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SUMMARY

The effect of the hydrophilic
polymers alginic acid and
polyethylene glycol 2000 (PEG
2000) as well as maize starch
on in vitro dissolution
profiles of frusemide sustained
release granules prepared with
a hydrogenated vegetable oil
(Lubritab®) was investigated.

INTRODUCTION

Numerous articles have been
published describing the effects
of different excipients on drug
release from capsules (1 - 6).
However, only few of these
discussed the rate of
disinTEGRating agents in capsule
formulations. Some earlier
reports on this have shown
mixed results (4 - 6).

Encapsulation of drug powders
or granules could be employed
in the formulation of sustained
and sustained release dosage forms.
There are many approaches that
are currently employed in the
formulation of sustained release
dosage forms. One of these
approaches involves dispersing
or suspending the drug in a
mixture of oils and waxes. Here,
the melt is either dispersed by
spray congealing or the
solidified drug-vehicle mass is
mixed to a proper particle size.
The granules obtained are
mixed proportionately with
immediate release granules and
either tabletized or encapsulated
(7).

Frusemide is a loop diuretic
used in the management of
cardiovascular and renal
diseases such as hypertension,
congestive heart failure,
hypercalcaemia, diabetes
insipidus, inappropriate
secretion of antidiuretic
hormones, edema as well as
drug intoxication (8). During
long therapy with this drug,
patient non-compliance
represents a major problem.
This problem could easily be
overcome with sustained release
microcapsules of frusemide
capable of improving patient
compliance have been reported
(9). The present study was
undertaken in order to prepare
sustained release frusemide
granules using a hydrogenated
vegetable oil (Lubritab) as a
matrix and to investigate the
effect of three polymers - maize
starch, alginic acid and
polyethylene glycol 2000 (PEG
2000) on in vitro drug release
from the encapsulated granules.

EXPERIMENTAL

Materials: The following
materials/chemicals were used
as procured from their
manufacturers without further
purification - frusemide
(Heochst, Germany), maize
starch (BDH, England), alginic
acid, monobasic potassium
phosphate (Fluka, Germany),
sodium hydroxide (May & Baker,
England), polyethylene glycol
2000 (Merck, Germany),
Lubritab (kapitul city product,
U.S.A.).

METHOD

Preparation of Frusemide
Granules: Frusemide granules
were prepared using the fusion
method previously reported
(10). A 50g batch of granules
was formulated to contain 60,
20 and 20%®. of lubritab,
frusemide and lactose
respectively. Frusemide powder
and lactose were mixed together
for 5 minutes on a mortar with a
pestle in a geometric dilution.
The mixture was added with
stirring to the molten lubritab
until the melt solidified. This was
to ensure even distribution of the
drug. The solid mass was
ground in a mortar and
screened through a 0.600mm
stainless steel sieve.
Granules were air dried overnight under room temperature of 28 ± 1°C. Granules at frusenide containing 5% w/w of either maize starch, alginate acid or PEG 2000 were similarly prepared so that each batch of granules contained lubricant, 60%, frusenide, 20% and (24%) per cent of lactose (X, represents 5% w/w, of either of the hydrophilic polymers).

Encapsulation of Granules

The granules were manually filled into No. 1,0 hard gelatin capsules. Each capsule contained frusenide granules equivalent to 75 mg of the pure drug. File capsules were stored in a desiccator. Capsules were evaluated for weight uniformity, content uniformity, absolute drug content and disintegration time tests using the USP XXX 1980 methods. The disintegration time tests were performed in 0.1 N NaOH maintained at 37 ± 1°C.

DissoLution Profile Studies

The dissolution profiles of the capsules were determined using the Static Basket-Magnetic Stirrer Assembly (10) 24 hours after encapsulation. The dissolution medium consisted 900 mL of freshly prepared 0.1 N NaOH maintained at 37 ± 1°C. The magnetic stirrer was operated at 100 rpm by switching on a thermostated hot plate. In each case, one capsule was placed in the basket and guided with a disc to prevent it from floating. Samples were withdrawn at predetermined time intervals with a pipette fitted with a non-absorbent cotton wool, and analyzed spectrophotometrically at 273 nm in a UV/VIS spectrophotometer. Dissolution studies were also performed in 0.1N HCl and in simulated intestinal fluid without pancreatin (SIM) under similar conditions.

Results and Discussion

The mean weights, content uniformity and absolute drug content of the capsules are shown in Table 1. Values presented, with their co-efficient of variation indicate that all the capsule batches could be considered to have met the USP XXX 1980 requirements.

The granules were non-disintegrating even after 6 hours. The capsule shells merely ruptured within 5 minutes.

<table>
<thead>
<tr>
<th>Table 1: Mean Values of Properties of Frusenide Capsules</th>
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<td>Weight (mg)</td>
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<tr>
<td>Moisture (%)</td>
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<tr>
<td>Content Uniformity (%)</td>
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<td>Absorbable Drug Counting (%)</td>
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*Values in brackets represent maximum % of moisture (%).

DissoLution Profiles

The dissolution profiles of frusenide from the encapsulated granules are shown in Figure 1, while some dissolution parameters of the drug are presented in Table 2. There was a release lag period of 2 hours before frusenide was released from the granules in the control batch that contained non of the hydrophilic polymers. This lag period may represent the time it took for the dissolution medium to wet the granules sufficiently enough to cause fluid penetration and subsequent leaching out of the dissolved drug. Lubrithab is a hydrophilic hydrogenated vegetable oil which hydrates very slowly. The presence of 5% (w/w) maize starch or alginate acid or PEG 2000 led to a one hour reduction in the release lag period. The rate of release of frusenide was significantly (p < 0.05) enhanced by either of the hydrophilic polymers. Hydrophilic polymers such as maize starch and alginate acid are said to enhance drug release by creating channels through which dissolved drugs are leached out (11). Maize starch may also enhance drug release due to its action as disintegration inducer (12). Similar action was reported with sodium alginate at low concentrations (13). Enhancement of drug release by maize starch and alginate acid from a non-disintegrating plastic matrix has been reported (14). Polyethylene glycol 2000 is a surface active agent which by causing a reduction in interfacial tension enhanced the hydration of the granules leading to increased fluid penetration into the granule matrix. This may account for the enhanced release of frusenide obtained with the polymer. All three hydrophilic polymers caused marked reduction in T50 and T70 (time, taken for 50 and 70% of frusenide to be released respectively) and increase in Cmax (maximum cumulative frusenide released). These values are shown in Table 2.
The disparity in the absolute drug contents in milligram (table 1) and the Cratio, in percentage (table 2) could be accounted for by variations in weights and drug contents that are normally encountered in hand-filled encapsulated dosage forms. Absolute drug content represents an average of the contents of at least twenty capsules, while dissolution profiles are normally carried out with one or two capsules which contents may be higher than the average content of twenty capsules. Figure 1 shows that the release of each drug from 2% and 5% of the solution is expected to increase in SIF. However, the opposite occurred indicating that the drug release in this medium was largely dependent on the solubility of the matrix (Lubritab) in the medium. The presence of salts of the SIF may have reduced the hydration of the granules. Less than 5% cumulative drug release was obtained in 0.1N HCl and this was not represented graphically. A similar poor release of frusmean in this medium has been reported (9) and this was attributed to the poor solubility of the drug in 0.1N HCl.

Figures 3 and 4 show the release profiles of frusmean plotted according to the Higuchi matrix and the diffusion-law (15) and first order release kinetics. Release of the drug from this matrix followed the Higuchi diffusion model as indicated by one linear regression equation (figure 3).

The presence of the hydrophilic polymers led to more than one regression line in the release process. These regression lines represent the changes that took place in the drug liberation process (16-18) and may indicate modification and modulation of the drug release by the hydrophilic polymers. The linearity of the first order plots (figure 4) indicate, that in addition to diffusion mechanism, frusmean release followed first order release kinetics in all the systems investigated. This model appears to offer a better interpretation of frusmean release from the wax matrix in the presence of the hydrophilic polymers than the Higuchi diffusion model.

CONCLUSION

Lubritab could be employed in the formulation of sustained release frusmean granules. Improved release characteristics of the drug could be achieved by the incorporation of hydrophilic polymers such as micro starch, alginic acid or PEG 2000.
Fig. 1: Dissolution profile of frusemide in 0.1N NaOH

- $x$: Lubritab + maize starch
- $\triangle$: Lubritab + PEG 2000
- $\Delta$: Lubritab + alginic acid
- $o$: Lubritab

Time (hr)

% Frusemide released
2: Dissolution profile of frusemide from Lubritab

○ = D+INNOH, △ = SIF
Fig 3. Higuchi diffusion plot for the release of frusemide in 0.1NNaOH
O = Lubritab, x = Lubritab + maize starch
* = Lubritab + PEG2000, □ = Lubritab + algic acid
**Fig. 4.** First order release kinetics of the release of frusemide in 0.1N NaOH

- $o$: Lubritab
- $x$: Lubritab + maize starch
- $*$: Lubritab + PEG2000
- $+$: Lubritab + alginic acid