Formulation and investigation of diclofenac sodium containing drug products with modified release

Ph.D. thesis

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SUMMARY

The aim of my work was to develop pH sensitive multiparticulate system providing the drug liberation with increasing pH only in the intestine after leaving the stomach. Therefore a stomach protective dosage form was developed without the application of any type of coating. The model active compound was diclofenac sodium mainly used as anti-inflammatory agent, but it is widely used in arteriosclerosis too. The most frequently side effects of orally administered NSAID are gastric ulcer and hemorrhage in stomach.

Two different methods (coacervation and in situ gelation) were used to prepare microcapsules as multiparticulate dosage form and their physical and mechanical properties were checked.

The in situ gelation method was studied in detailed while the coacervation was not successful to prepare suitable particles.

Using three-component gel system the parameters influencing the production of microcapsules were optimized on the base of swelling and erosion determinations and by DSC method. The dissolution properties of different samples were evaluated by mathematical models describing the mechanism of the process. The absorption was simulated in vitro and using survivor intestinal ring, while the ulcerogenity was tested in vivo in rats. The changing of crystal form during preparation has deep impact on the structure of microcapsules, which was studied in free films by NIRS, X-ray and DSC method.

From the prepared microcapsules tablet with similar liberation profile to marketed Voltaren® tablet and transdermal patches with prolonged drug liberation were prepared.
INTRODUCTION

Nowadays among dosage forms the multiparticulate systems involving microcapsules, gain more emphasis. One of the advantages of these systems opposite to conventional forms is that they show uniform gastrointestinal distribution and absorption and by mixing the particulates with different drug liberation profile controlled release preparations may be produced. Encapsulation is a suitable method to incorporate solid, liquid and gaseous materials into a system covered by a shell, to produce solid dosage forms. Both conventional and biological materials may be involved. For the production several methods are available depending on the behavior of active ingredient and the required drug release profile. Applying microcapsules the fluctuation and accumulation of drug in blood may be avoided and the inter- and intrapersonal variation may be highly reduced. The patients may be treated flexible according the demands, e.g. cracking of controlled release tablets, or application of microreservoir type transdermal systems.

NSAIDs are used first of all to treat inflammation but may be applied in rheumatic diseases too. Some of the unwanted side effects is the ulcerogenicity, developing during chronic treatment, based on the direct contact with mucosa membrane of stomach and the inhibition of prostaglandin synthesis. To prevent these phenomena NSAID containing solid dosage forms has to be coated, which prohibit the cracking of products and damage of coating may result fatal events. To overcome this problem microencapsulation and than tablettiong may be used which provides the production of dosage form with the same liberation profile and cracking is possible too.
AIM OF WORK

1. Development of diclofenac sodium containing solid dosage form with controlled release.
   1.1. Production of microcapsules with coacervation method.
   1.2. Microcapsule production with in situ gelation method.
       1.2.1. Optimization of composition by changing the ratio of gel forming agents,
               alteration of the concentration of cross-connection providing material,
               changeover the hardening time.
2. Test of production steps and microcapsule properties.
   2.1. Physical and chemical investigation of microcapsules.
   2.2. Test of active ingredient enclosing capacity.
   2.3. Role of active in production steps.
   2.4. In vivo test for ulcerogenity inhibition.
   2.5. Determination of drug release profile by dissolution test.
4. Preparation of tablets from optimal microcapsule compositions.
   4.1. Comparison of dissolution profile with that of tablets is on the market.
5. Production of free films to study the possible crystal form changing during manufacturing process.
6. Transdermal systems production using produced microcapsules and in situ gelation in previously optimized membranes.
7. Prediction calculations to simulate blood level curves from prepared product.
METHODS

Microcapsules were produced using coacervation and in situ gelation methods. Rate and extent of equilibrium water uptake, the erosion in acidic medium were determined by gravimetric method. The role of active ingredient on gel-structure formation was investigated by rheometry (HAAKE VT550 Rheometer). The changing of crystal form during production was checked by NIR (UV/VIS/NIR U-3501 Hitachi Spectrophotometer), by X-ray diffraction (Philip 1050) and by DSC (Haake SII Extar6000) in free films and microcapsules. The sphericity was determined by Nikon SMZ1000 stereomicroscope using Image Pro Plus picture analyzer software. The diclofenac content was tested by HPLC method during the determination of encapsulation efficacy. The solubility of compound was measured by Dissotest CE-6 flow- through-cell apparatus. Drug liberation was checked by PharmaTest PTWS dissolution tester by official methods and by continuous changing of dissolution medium pH using Sartorius Dissolution Tester. The active ingredient content of products were detected by Shimadzu UV-1650 PC UV-Visible spectrophotometer off-line during dissolution tests. During evaluation of curves linear regression method and according to dosage forms different mathematical models (Webull-, Baker-Lonsdale-, Kormeyer-Peppas models) were used and the correlation coefficients were given. The protecting ability of microcapsules was evaluated by in vivo ulcerogenity test, and the absorption readiness was checked by Cabale in vitro intestinal ring method.

The microcapsules were compressed into tablets with Diaf Excentric Tabletting Machine. The microreservoir type patches were prepared from dry and freshly prepared microcapsules and by in situ gelation in membrane respectively. The drug liberation profile was determined by Pharmatest PTWS dissolution apparatus applying rotating basket and official device for transdermal preparations.

Stability tests were performed according to ICH Guidelines applying HPLC method and dissolution determinations.

Microsoft excel program, developed the calculation in our laboratory was applied to simulate the blood level curves according to different dosage forms and doses.
CONCLUSIONS

The following statements may be done on the base of results:

- Three component gel system build up from hidroxy ethylcellulose, hidroxy propylmethyl cellulose and sodium alginate is suitable for the preparation of diclofenac sodium containing microcapsules.

- Phosphate buffer as solvent in gel system allows producing stabile diclofenac sodium containing microcapsules.

- The gel system has impact on crystal form changing during the production but only the size of crystals may be different.

- The encapsulation efficacy of three component system (alginate, HEC, HPMC) is highly increased opposite to two (alginate-HPMC, alginate-HEC) or one component (alginate) systems.

- In acidic medium depending on the number of components and the ratio of gel forming agents the drug liberation was less than 10%.

- In artificial intestinal juice the drug liberation was quicker from three-component systems than from two-, or one component ones.

- Drug liberation profile may be influenced by changing the hardening time and/or calcium chloride as cross-linking agent concentration.
Based on results it may be stated that intestinal drug liberation of microcapsules prepared by in situ gelation method can be changed by the ratio of gel forming agents, in connection with the different swelling of the system. The rate of water uptake (EWU) increased by increasing amount of HEC, which resulted in the increase of drug liberation rate. Enhancing the amount of HPMC shows opposite effect.

Enhancing the amount of HEC the erosion was larger, while the elevation of HPMC percent resulted in opposite tendency.

Results of in vivo ulcerogenity tests shows much more safety GIT profile for the produced microcapsules comparing to diclofenac solution.

The dissolution profile of marketed product Voltaren® tablet was similar to the tablet prepared from microcapsules with the same dose.

The microreservoir type transdermal patch system has controlled release property.

Based on the results it may be stated that diclofenac sodium containing microcapsule produced from three component gel system is stable, and has safe GIT profile. To use these NSAID containing microcapsules modified release preparation may be formulated, which protect the mucosa membrane in stomach without any gastroresistant coating. At the same time they are suitable to prepare microreservoir type transdermal patch with prolonged action.
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