The effect of chitosan on the stability and morphological parameters of tablets with *Epilobium parviflorum* Schreb. extract

ZBIGNIEW MARCZYŃSKI, KAZIMIERA HENRYKA BODEK

Department of Pharmacy and Applied Pharmacy
Medical University of Lodz

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**Summary**

The study is a continuation of research on manufacturing oral solid drug form containing extract from *Epilobium parviflorum* Schreb. This study aims at investigating the usefulness of selected high-molecular substances with particular consideration of chitosan (Ch), silicified microcrystalline cellulose (Prosolv) and croscarmellose sodium (Vivasol) as a carrier of *E. parviflorum* Schreb. extract in oral solid drug form in the process of direct tableting.

In case one series the alternative technological process (with initial granulation) has been applied. The polymer carriers of extract were selected so as to obtain shorter disintegration time in relation to earlier published studies and stability after longer time of storage. The effect of chitosan on selected morphological parameters of practical relevance during storage was estimated.

The obtained results allow to state that the applied high-molecular adjuvant substances proved to be useful in adequate proportions in the production of tablets from dry extract from *Epilobium parviflorum* Schreb. through direct pressing of the tablet mass. The tablet properties all series were accordance with obligatory standards also after longer time of storage (12 months storage). The tablets formed from *E. parviflorum* Schreb. extract with chitosan can be included into preparations of sustained release time of the biologically active substances.
INTRODUCTION

Polymer compounds are a large group of adjuvant substances applied in formulation of drugs of different purpose. Among them polysaccharides - natural biopolymers play a significant role. The study aimed at testing the usefulness of chitosan derived from the chitin of shrimp-shell wastes as a filling and binding substance in the process of direct tabletting of dry extract from *Epilobium parviflorum* Schreb. The deacetylated chitin, colloquially called chitosan, is a water-insoluble polykation. It also belongs to a group of natural biopolymers which degrade enzymatically. Applied as an auxiliary substance, it makes it possible to obtain many different dosage forms. Chitosan has been used as an excipient for direct tabletting of pharmaceuticals to enhance the dissolution properties of some less soluble drugs and to prepare the sustained release drugs [1-4].

Chitosan, obtained from krill chitin, meets the standard requirements for auxiliary substances used in direct tabletting. When present at 50% of the amount of tablet mass, it behaves as a disintegrant. Tablets prepared with the addition of chitosan may, following long-term storage, show a decrease in hardness. However, their disintegration time either remains constant or is reduced [3].

The aim of the study was to obtain oral solid drug form – an uncoated tablet - from dry extract from *Epilobium parviflorum* Schreb. using macromolecular adjuvant substances (Chitosan, Prosolv, Vivasol) in adequate proportions and to investigate their effect on the determined in Polish Pharmacopoeia VI (PP VI) [5] physiochemical properties and pharmaceutical availability of biologically active substances from tablets. When starting manufacturing of tablets with dry extract from *Epilobium parviflorum* Schreb. the following assumptions were made:

- the tablets would be obtained through direct pressing of the tablet mass,
- to compare, a series would be produced with initial granulation,
- the tablets should be characterized by quick disintegration and high pharmaceutical availability of biologically active substances,
the tablet properties must be in accordance with obligatory standards also after longer time of storage,

the study would assess the usefulness of chitosan in obtaining oral solid drug – an uncoated tablet.

The study is a continuation of research on manufacturing oral solid drug form containing extract from *Epilobium parviflorum* Schreb. [6]. The polymer carriers of extract were selected so as to obtain shorter disintegration time in relation to earlier published studies [7].

The so far carried out phytochemical and pharmacological investigations fully justify the application of *Epilobium parviflorum* Schreb. and other species from *Epilobium* genus in the treatment of benign pathologies of prostatic gland. Aqueous extracts from *Epilobium parviflorum* demonstrate diuretic, antibacterial, anti-inflammatory, antineoplastic and immunostimulating activity [8-10]. According to current knowledge the following flavonoids are active bodies of this plant: kempherol, quercetin, miricetin and their glycoside derivatives. *Epilobium* species also contain β-sitosterol and its derivatives. Significant therapeutic value of this material and lack of side effects incline towards its introduction into medical practice.

**MATERIAL AND METHODS**

**Materials**

Dry extract from *Epilobium parviflorum* Schreb. (Phytopharm Klęka S.A.) in the ratio 4.7 – 5.0 : 1 (extraction medium - water) standardized on the content of flavonoids 0.7% expressed in quercetin was the study material.

Shrimp chitosan of deacetylation degree 90.3% and viscosimetry molecular weight 201.7 kDa (Tech-Food Trading Sp. z o.o. Warsaw); microcrystalline cellulose with 2% addition of silicon dioxide (Prosolv SMCC 50 – JRS Pharma); croscarmellose sodium salt (Vivasol – JRS Pharma); polyvinylpyrrolidone (Polyplasdone XL-10 – JRS Pharma); sodium stearyl fumarate (PRUV – JRS Pharma).

**Apparatus**

Reciprocating instrumented tableting machine Korsch, EK-O type (Erweka), concave 12 mm punches; friabilator (Erweka); spectrophotometer Nicole Evolution 300, version 1.0, Spectro-Lab; apparatus for testing disintegration rate (Erweka ZT 53); spatula apparatus (6-
point) for testing the rate of release of therapeutic substance from tablets, MUS 1; bath thermostat, PGW E-1, Medingen; high-speed mixer (Erweka).

**Technology of model tablets manufacturing**

The tablets were manufactured in a reciprocating instrumented tabletting machine (Korsch, Erweka) equipped with concave 12 mm punches. Six series of tablets containing dry extract from *Epilobium parviflorum* Schreb. were produced (250 mg, 50% in a tablet) with 49% portion of fillers and disintegrants (Chitosan, Prosolv SMCC 50, Vivasol, Polyplasdone XL-10) and 1% content of lubricant – sodium stearyl fumarate. All substances were weighed and expressed in 100 tablets 500 mg each. The components of tablet mass were mixed thoroughly and tableted. In case one series (series six) the alternative technological process has been applied. This series was produced with the help pharmacopeal ethanol for granulate kneading. Pharmacopeal ethanol was used to increase the powder density, which did not affect the quantitative composition of the extract, while at the same time enabled obtaining comparable powder density of the extract with the used auxiliary substance (chitosan). The composition of each series is presented in table I.

**Tablets quality evaluation**

Then, they were subjected to morphological parameters of obtained tablets. The tablets were tested for their appearance, size, determination of mean mass, determination of mechanical resistance (crushing strength), determination of disintegration time, determination of the rate of therapeutic substance release. The methodology of the study, the size of the samples collected for the analysis and the limits of acceptable deviation from standard were based on general and detailed principles of PP VI [11]. The statistical hardness of the manufactured tablets was also estimated. Morphological and mechanical parameters of the model tablets were investigated *ex tempore* as well as after 12 months’ storage in closed packing at 20 ºC.

The tablets series 1 did not have the required mass (500 mg) due to insufficient powder density (high degree of fluffiness of chitosan). The average mass of tablets carry out about 440 mg, therefore we were not successful in producing tablets series 1.
Determination of the therapeutic substance rate of release

The rate of active substances release (flavonoids) from the obtained tablets (series 2-6) to the acceptor fluid (0.1 mol/l HCl) was determined with spatula method. The concentration of the released substances was determined spectrophotometrically with Nicolet Evolution 300 spectrophotometer (1cm cuvette) at analytical wave length $\lambda = 256$ nm in comparison with reference material, that is the tablets manufactured only from adjuvant substances.

RESULTS AND DISCUSSION

The results of the carried out studies on manufacturing uncoated tablets from dry extract from *Epilobium parviflorum* Schreb. with the help of macromolecular adjuvant substances are presented in the experimental part. The tablets manufactured with the method of direct tabletting differed in kind and proportion of the used adjuvant substances. The effect of the applied adjuvant substances on mechanical resistance and disintegration time of the produced tablets was determined. The physicochemical properties of the tablets are presented in table II.

The shown in table II results were subjected to statistical analysis as means from the determinations. The manufactured tablets demonstrated normal, physicochemical parameters, consistent with the requirements of PP VI [11]. Each series had smooth surface and the same shape. Low values of deviation from mean mass (tab. II) demonstrated high homogeneousness of the produced tablet mass. No spalls or mechanical damage were found which was confirmed by mechanical resistance test (the mass loss did not exceed 1%). The tablets disintegration process was uniform and was significantly quicker than in tablets manufactured with the method of initial granulation [7].

The disintegration time of the tablets (prepared by the method of direct compressing) the prescription of which was based on the mixture of chitosan, silicified microcrystalline cellulose and croscarmellose sodium (series 2 and 4) did not exceed 15 min. However, application of initial granulation process resulted in prolongation of disintegration time of the produced tablets (series 6). Tablets this series demonstrated the lowest hardness (47,17 N/cm$^2$). Application of only silicified microcrystalline cellulose resulted in significant increase of hardness of series 5 tablets (to 88.33 N/cm$^2$).

The morphological parameters of tablets prepared with the addition of chitosan were determined after 12 months storage. The obtained results allow to conclude that the tablets
show a increase in hardness, which results in practice in an decrease in friability (F, %) and their disintegration time is insignificantly prolonged. Figure present the effectiveness of biologically active substances release from particular tablet series.

The release rate of bioactive substances from tablet series was significantly influenced by both, the components of tablet and by the method prepared of tablet. Tablets series 3 and tablets series 6 demonstrating low pharmaceutical availability (about 15% to 20% after 60 min of release). Higher availability of about 60% after 60 min of release demonstrated tablets from the other series.

The obtained results allow to conclude that the applied adjuvant substances appeared to be useful in adequate proportions in manufacturing tablets from dry extract of *Epilobium parviflorum* Schreb. Significant shortening of tablets disintegration time was achieved as compared to earlier produced ones with the method of initial granulation [7]. Tablets series 6 demonstrating longer disintegration time can be administered as tablets for crushing in teeth.

**CONCLUSIONS**

1. The tablets formed from *E. parviflorum* Schreb. extract with chitosan can be included into preparations of sustained release time of the biologically active substances.

2. The applied macromolecular adjuvant substances (chitosan, silicified microcrystalline cellulose and croscarmellose) appeared to be useful in adequate proportions in the process of direct tableting of dry extract from *Epilobium parviflorum* Schreb.

3. Generally, a significant shortening of the tablets disintegration time was obtained as compared to earlier produced tablets with the method of initial granulation.

4. Tablets containing dry extract from *Epilobium parviflorum* Schreb. as compared to available herbal mixtures and aqueous extracts can be more comfortable in use, first of all, in prostate gland disease.

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