		5.04	
SD	0.0084	±	0.0037	±	0.0012	
CV (%)	0.021		0.080		0.023	
Weight (mg)	250		251		250	
SD	0.688	±	1.486	±	0.794	
CV (%)	0.317		0.592		0.275	
Disintegration time						
(min)	357		415		474	
SD	1.44	±	1.92	±	2.95	
CV (%)	0.39		4.62		0.624	

The friability of the tablets was dependent on the concentration of the gums with the higher concentration of the gum having lower friability. This was also true of the hardness values. Hardness and friability tests are useful for predicting the resistance of tablets to abrasion and shock during handling and transport. Hardness is a function of the die fill. In this study, the mucuna gum is added in form of fine dry powder (particle size 0.75mm) and acts as a dry binder to help in the compression of the lactose granules. The higher hardness values obtained with 50% "/w concentration of the gum may be associated with the greater fines imparted to the lactose granules.

The small standard deviabins and coefficients of variation in the weight uniformity tests showed that the weights were uniform for all three batches.

The disintegration times were long ranging from 357 to 474 min. Such long disintegration times are desirable in sustained-release tablets, since disintegration is one of the rate - limiting steps in the release and absorption of a drug from a drug product. During the disintegration a visual swelling of the tablet could be observed. This gelatinization process could be visually observed and at the end of the disintegration test the mucuna gum did not pass completely into solution.

Figure 1 shows the dissolution profiles of theophylline from the sustained-release products in 0.1N HC1. The quantity of drug released was dependent on the concentration of the gums as well as time. As time progressed, more of the drug was released. The release curve did not reach a maximum during which the dissolution test was carried out showing that equilibrium was not attained.

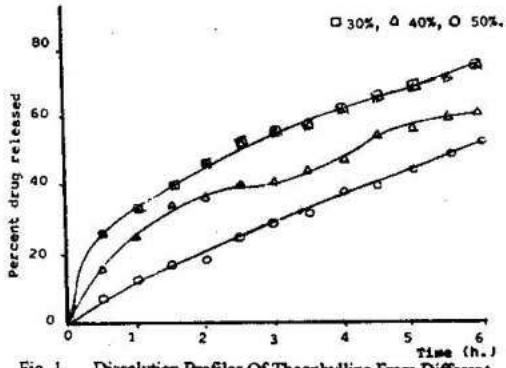

Fig. 1 Dissolution Profiles Of Theophylline From Different Batches Of Sustained – Release Tables Containing Pucana Gum.

From the graphs the time for ninety percent of the drug to be released (t_{90}) could not be reached for some of the batches studied. Similarly, the time for fifty percent of the drug to be released (t_{50}) was prolonged for some of the batches. The t_{50} ranged from 1½ h for the batch with 30% "/w concentration to over 3 h for the batch with 50% "/w concentration of the gum.

In a system that gels and swells during disintegration and dissolution, the release of the embedded drug may be due to liquid permeation and diffusion of the dissolved drug (7). If the liquid permeation is the major determinant of drug release then the percentage not released should be linear when plotted as a function of the percentage of the drug in the unwetted core.

Figure 2 shows the plot of drug not released as a function of the drug in the unpermeated portion (unwetted

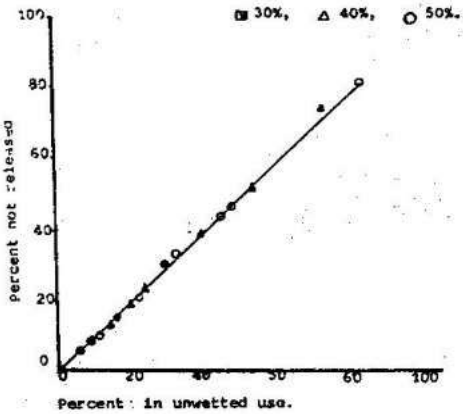

Fig. 2 The Percent Of Theophylline In Unwetted Use Plotted AsA Function Of The Percentage Of Unreleased Drug.

core). A linear relationship was observed showing this factor to be the major determinant of drug released. This is only possible under perfect sink condition whereby the drug in the gelled layer is dissolved and diffuses out immediately. The rate of gellation and diffusion would be dependent on the nature of the polymer as well as the incorporated drug (8,9).

Figure 3 shows the percentage of drug not released plotted as function of time. Similarly, the percentage of the drug in the unwetted core is also shown in that figure. The percentage not released and percentage of drug in the unwetted core decreased progressively with time. This was dependent on the concentration of the gum in each batch. Figure 4 shows the logarithmic transformation of figure 3 according to the first order release rate equation:

$$\text{Log. } A = \text{Log } A_o - \frac{Kt}{2.303} \quad \ldots\ldots \text{Eq. 4}$$

where A is the quantity of drug remaining to be released at time, t and A_o is the initial content of the active ingredient in the drug product; while K is a release rate constant.

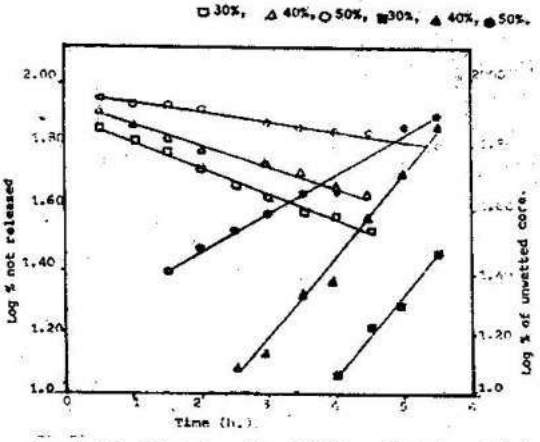

Fig. 3/4 Plot Of The Logarithm Of % Drug Not Released And Log. % Unwetted Against Time

From Figure 4, it is clear that the rate of drug release does not tally with the rate of liquid permeation. This may be associated with the solubility of the incorporated drug, theophylline. Thus the rate of drug released. The delay may be associated with the time taken for the liquid to penetrate into the tablet, and for the dissolution of the drug to take place before diffusion outwards.

Figure 5 shows the plot of the release of theophylline according to the Higuchi porous diffusion law (7). The plots obtained were linear which shows that diffusion is the major mechanism by which the drug is released after liquid permeation and dissolution.

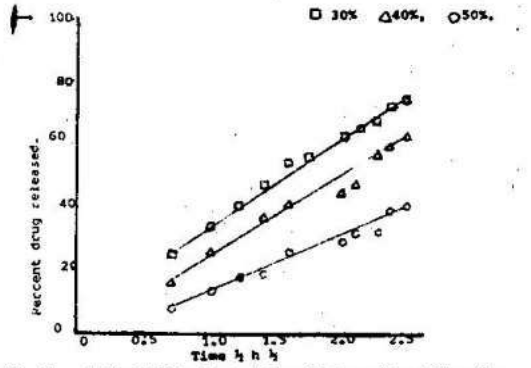

Fig. 5 A Plot Of The Percent Drug Released As A Function Of The Square Root Of Time.

Conclusion

Mucuna gum could be used as a dry binder in the formulation of sustained - release dosage forms of theophylline. The t_{50} for the release of the incorporated drug were long. The t_{90} could not be attained in 6 h. The quantity of drug released was dependent on the concentration of the gum in the system.

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