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التوثيق الالكتروني والميكرو فيلم

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التوثيق الالكتروني والميكروفيلم

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بعض الوثائق الأصلية تالفة



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بالرسالة صفحات

لم ترد بالأصل

***A Pharmaceutical Study on Some Sustained
Release Solid Dosage Forms Containing
Tiaprofenic Acid***

***A Thesis Presented
By***

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(Pharmaceutics)***

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ABSTRACT

ABSTRACT

Tiaprofenic acid is a non-steroidal anti-inflammatory drug used in the treatment of various musculo-skeletal disorders and painful conditions. The drug has proven therapeutic efficacy, tolerability and safety. The short plasma half-life, 1 – 2 hours, following oral dosing necessitates a three-time a day administration of the drug to maintain peak and trough concentrations within the therapeutic range. Patient compliance is known to be fairly poor with such frequent dosing regimen. Furthermore, the conventional dosage forms do not provide protection against the side effects associated with non-steroidal anti-inflammatory drugs such as the irritation of the gastrointestinal mucosa. Thus clinical benefit and related advantages are likely if such a drug were to be administered as a modified release dosage form. A multiple-unit system was proposed here in view of the many advantages that those dosage forms offer. Accordingly, the work in this thesis is divided into three parts, namely, preparation and evaluation of tiaprofenic acid-cellulose acetate butyrate microcapsules, preparation and evaluation of tiaprofenic acid microcapsules using natural polymers, and pharmacodynamic activity of tiaprofenic acid from various microcapsule preparations.

Part I: Preparation and Evaluation of Tiaprofenic Acid- Cellulose Acetate Butyrate Microcapsules

The work in this part included the preparation of tiaprofenic acid microcapsules using cellulose acetate butyrate polymer by solvent evaporation technique. Three different emulsifiers, namely sodium lauryl sulfate, polyvinyl alcohol and polyvinyl pyrrolidone, were employed

alone and as mixtures. Preliminary experiments were carried out to determine practically the volume range of both the external aqueous phase and the internal organic phase, the concentration range of the emulsifier and the drug to polymer ratio. The prepared microcapsules were evaluated for their morphology and surface structure, average particle size, yield, drug loading efficiency, and their release pattern.

Preliminary Experiments:

To determine the optimum external phase volume, two distilled water volumes, namely, 120 and 240 ml were tested. Both the volumes produced spherical microcapsules without aggregation, thus the judgment was based mainly on the drug content. 120 ml distilled water resulted in higher drug loading efficiency due to the decrease in the aqueous phase volume per unit weight drug charged to the system. Thus 120 ml distilled water was used in the forgoing experiments. 20, 40 and 80 ml, were employed as internal organic phase volumes. Using 80 ml methylene chloride increased the time needed for the experiment to 360 minutes without further increase in the drug content, thus, this volume was excluded from further investigations. A series of microcapsules was prepared using different quantities of sodium lauryl sulfate. Concentrations below 0.3 % were not successful in producing microcapsules because the optimal packing concentration of the emulsifier was not achieved. Hence, 0.3, 0.45 and 0.6 % were suggested for further investigation. The total drug release after 8 hours for D: P ratio of 1: 0.5 was 72.6 % compared to 55 % for 1: 1 and 12.35 % for 1: 2. The marked delay in the release rate on using 1: 2 suggested the exclusion of this D: P ratio from further investigations.

Microcapsules Prepared Using Sodium lauryl sulfate:

Sodium lauryl sulfate was used in three concentrations, 0.3, 0.45 and 0.6%. Microcapsules were prepared in two D: P ratios (1: 0.5 and 1: 1), using 120 ml distilled water and 20 and 40 ml methylene chloride. The prepared microcapsules were evaluated as follows:

- 1 – Microcapsules were examined using both optical and scanning electron microscope. They were discrete, spherical, freely flowing and their surface was smooth at both drug to polymer ratios of 1: 0.5 and 1: 1.
- 2 – Mean microcapsules diameter was determined, using Coulter Counter technique, and was found to increase on increasing the polymer amount, decreasing the organic solvent volume and decreasing the sodium lauryl sulfate concentration.
- 3 – The increase in both the polymer amount and the emulsifier concentration markedly decreased the microcapsule yield. The change in the organic phase volume had no marked effect on the percentage yield of the microcapsules.
- 4 – Statistical analysis of the drug loading efficiency data proved the absence of a significant effect for the change in both the D: P ratio and the emulsifier concentration on the drug content of all the microcapsules. The drug loading efficiency significantly increased with the increase in the methylene chloride volume.
- 5 – Microcapsules equivalent to 300 mg of the drug were filled in capsule shell and their dissolution profiles were studied throughout the pH range 1.2—7.4. Time for 50 % of the drug to be released ($t_{50\%}$) was used to

explain the effect of the different formulation variables on the release profile. The drug release decreased with increasing the polymer amount. Applying a t test proved the existence of a significant effect for the change in the organic phase volume on $t_{50\%}$. This effect varied according to the D: P ratio. The analysis of variance showed nonsignificant effect for the change in the sodium lauryl sulfate concentration on the release pattern for all microcapsules except for those prepared applying 1: 0.5 D: P ratio and 20 ml methylene chloride.

6 – Examining the microcapsules surface after exposure to the dissolution medium revealed that the microcapsules did not fragment or alter in shape or size and that the surface pores enlarged in size. It was suggested that the drug release may be by passage through the microcapsule surface pores

7 – The drug was released faster in the alkaline medium compared to the acidic medium due to the greater solubility of cellulose acetate butyrate at higher pH values. The drug was released from the microcapsules by first-order release pattern at pH values 1.2, 5.2 and 7.4.

Microcapsules Prepared Using Polyvinyl Alcohol:

The microcapsules were prepared following the formulation parameters that were proven to be optimum in case of sodium lauryl sulfate, which were, 120 ml distilled water, 40 ml methylene chloride and D: P ratios of 1: 0.5 and 1: 1. On evaluation of the prepared microcapsules, the following was noticed:

1 – On using 0.15 % polyvinyl alcohol alone, the polymer was polymerized around the rotating shaft during the preparation process