SUSTAINED RELEASE PREPARATIONS BY MICROENCAPSULATION

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DEDICATION

This work is dedicated to my son Mwongera on his second birthday.

ACKNOWLEDGEMENTS

I wish to thank Dr. Sinha for supplying me with all the materials required for the experiment, for supervising my work and for reading the original manuscript, all so willingly.

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INTRODUCTION

MICROENCAPSULATION FOR SUSTAINED RELEASE

Microencapsulation is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. It is different from macrocoating in that the former involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size (1, 3).

Microencapsulation provides the means of:

i. Converting liquids to solids

ii. Altering colloidal and surface properties

iii. Controlling the release characteristics or availablility of coated drugs

Since microencapsulation involves coating of very small particles, the particles can be used to make a wide variety of dosage forms and product applications which would not have been possible. The applications include:

i. Taste-masking in tablets, powders, suspensions

ii. Single layer tablets containing chemically incorpatible ingredients

iii. New formulations concept for creams, ointments, aerosols, dressing, plaster, suppositories and injectables

iv. Sustained release preparations

v. Pharmaceutically related areas of hygiene, diagnostic aids and medical equipment

This process that has so many advantageous applications has also its own disadvantages. The problems involved include:

i. No single microencapsulated process is adaptable to all core material candidates or product applications

ii. There can be incomplete or discontinous coating

iii. Inadequate stability for shelf-life of sensitive pharmaceuticals

iv. Non-reproducible and unstable release characteristics of coated products

v. It is a very expensive process and so the products obtained are equally expensive

In undertaking microencapsulation, certain factors have to be considered. The success of the process involves the understanding of general properties of microcapsules. These properties include nature of the core and coating materials, the stability and release characteristics of the coated materials. The core material is the specific material to be coated and can be a liquid or a solid. The liquid core is normally dissolved or dispersed in another material. A solid core can be a mixture of active constituents, stabilizers, diluents, excipients and release rate retardants or accelerators. Since the core material can be greatly varied, this allows formulation of any desired microcapsule properties.

The coating material used for a particular drug depends on:

i. Specific dosage or product requirements, eg. stabilization, reduced volatility, release characteristics, environmental conditions, taste masking, surface properties for dissemination, permselectivity of enzyme, substrate and reaction products, selective sorption etc.

ii. The microencapsulation method that is suited best to accomplish the coated product objectives

iii. The ability of the material to satisfy the product objectives and requirements

An ideal coating material should be able to form a film that is cohesive with the core material, provide desired coating properties such as strength, flexibility, impermeability, optical properties and stability.

Sustained release properties are substances that are designed to give a prolonged therapeutic action after administration. This indicates an extended period of action for a given drug in special dosage form. However, the efficacy and in some cases the practicability of long acting oral products depends on the g.i.t as an absorption site.

The sustained release preparation so made has advantages in that:

i. It is convenient as the necessity for dosage several times during the day is eliminated

ii. It ensures a slow and consistent supply of drug to the organism depending on the type formulated or required eg slow release potassium tablets (slow K).

iii. It is easy to eliminate the undesirable side effects eg. g.i.t. intation that is common in N.S.A.I.Ds

iv. In antibiotics, long acting drugs ensure that there is prevention of missed doses because of patients forgetfulness. This could lead to serious consequencies such as resistance of bacteria to that particular antibiotic. It also ensures that the ill person does not interrupt his sleep to take the medication.

The sustained release preparation also has limitations and so care should be exercised in order to get the required formulation with the expected behaviour. These limitations are:

i. Possible lack of precision of dosage due to varying rate of emptying of the stomach which depends on factors such

as volume and type of meal, physiological state of the body, etc.

ii. The long acting product may not release the drug as completely or efficiently as the non-long acting form due to poor design

iii. In poisoning with long acting drugs, the administration of antidote may be very difficult

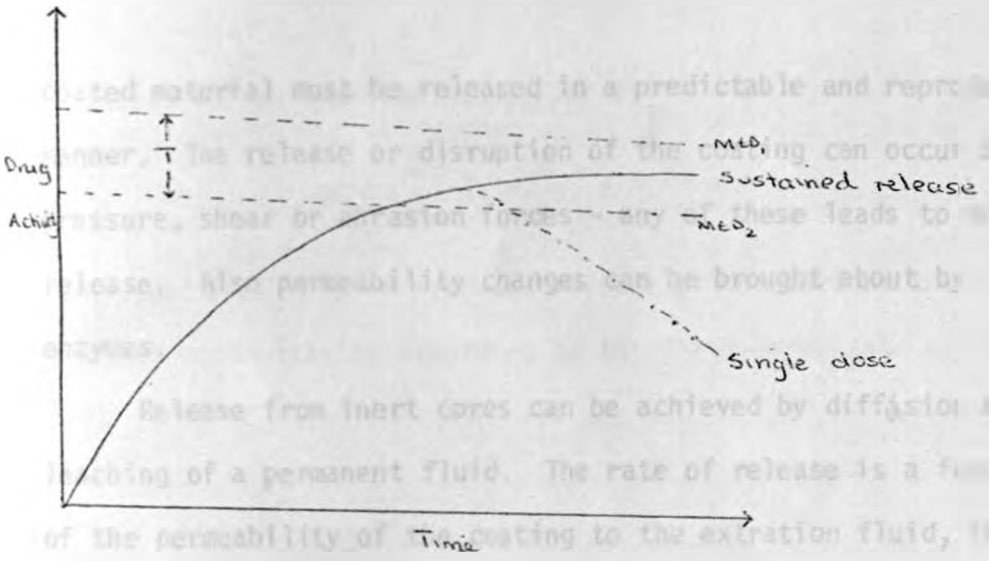
iv. It is an expensive and precision requiring process and so needs a trained person. This makes the product very expensive and so not as popular with the masses especially the poor

v. Overdosage may result due to frequent administration leading to high blood levels of drug as a result of repetition of the loading dose. This can lead to cummulation

vi. The drug is unstable and so can change on storage

The sustained release medications are meant to maintain a given level of activity from the drug. The net effect of product construction and physiological factors is such that the drug becomes available only for absorption at a constant rate. This rate should be equal to the activity of disappearance rate in the body after the absorption.

The sustained release is not suitable for drugs to be given at night as repeated dosing could lead to undesirably high levels in the blood. This then means that sustained release is for drugs that have high rates of disappearance in the body. The ideal behaviour of a sustained release is shown below.



MED_1 - Maximum effective dose

MED_2 - Minimum effective dose

T - Therapeutic range

The first dose is the loading dose and delayed release dose in construction of sustained release. The second and the succeeding doses only replenish the depleted drug in the blood. The second dose consists only of the delayed release and is given only when the level of the drug falls below the minimum effective dose to ensure there is no overdose or accumualtion of drug in the blood.

Comparing the single dose drug and the sustained release, one will notice that the single dose concentration falls below the minimum effective dose much faster than the sustained release. This calls for much more frequent administration of drug as explained earlier.

The selected release characteristics in the sustained release preparation is that, the release properties of micro-encapsulated materials require detailed consideration as the

coated material must be released in a predictable and reproducible manner. The release or disruption of the coating can occur by pressure, shear or abrasion forces - any of these leads to drug release. Also permeability changes can be brought about by enzymes.

Release from inert cores can be achieved by diffusion or leaching of a permanent fluid. The rate of release is a function of the permeability of the coating to the extration fluid, the permselectivity, if any, of the coating material to the core material solute, the disolution rate of the core material, the coating thickness and the concentration gradient existing across the coating membrane. The release of drug from the microcapsules all show first order kinetics. The rate of release of the drug is proportional to the amount of the drug remaining.

$$da/dt = K_r a$$

$$a = a_0 e^{-K_r t}$$

$$\ln a/a_c = K_r t$$

a_c - Total dose in preparation

a - Fraction of the total dose remaining in the coated preparation at the time

K_r - Apparent first order release constant

In sustained release preparation that is formulated to release a fraction (f_i) of the dose immediately and another fraction (f_r) exponentially as equated above, the amount of drug

release (a_r) by any time thereafter is

$$a_r = a_0 f_1 + a_0 f_r (1 - e^{-k_r t})$$

Many sustained release products release all or part of their drug content exponentially according to the first order rate equation.

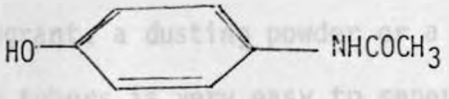
PROCEDURE

In the process of microencapsulation for sustained release, paracetamol was used as the core material and both stach and gelatin were used a coating materials but were applied separately.

Paracetamol

Paracetamol was used in order to make a sustained release preparation, to mask the bitter taste (especially for children) and to reduce the gastrointestinal irritation that is common in all non-steroidal anti-inflammatory drugs (N.S.A.Ds). Paracetamol is very commonly used for various ailments and is used in very high doses in certain conditions.

Paracetamol itself is 4-acetoamidophenol containing not less than 98.0% and not more than 101% of $C_8H_9NO_2$ calculated in reference to the dried substance (5).



4 - Acetoamidophenol (acetaminophen)

It is white crystals or powder, odourless and tastes bitter. It is unstable in light due to the presence of excess electrons from benzene ring and the N and O lone pair of electrons.

Paracetamol has analgesic, antipyretic actions and so it is used in the treatment of pain in minor conditions such as toothache, headache, rheumatism and neuralgia. It is given by mouth in a dosage of 0.5 g to 1 g every three or four hours with a maximum of 4 g in 24 hours for adults. This clearly indicates that the dosage

is too high and toxicity is bound to occur due to high levels of acidic paracetamol in the g.i.t. If given for a long time there can be gastrointestinal bleeding and hypersensitivity of mucous membranes of the nose and the throat leading to an asthma-like condition. It is with this in mind that it was decided to micro-encapsulate paracetamol for sustained release.

Starch

Starch is produced in large quantities in green leaves as the temporary storage form of photosynthetic products. As a permanent reserve food material for the plant, it occurs in seeds and in the pith, in the medullary rays and the cortex of the stems and also in the roots of perennials and other plants.

The official starches used in pharmaceutical industry are potato, corn and wheat. In industry, starch can be used as a binder, a disintegrant, a dusting powder or a filler.

Starch from tubers is very easy to seperate and is easily available and cheap. It is therefore used widely in industry and that is why it was chosen as the coating material in this experiment.

Gelatin

Gelatin is obtained by the partial hydrolysis of collagen derived from connective tissue and bones of animals. It is used in pharmaceutical undustry as an encapsulating agent, a suspending agent, a tablet binder or a coating agent.

Gelatin is used as 10% - 20% solution. The solution should be freshly prepared when needed and used while it is still warm because it solidifies.

MATERIALS AND APPARATUS

1. Gelatin B.P. 10% W/W solution in water
2. Maize starch B.P. 10% W/W solution in water
3. Paracetamol powder 500 g
4. Empty capsule shells size 0, 1 and 2
5. Beakers
6. Granulator Erweka AR 400
7. Mixing pan
8. Sieve 710 nm
9. Oven
10. Thermometer
11. Hot plate
12. Disolution apparatus
13. Accurate weighing satorius balance
14. U.V. spectonic 21
15. Miscellaneous items - volumetric flasks, beakers, fillers, syringes, stop watch

GENERAL METHOD

About 50 g of paracetamol powder were weighed into eight batches using a satorius balance. Each of the eight batches was

treated with varying amounts of maize starch or gelating solution using various methods. The methods used were mixing, pouring, spraying and slurring of the binder into the powder until enough was incorporated to allow granulation. The relative amounts of the individual binder used are as shown below:

For Starch

Method	Amount of the Solution Used	Percentage in Granules
Mixing	8.0 ml	1.6%
Pouring	16.0 ml	3.2%
Spraying	37.0 ml	7.4%
Slurring	68.0 ml	13.6%

For Gelatin

Method	Amount of the Solution Used	Percentage in Granules
Mixing	4.5 ml	0.9%
Pouring	5.0 ml	1.0%
Spraying	30.0 ml	6.0%
Slurring	38.0 ml	7.6%

Another 50 g of paracetamol powder was left untreated in order to observe the differences in behaviour between the untreated paracetamol and the microcapsules.

The wet masses thus prepared were passed through a 710 nm sieve using a granulator. The granules obtained were dried in an oven at about 40^{o} for 20 minutes and regranulated to break up any lumps which could have been formed during drying. The granules were then filled into the hard gelatin capsules. Even after the granules were compressed several times, only 250 mg of the granules could be accommodated in each capsule. 250 mg is half of the normal dosage form of paracetamol. Ten capsules were filled with the granules with special care being taken to make sure that equal quantities were placed in each capsule. This was done in order to ensure the uniformity of the weight on sampling.

The capsules were then subjected to a dissolution test using a B.P. dissolution apparatus in order to show, if any, sustained release properties of the granules.

DESCRIPTION OF THE PROCESSES IN THE METHOD

Preparation of the Starch Solution

Cold powder was dispersed in purified cold water to make a 10% W/W solution and warmed in a water bath while being stirred continously until a translucent paste formed. It was used when it was fresh to avoid fermentation which would have led to the breaking up of the starch granules.

Preparation of the Gelatin Solution

The gelatin was added to purified cold water and allowed to stand until hydrated. It was then warmed in a water bath to

disolve the gelatin and the solution was made up to final volume on a weight basis to give a 10% W/W solution. The solution should be freshly prepared as needed and used while still warm to avoid solidification.

Preparation of the Granules

By mixing. Small quantities of the appropriate binder were poured a little at a time and mixed using fingers until the mass formed a lump when it was pressed.

By pouring. The powder was put in a rotating pan and a thin stream of the solution was poured slowly into it until the mass was said to be wet enough for granulating.

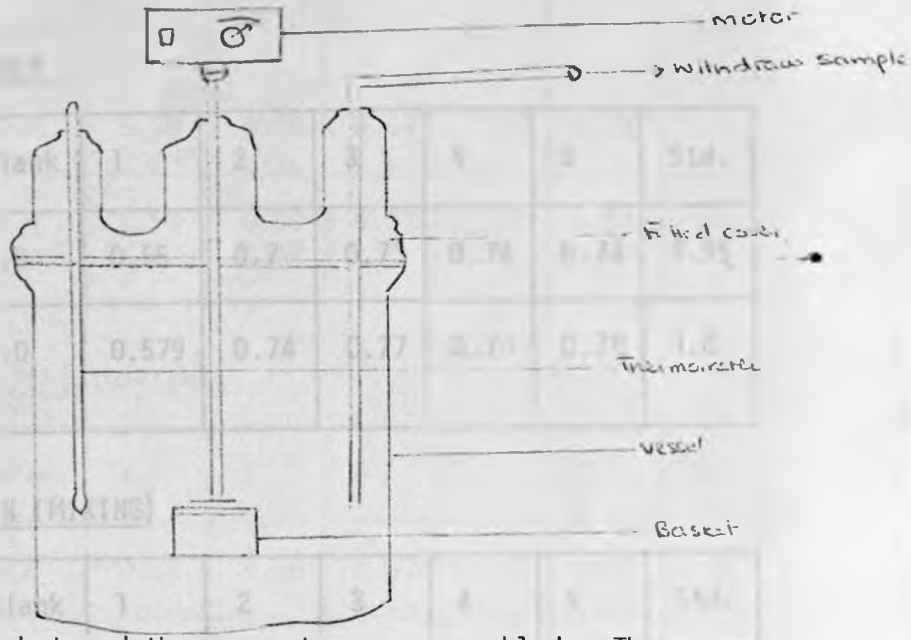
By spraying. Using a spray atomizer, the solution was sprayed into a rotating pan containing the powder for efficient and uniform mixing. This was done until a wet mass - wet enough to allow granulation - was obtained.

By slurring. A slurry of powder and solution was made and poured into a rotating pan. A stream of warm air was passed through to remove the excess moisture in order to allow granulation.

Determination of the Dissolution Rate

The apparatus was positioned in a water bath to keep the dissolution liquid (water) at 37 ± 0.5 ^{o}C during the test. This simulated the body temparature. The variable speed of the motor was set for 100 revolutions/min. The vessel was filled with 1 L of freshly distilled water and allowed to warm to 37 ^{o}C. A capsule

Diagram of apparatus



was placed in the basket and the apparatus was assembled. The basket was immersed so that there was a distance of about 2 cm between it and the bottom of the vessel. The samples were withdrawn after every 7 minutes, as the basket rotated from a fixed point, ie, a constant distance from the bottom. This process took 35 minutes after which the samples were analysed by U.V. spechonic 21. This was repeated for five additional dosage units and the average obtained is shown on the tables of results.

The analysis of the samples involved diluting 1.0 ml of the sample withdrawn at each time to 25 ml using 0.1 M sodium hydroxide solution. A standard was also prepared by diluting 1.0 ml of 10 ug/ml solution to 10 ml using the same sodium hydroxide solution. The standard contained 1 ug/ml of paracetamol. The wavelength of absorption was 256 nm.

RESULTS

PARACETAMOL POWDER ONLY

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.55	0.7	0.73	0.74	0.74	0.95
Concentration ug/ml	0.0	0.579	0.74	0.77	0.78	0.78	1.0

PARACETAMOL - GELATIN (MIXING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.58	0.7	0.73	0.74	0.74	1.0
Concentration ug/ml	0.0	0.58	0.7	0.73	0.74	0.74	1.0

PARACETAMOL - GELATIN (POURING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.7	0.7	0.72	0.7	0.72	0.98
Concentration ug/ml	0.0	0.71	0.71	0.73	0.71	0.73	1.0

PARACETAMOL - GELATIN (SPRAYING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.58	0.59	0.59	0.56	0.59	1.0
Concentration ug/ml	0.0	0.58	0.59	0.59	0.56	0.59	1.0

PARACETAMOL - GELATIN (SLURRYING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.52	0.56	0.57	0.57	0.57	0.95
Concentration ug/ml	0.0	0.55	0.59	0.6	0.6	0.6	1.0

PARACETAMOL - STARCH (MIXING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.74	0.76	0.78	0.76	0.76	1.0
Concentration ug/ml	0.0	0.74	0.76	0.78	0.76	0.76	1.0

PARACETAMOL - STARCH (MIXING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.56	0.57	0.58	0.58	0.58	0.95
Concentration ug/ml	0.0	0.58	0.6	0.611	0.611	0.611	1.0

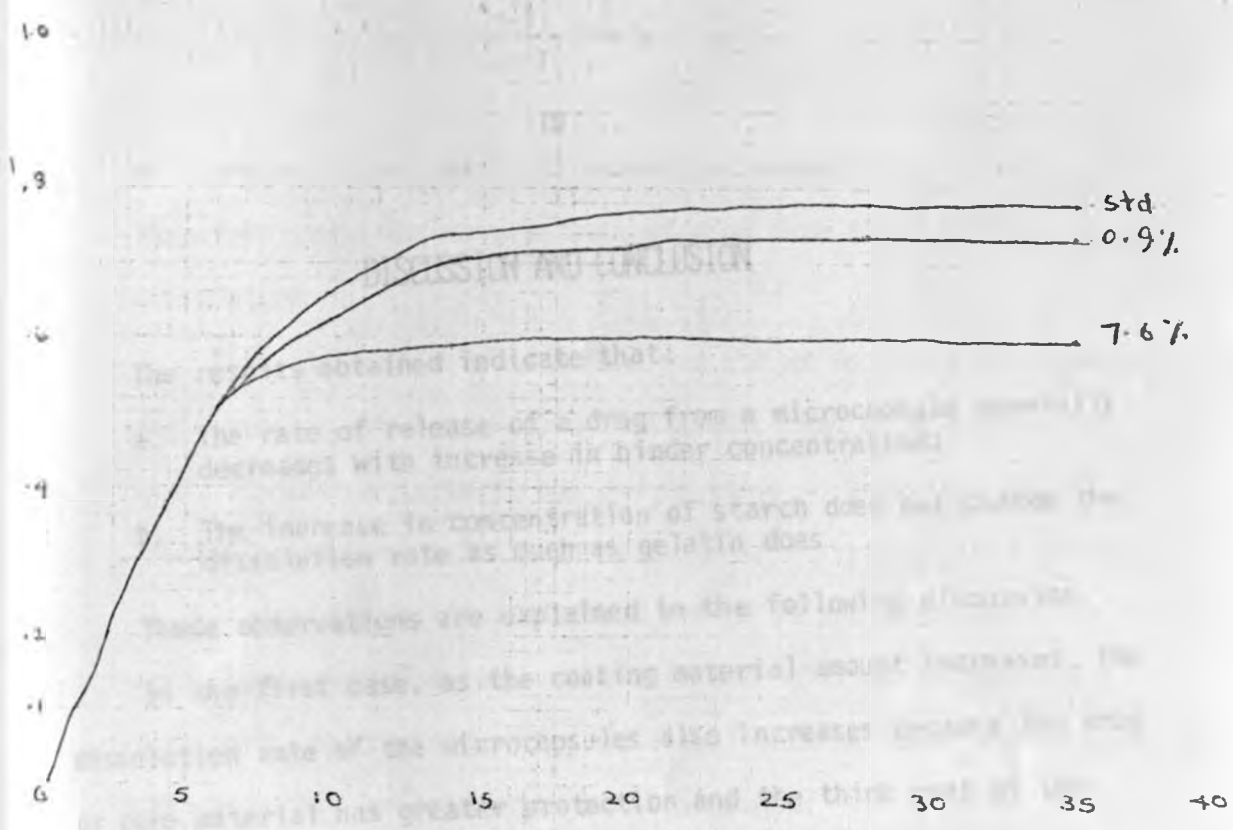
PARACETAMOL - STARCH (SPRAYING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.59	0.62	0.62	0.62	0.61	1.0
Concentration ug/ml	0.0	0.59	0.62	0.62	0.62	0.61	1.0

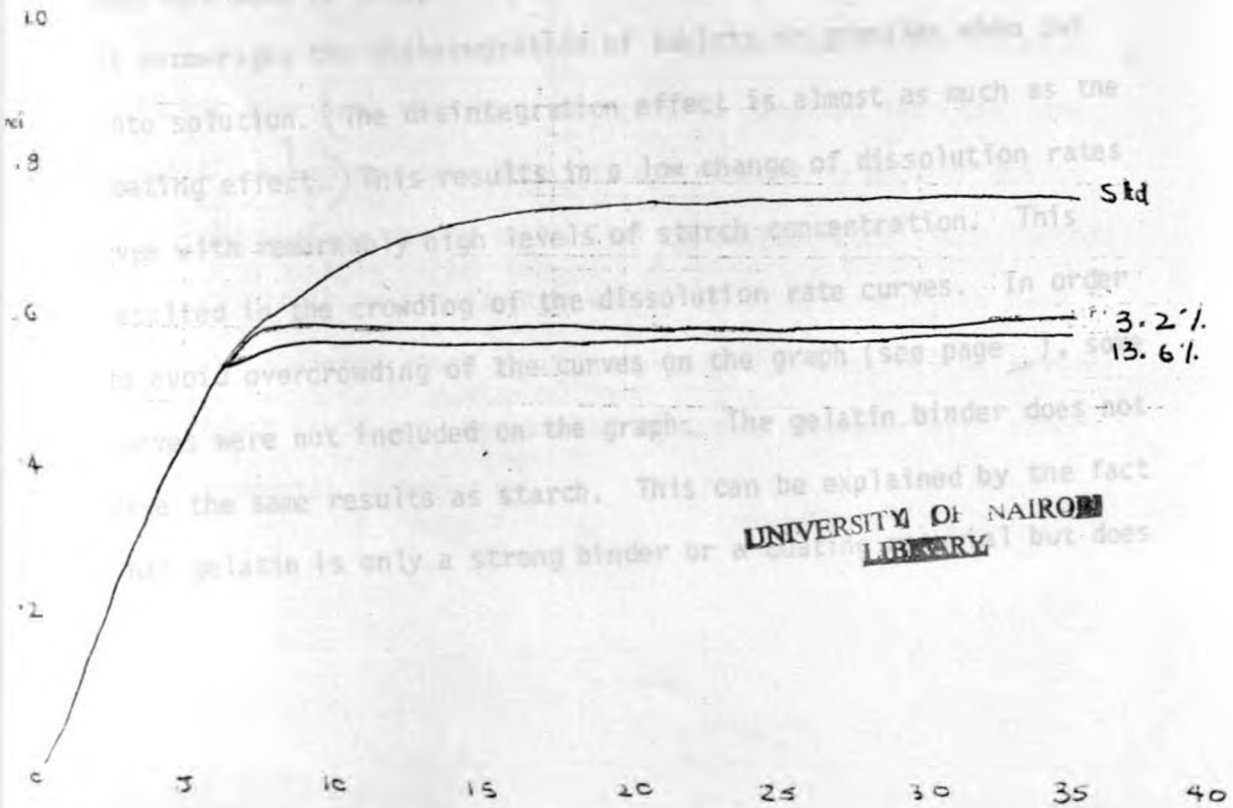
PARACETAMOL - STARCH (SLURRYING)

Sample	Blank	1	2	3	4	5	Std.
Absorbance	0.0	0.53	0.535	0.54	0.55	0.55	0.92
Concentration ug/ml	0.0	0.57	0.58	0.587	0.598	0.598	1.0

MICROCAPSULES:



b) DISSOLUTION RATE FOR PARACETAMOL-STARCH MICROCAPSULES.



DISCUSSION AND CONCLUSION

The results obtained indicate that:

a. The rate of release of a drug from a microcapsule generally decreases with increase in binder concentration;

b. The increase in concentration of starch does not change the dissolution rate as much as gelatin does.

These observations are explained in the following discussion.

In the first case, as the coating material amount increases, the dissolution rate of the microcapsules also increases because the drug or core material has greater protection and the thick coat of the coating material has to be washed out first before the drug powder can be released and then undergo dissolution. This would mean that longer dissolution time is expected for a batch with 15.0% coating material than that with 10% concentration of coating material.

The dissolution rate for starch batches with varying amounts does not seem to change very much as starch itself is a disintegrant. It encourages the disintegration of tablets or granules when put into solution. The disintegration effect is almost as much as the coating effect. This results in a low change of dissolution rates even with remarkably high levels of starch concentration. This resulted in the crowding of the dissolution rate curves. In order to avoid overcrowding of the curves on the graph (see page), some curves were not included on the graph. The gelatin binder does not give the same results as starch. This can be explained by the fact that gelatin is only a strong binder or a coating material but does

not have any significant disintegration properties. It does not therefore cause the easy release of drug from microcapsules during dissolution.

This dissolution rate method was chosen as a way of comparing and assessing the behaviour of different forms of microcapsules. It is fast, easy to carry out and so it is a convenient method of assessing the properties such as dissolution rates. This method is, however, an unofficial method and so is not very promising as an accurate method of assessment. The conditions and apparatus used vary from individual to individual because there are no set out conditions or apparatus for this method. For example, results obtained by a person using USP apparatus would vary from those obtained by a person using B.P. apparatus because of the difference in the shapes of the two apparatus: the USP apparatus is round-bottomed while the B.P. apparatus is not. This has led in the obtaining of different values for the same batch of drug which, pharmaceutically, is supposed to be uniform. The method of assessment of dissolution rate differs from one monograph to another. It has also been seen that the results obtained from the same batch of drug can vary from one environment to another due to factors such as sound, mechanical agitation, etc. Such factors are difficult to standardize and so it is neccessary to have special isolated rooms which have acoustics controlling devices to reduce sound and mechanical agitation together with other environmental factors.

The accuracy of the results could be affected by the method and apparatus used in the preparation of the granules and the microcapsules. In the case of this experiment, it was impossible to obtain an atomizer spray to use in the spraying of the coating material to the core material (drug), so one was made from a plastic bottle. The spray so made had large holes and was not very effecient in the spraying of the coating material suspension since the drug powder was being blown off. Also the mixing of the drug and the coating material was not intimate because of the large size droplets of the coating material.

In the filling of the capsules, the compression force could not be standardized because it was carried out manually. This could mean more tight packing of granules in one capsule and not in another. Also compression meant breaking up of the microcapsules back into powder form. This could result in the change of behaviour of that particular capsule from the expected; ie, it could cause a faster dissolution rate than expected.

During the determination of the dissolution rate, the point of withdrawal of the samples could not be standardized for all batches. This was not practicable because the dissolution apparatus was being used by other persons making totally different observations such as the speed and point of withdrawal. This could have led to inaccuracies in the experiment as already reported above. The speed indicator of the machine was not in proper working condition and so it was difficult to replicate the same speed for all samples.

Other than these few problems encountered, the experiment was very successfully carried out and the results obtained are very encouraging.

The results indicate that it is very encouraging to undertake the manufacturing of sustained release preparations of N.S.A.I.D to reduce the frequency of administration of drugs and therefore to minimise the occurence of the numerous toxic effects. Most of the few sustained release products in the market are under patent and so their methods of preparation, the coating materials used and their concentration are only known to their manufacturers. This calls for more research in the sustained release medications and the encouragement of their manufacturing in the third world countries; in order to save the foreign exchange that is used in the importation of these medications.

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