Colon specific delivery system based on ethylcellulose-alginates microspheres loaded with mesalazine

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Abstract:

The effectiveness of any medical therapy is determined not only by the therapeutic agent's pharmacokinetic and pharmacodynamic activity, but also, to a significant part, by its bioavailability at the site of action in the human system. Orally administered nano/micro drug systems (Novel Drug Delivery Systems: NDDs) exhibit their higher effectiveness in colon therapy, particularly for bowel diseases such as Crohn's disease, ulcerative colitis, colon cancer by augmenting drug bioavailability through the protection of the drugs molecules from the acidic area and increasing penetration into the intestinal membrane.

The aim of the present work was to prepare and characterize mesalazine (5-aminosalicylic acid) loaded microspheres consisting of different ratios of sodium alginates (ALG) and ethylcellulose (EC) using emulsion solvent evaporation method for intestinal release. Properties of the microspheres such as surface morphology and size, FT-IR, DTA, TGA, drug content, drug release behavior, percentage drug entrapment, percentage yield of in vitro drug release were evaluated to investigate the more suitable preparation parameters. Drug release studies were carried out in acidic medium (pH=1.2) for 2h and in phosphate buffer solution (pH=6.8) up to 8h. Ideal slow release of (5-ASA) was highly affected by this coating. Mesalazine had low dissolution ratio in acidic gastric conditions and microspheres exhibited less than 20% of active ingredient release in gastric solution, while more than 50% was released over 7 h in the intestinal conditions medium. The results showed that the sustained release systems thus prepared are suitable for vectorized delivery of the drug if they are administered for colon therapy.

Key words: mesalazine, solvent evaporation method, microencapsulation, NDDs system.

Introduction

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Oral drug delivery system represents one of the frontier areas of drug delivery systems. Such a dosage form manages common concern which exists in area of cost-efficient treatment, patient compliance, optimum drug delivery and bioavailability[1] . Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles… which modulates the release and absorption characteristics of the drug[2].

Microspheres constitute an important part of this particulate drug delivery system by virtue of their small size and efficient carrier characteristics. However, the success of this novel drug delivery system is limited due to their short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with absorbing gastric mucosal membranes[3].

In the present study, an attempt has been made to prepare 5-ASA microspheres prepared by emulsion-solvent evaporation technique using different ratios of ALG and EC.

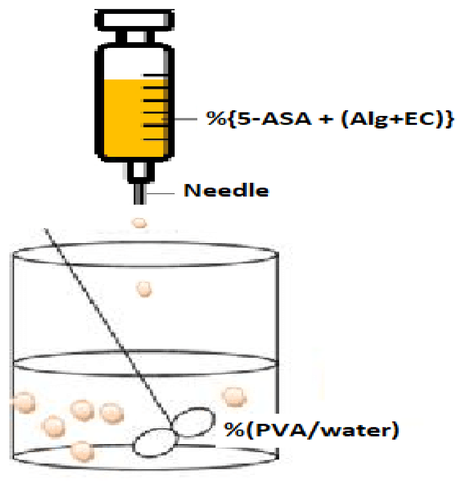


Fig 1: 5-ASA microspheres preparation

Results and discussion

Determination of drug content

$$\text{Drug content}\% = \frac{\text{mass of active agent extracted}*100}{\text{mass of microparticles}}$$

$$\text{Drug released }\% = \frac{\text{mass of active agent in microsphères}}{\text{initial mass of active agent}} * 100$$

Expérience	% Drug content	% Drug released
1	1%	12,8%
2	1%	9,9%
3	2%	25,8%
4	2%	22,0%
5	10%	29,0%
6	16%	46,6%
7	11%	33,4%
8	21%	61,9%
9	15%	44,7%

Table 1: Determination of drug content of all formulations in pH=1,2

FTIR analysis

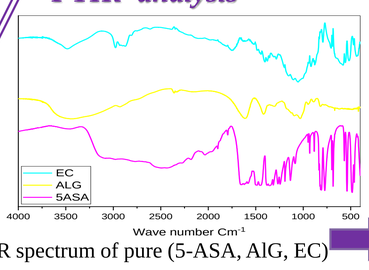


Fig 2:FTIR spectrum of pure (5-ASA, AlG, EC)

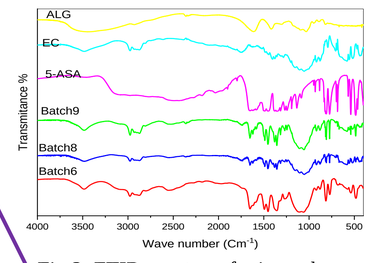


Fig 3 :FTIR spectra of microspheres

The appearance of the characteristic bands of 5-ASA at 1570, 1625 cm-1 and bands from 1490cm-1 to 1255cm-1 in The FTIR spectra of microspheres shows the happened encapsulation.

Release kinetics in the gastric meduim

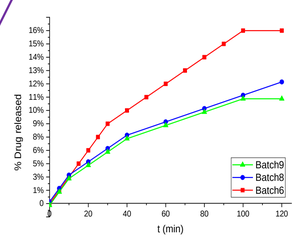


Fig 6: Release profiles of 5-ASA from microparticles in pH=1,2

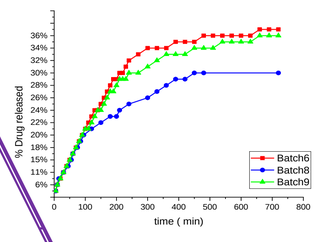


Fig 7: Release profiles of 5-ASA from microparticles in pH=6,8

Mathematical modeling of release profiles in the gastric meduim

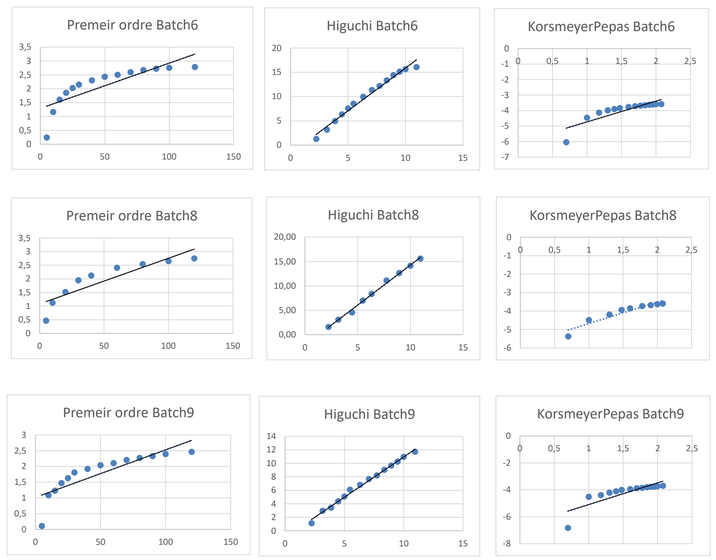


Fig8 : The release kinetics and mathematical modeling studies of batches 6,8 et 9

➢ 5-ASA microspheres exibit a diffusion mechanism release.

Thermogravimetric Analysis (TGA)

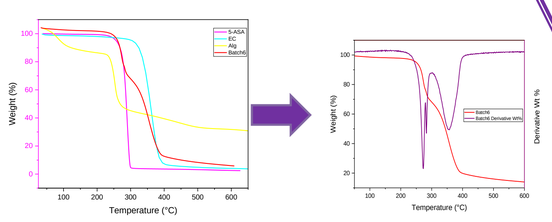
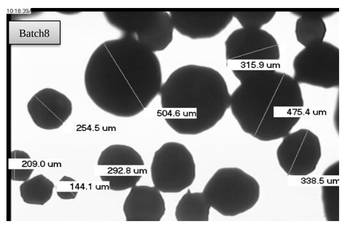


Fig 4:TGA/TDA of microspheres

The thermogram for batch 06 was recorded in the temperature range of 25–600 ◦C, which shows three steps weight loss patterns. It is observed that this complex lost 29.15% in the temperature range from 50 to 270 ◦C designating the removal of ALG then 5-ASA at 286°C. Beyond this temperature, the complex starts decomposition. Finally the TGA curve displayed a plateau around 356◦C, consistenting EC.

Optical microscopy of microparticles



Microspheres with a spherical shape range (200µm-300µm) for the formulation batch8

Fig 5 :Optical microscopy of microspheres (batch 08)

Conclusion

The colon targeted microspheres 5-ASA were prepared by emulsion solvent evaporation technique. Based on the results of the physicochemical characterization and in vitro drug release stadies:

- The dual cross-linked alginate-ethylcellulose formulation was developed as a sustained release multi-particulate delivery system that may be effective to achieve desired targeted specificity.
- The release kinetics and mathematical modeling studies carried out for optimized formulation shown that the optimized formulations were of non fickian mechanism that was governed by both diffusion and erosion controlled.
- The system followed Higuchi and Korsemeyer peppas model fittings that interpreted for sustained and controlled drug releases. In conclusion, this work presents possible approaches for the modified release of conventional drug into newer system with a potential for colonic drug delivery and treatment of inflammatory bowel diseases.

References

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