PROLONGED RELEASE FORMULATION WITH TAPIOCA

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SUMMARY

Drug release from lactose and tapioca granules have been studied. With granules containing 76% of the drug (paracetamol) lactose released 100% of its content of drug in 30 mins whilst tapioca released a similar amount of the drug in 15 mins. Release over longer periods was obtained when the contents of tapioca in the granules was increased whilst decreasing the content of the drug. Fast release from lactose granules was associated with its rapid dissolution in the leaching fluid whilst the slower release from tapioca granules was associated with intra-granular cohesiveness preventing disintegration to smaller particles. The release was dissolution controlled and was consistent with a first order kinetic. It is suggested that the encapsulation of both types of granules in one dose may provide an initially high release and therapeutic levels could be mentained over long periods.

INTRODUCTION

Tapioca is a carbohydrate-based food material obtained from the peeled and rasped roots of cassava *(Manihot utilisima)*. It is commercially available in the Delta areas of Nigeria in the form of irregularly shaped and buff-coloured cakes. Process for purification and size reduction to fine powder have earlier been described.[1] In that study the potential of tapioca as an additive in tablet manufacture was also investigated; it was shown that tapioca modifies various tablet properties including an increase in disintegration time and a decrease in the release rate of medicament. The lower release rates associated with higher tapioca contents may find application in design of controlled release devices; for instance fast release of drug from lactose granules and slow release from tapioca granules may together provide rapid onset of drug action while at the same time prolonging its duration of action. In the present study, this model of prolonged release was studied using lactose and tapioca separately as diluents and drug release from such granules was determined.

MATERIALS AND METHODS

Materials

Tapioca was obtained from Sapele, in the form of white to buff coloured cakes. Impurities including fibres, 10.5% and foreign organic matters 0.3% were removed by a purification process described earlier.[1] The first aqueous washing was slightly acidic pH 6.5 but became neutral after washing several times with water. Tapioca powder produced during the purification process was dried at 60°C, for 8 hours in a hot air oven before its use in granulation. Lactose BP (in fine powder) was also used as diluent. Paracetamol BP (in fine powder) was selected as the test drug while polyvinylpyrrolidone, PVP (BDH) was used as binder during granulation.

Granulation Technique:

50g paracetamol powder and 15g lactose or tapioca powder were blended together for 10 mins in a Kenwood mixer (Laboratory Model). The blend was granulated with about 15ml of 5% PVP solution (divided into three of 5ml portions) and mixed for 5 mins after the addition of each aliquot. The moist mass was pressed through sieve mesh size 10 and dried on trays in a hot air oven 50°C, 4h. The half-dried mass was pressed through sieve mesh 12 and re-dried 60°C, 2h. The dried mass was pressed through sieve mesh 16. In a different experiment the proportion of paracetamol to tapioca in the granules was varied (see table 1).

Table 1: Drug release from granules varying in content of tapioca and paracetamol.

Tapioca content, % w/w	23	40	50	60
Paracetamol Content %w/w	76	59	49	39
PVP (binder) Content % w/w	1	1	1	1
Paracetamol in the first 10 mins, mg	305	226	169	125
Overall release rate mg h^{-1}	456	257	191	134

Drug Release Studies:

Granules were separated into different sizes with a sieve shaker and those that passed through sieve mesh 16 but retained on sieve mesh 20 were used for the study; about 85% of the granules were in this size range. Paracetamol is predominantly absorbed in the stomach[2], consequently its release was carried out using the USP simulated gastric fluid (concentrated hydrochloric acid 7ml, sodium chloride 2g, and water to 1 litre).

Granules, 0.65g (average weight of paracetamol tablet BP) was placed in a conical flask and 250ml simulated gastric fluid at 37°C was added. Flasks were shaken, 75 oscillations min^{-1} in a water bath maintained at 37 + 0.5°C. 2ml samples were withdrawn at selected time intervals using a 2ml pipette plugged with a glass wool. Samples were diluted with the simulated gastric fluid, 100 to 500 times before their absorbances were determined with a spectro-photometer (unicam SP1800) at max, 257 nm. Presence of dissolved lactose did not affect absorbance at this wavelength. The amount of drug released was calculated from a spectro-photometric standard curve of paracetamol. In another experiment 0.4g of lactose granules (containing lactose 23%, paracetamol 76%, binder 1%) and 0.5g tapioca granule (containing tapioca 60%, paracetamol 39%, binder 1%) were filled into gelatin capsule. This mixture contains 500mg paracetamol per capsule. Drug release from the encapsulated granules was determined using the method described above for the free (uncapsulated) granules. The experiments were carried out in triplicate.

RESULTS AND DISCCUSSION

Paracetamol is rapidly absorbed after oral administration[2] but its serum half life is short[3], about 1.9h thus necesitating frequent dosage. Drugs exhibiting such biopharmaceutical properties may be formulated as prolonged release dosage forms by use of suitable additives[4]. The amounts of paracetamol released form lactose and tapioca granules, each contraining 76% of the drug are shown in fig. 1. Drug release from lactose granules was on average about 5 times faster than the release from tapioca granules, for instance 100% release from lactose granules was obtained in 30 mins while the same extent of release from tapioca granules was obtained in 150 mins. Lactose dissolves in the leaching fluid thus releasing its content of the drug fast. Tapioca on the other hand, is insoluble in the fluid; its wet cohesiveness[1] also retards disintegration of granules into smaller particles resulting in lower release rates generally. The fast release of drug from lactose granules will lead to rapid absorption but its rapid elimination from serum [3] without replenishment suggests that drug bio-availability rate has not been optimised. Tapioca granules on the other hand released a considerable amount of the drug initially (about 60% in the first 10 mins.) See fig. 1; in practical situations the continued release of the remaining 40% drug over 150 mins (See fig. 1) can however not be used to design a convenient once oı twice a day dosage form.

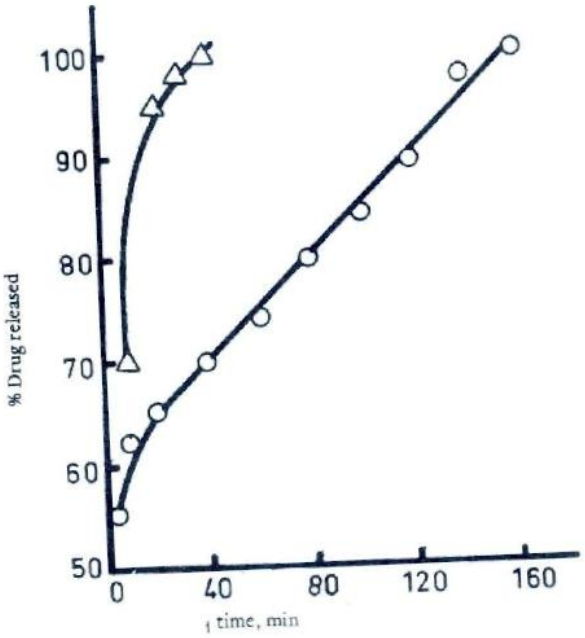
In formulations in which the proportion of tapioca in the granules was increased 23 to 60% whilst that of paracetamol was decreased 76 to 39%, release rate was reduced by 70% (table 1). Drug release from these formulations was consistent with a first order kinetic suggesting that the release was dissolution rather than diffusion controlled; thus[5]:

$$\log Mt = \log Mo - \tfrac{1}{2}.303\ kt \quad (1)$$

$$\log Mt/Mo = \tfrac{1}{2}.303\ kt \quad (2)$$

Where Mo is the initial mass of drug in the granules, Mt is the mass of drug in the granules after time t, and k is the release rate constant. A plot of log Mt/Mo versus t was linear (fig.2) with a slope, k/2.303 from which the values of k were estimated. k, $\%h^{-1}$ was converted to overall release rate, mgh^{-1} from a knowledge of the initial content of drug in each type of granules.

The decrease in release rate was accompanied by a decrease



Fi Fig. 1 *Difference in the release of paracetamol at 37°C from lactose and tapioca, granules. Content of paracetamol in each type of granules was 77%*

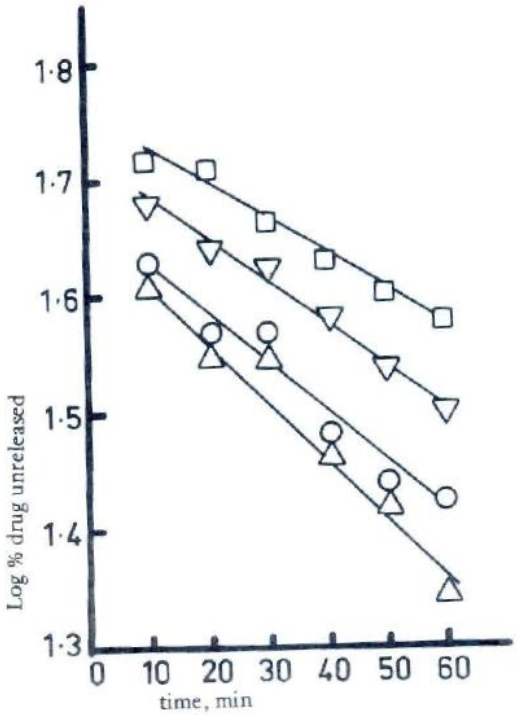


Fig. 2 First order release of paracetamol from granules varying in tapioca and paracetamol content: tapioca 23%, paracetmol 77%, tapioca 40% paracetamol 60%, tapioca 50% paracetamol 50%, tapioca 60% paracetamol 50%

in the amount of drug released in the first 10 mins (table 1). In order to obtain an initially high release followed by a slow and prolonged release, 0.4g of the lactose granules containing 76% paracetamol and 0.5g of tapioca granules containing 39% paracetamol (See table 1) were togerther filled in a gelatin capsule. Initial release of drug from this dosage form was adequate about 60% (i.e. 300 mg) and the remaining 40% (i.e. 200 mg) drug was released slowly over 3h (fig. 3).

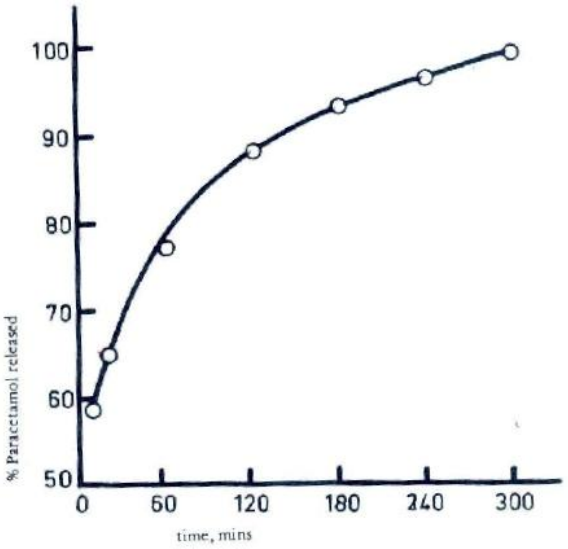


Fig 3 Release of paracetamol at 37°C from encapsulated granules of lactose 0.4g and tapioca 0.5g Content of paracetamol in lactose granules was 77% and its content in tapioca granules was 40%.

Rapid release of drug from the lactose granules will contribute to the retardation of drug release from tapioca granules because of the decrease in concentration gradient for mass transfer into leaching fluid.

The results suggest that the inclusion of medicated granules of lactose and tapioca in one dose may together be used to optimise drug release with the advantage of rapid onset and prolonged action of drug. Since granules made of pure tapioca (without admixture with lactose) are not readily compressible[1], the encapsulation of both types of granules will be prefered to their compression into multilayered tablets.

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