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REVIEW

Soy polysaccharides therapeutic and technological aspects

Robert-Alexandru Vlad[1], Paula Antonoaea[1*], Emoke Margit Redai[1], Daniela-Lucia Muntean[2], Nicoleta Todoran[1], Magdalena Bîrsan[1,3], Anamaria Tataru[1], Adriana Ciurba[1]

1. Pharmaceutical Technology and Cosmetology Department, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania
2. Analytical Chemistry and Drug Analysis Department, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania
3. Drug Industry and Pharmaceutical Biotechnology Department, "Grigore T. Popa" University of Medicine and Pharmacy from Iași, Iași, Romania

Soy polysaccharides represent a multipurpose class of chemicals that include both therapeutical and technological properties. Since they have been first time introduced in the pharmaceutical field, Soy polysaccharides were used in two different pharmaceutical formulations; sublingual tablets and in colon drug delivery. For the sublingual tablets, Soy polysaccharides under the brand name of Emcosoy© - were used as a superdisintegrant in concentrations between 4-8% showing comparable results with the artificial superdisintegrants (sodium starch glycolate, sodium croscarmellose, and polyvinylpyrrolidone). The second technological field where Soy polysaccharides were used is represented by colon drug delivery where it was used in combination with ethylcellulose showing a prolonged lag time compared to the results found in the literature. The medicinal effect of these polysaccharides consists of treating diarrhea. As it will be presented in the article, these chemical compounds tend to decrease the aqueous stool time in patients with diarrhea and to conduct to a softer stool in healthy patients. In conclusion, these polysaccharides present multiple purposes possessing a medicinal effect and also the possibility of being used as a double-faceted pharmaceutical excipient.

Keywords: soy polysaccharides, excipient, superdisintegrant, colon drug delivery, therapeutic effect

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Introduction

Soy polysaccharides (SPS) represent a class of chemical products that occur usually in *Morchella esculenta* and *Glycine max* [1].

The polysaccharides have the capacity of decreasing the risk of developing tumors as a result of the antioxidant effect [2].

Besides this therapeutical effect, these classes of chemicals possess also an underutilized nutritional effect thereby, the soybean curd residues can be used also as a fertilizer [3].

Recent studies have shown that this class can be a helpful excipient, being used as a disintegration agent (Emcosoy© - EMCS) or as a colon drug delivery agent [4,5].

Until now few studies presented the superdisintegrant use of SPS. Sublingual formulations were developed where SPS was utilized as a superdisintegrant. Hosny and its collaborators took into consideration the API major problems represented by the low water solubility, first-pass metabolism, and gastrointestinal effects. Practically by developing a sublingual formulation all the disadvantages mentioned above will be avoided [5]. Since SPS represents a new superdisintegrant, future studies might include them for developing fast dissolving tablets and orodispersible tablets (ODTs). The main advantage exhibited by this excipient is represented by the fact that it is a natural polymer in contrast to other artificial excipients included in the superdisintegrant class such as sodium starch glycolate - SSG, sodium croscarmellose - CCS, or polyvinylpyrrolidone – XPVP. The excipients mentioned above are used in most of the formulations where a fast disintegration or a fast release is taken into consideration [6-14].

SPS is a soft white fibrous powder that has the following components cellulose, hemicellulose, pectin gum, and mucilage. The disintegration takes place taking into consideration its wicking mechanism by pulling the water into the tablet matrix. As a result, the disintegration time decreases, and the tensile strength is less affected [15].

In the study where soy-polysaccharides were used as colon drug delivery agents a mixture of soy-polysaccharides triethyl citrate, isopropyl alcohol methylene chloride, and ethylcellulose was used [4]. The pharmaceutical formulation obtained was a film on which a mixture of soy-polysaccharides and ethylcellulose was sprayed varying the spraying parameters and conditions [4]. The API used was chlorpheniramine an antihistaminic H_1 that usually is used in combination with other drugs such as paracetamol, C vitamin, and pseudoephedrine used for cold and flu treatment.

This study aimed to evaluate this multipurpose excipient and to present the therapeutic effects and its application in the pharmaceutical technology field.

Soy polysaccharides in the food industry

SPS can be used in the food industry as a result of its emulsifying and stabilizing effect. Thereby they can be used to obtain emulsions and suspensions. Notably, SPS can be used to improve the stability of different liquid nutrients

* Correspondence to: Paula Antonoaea
E-mail: paula.antonoaea@umfst.ro

and to increase the emulsifying effect when needed [16]. SPS represents a good component that can be used as an emulsifier taking into consideration its high-water solubility, low viscosity, and good thermostability [17]. Under different conditions of temperature and pH, the SPS can have different behaviors. Usually, between the 2-6 pH range and 40-120°C, the SPS remains fluid [18].

SPS forms a film that is responsible for the emulsifying effect; the formatted film can prevent the aggregation that might occur as a result of the electrostatic repulsion between the droplets [17]. To establish which component is responsible for the emulsifying effect two enzymes were used (pectinase and hemicellulase) to decompose the polysaccharide, noticing that two sugar chains responsible for the above-mentioned effect, are represented by β-galactan and α-arabinan. The amount of SPS needed to stabilize an oil-in-water emulsion is 4%. SPS is composed of two fractions one with a high molecular weight and one with a lower molecular weight, each one possessing different functions. The high molecular fractions are usually used to stabilize dispersions and to emulsify oil-in-water emulsions whilst the lower molecular fractions are used to protect the emulsified lipids from oxidative effects [19,20].

SPS has been included in different beverages with a high content of dietary fibers that decreases the risks of diabetes, improves bowel movements, and reduces blood cholesterol. A mixture of κ-carrageenan and 4% SPS is used as a stabilizer in a thickened milkshake beverage [21]. Another quality of food improvement presented by SPS includes the reduced viscosity of gelatinized starch preventing the noodles to adhere to each other [22,23].

Soy polysaccharides as a superdisintegrant

SPS was developed as a superdisintegrant excipient called Emcosoy© (EMCS). In the study conducted by Hosny and his collaborators, EMCS was used in five out of twelve formulations in concentrations of 4% (two out of five – F1, F2) or 8% (three out of five – F3, F4, F9) of the total mass (m/m). Since the amount of EMCS was varied to obtain tablets with a constant mass, other excipients mass was varied too, to determine their influence on the parameters studied (between the first two - F1, F2 the differences consisted in the amount of cellulose - Avicel© and EMCS), (between the formulations three and four – F3, F4 the differences consisted in the amount of EMCS and also cellulose - Avicel©). For the third and fourth formulation, xylitol was added whilst the citric acid was removed from the components list. In the last of the formulation where EMCS was used - F9, in a concentration of 8%; the xylitol and citric acid were removed from the formulation. The results for the five formulations selected from the study mentioned above showed small differences regarding the wetting time (25.3 sec for the second formulation and 32 sec for the third formulation, the other three formulations taken into consideration presenting wetting times between these two values. Another parameter studied was the water absorption ratio, where small differences between the formulations with EMCS were registered (53 for the third formulation and 60 for the second formulation). Another important parameter studied was the time required for 90% of the API to be released. In this case, important differences were registered as the second formulation presented a T_{90} of 5.25 min whilst the third formulation presented a T_{90} of 18.34 min [5]. The F2 formulation was considered the most suitable taking into consideration the parameters studied, so the F2 behavior in accelerated conditions was studied. The hardness, friability, drug content, wetting time, *in-vitro* dispersion time, and cumulative release after 5 minutes were analyzed but small differences were noticed. The hardness remained more than 6 kg/cm^3 after three months and the friability was also less than 0.5% after three months. The wetting time and *in vitro* dispersion time did not suffer from alterations after three months of keeping the tablets in accelerated conditions [5]. The API content was more than 98% whilst the cumulative release after 5 minutes decreased from 95.6% to 91%, maintaining at values over 90%. We can conclude that besides the EMCS content that influenced the T_{90} parameter, the other excipients amount influenced also the time required for 90% release. The second formulation presents good properties for a fast-releasing formulation, fact that might be helpful considering the API included in the sublingual matrix.

In another study conducted by Amayreh and her collaborators, the SPS mechanism of disintegration was evaluated by image analysis. Besides SPS, the other two superdisintegrants were evaluated to establish the appropriate concentration at which the disintegration occurs and the concentration at which the disintegration starts to decrease or is impeded. In this study, it has been observed that in the case of SPS the disintegration occurs faster at concentrations between 4-8%, and its mechanism is represented by swelling behavior. At concentrations of 1-2% or 16%, the disintegration did not occur or was negatively influenced. SPS must be used in the range mentioned before because is negatively affected by the hydrophobic lubricants. SPS could be used as a novel superdisintegrant with results in terms of disintegration comparable with the ones obtained if CCS, SSG, or XPVP is used. Due to its composition, an increased interest for this excipient might be in the nutraceutical market, where a natural superdisintegrant might be preferred instead of a synthetic one [24].

Soy polysaccharides as a possible colon drug delivery excipient?

Colon drug delivery (CDD) presents advantages in the management of various diseases such as colon cancer, Chron's disease, and ulcerative colon [25-27].

Incorporating APIs in a CDD represents a huge challenge taking into consideration the barriers that occur such as the pH in the gastrointestinal tract and its variation and the enzymes found in the gastric fluid [25-27]. Also, the in-

teractions with other drugs such as gastroprokinetic drugs or different physiological conditions should be considered.

The microbial flora consists of numerous anaerobic bacteria such as Bacteroides, Clostridium, Enterococci, Bifidobacteria, and Enterobacteria. The specified anaerobic bacteria secrete enzymes such as β-glucuronidase, β-xylosidase, α-arabinosidase, β-galactosidase, azo-reductase, nitroreductase, deaminase, and urea hydroxylase fact that implies developing a prodrug or using polysaccharides to prevent the fast release of the drug or a possible decomposition [4, 28-32].

In the study conducted by Ursekar et al., the SPS was used as a colon drug delivery agent in combination with ethylcellulose, the mixture serving as a first coating agent for the hard gelatin capsules developed. The second coating agent used was Eudragit© S100. The amount of coating agents used was 6% (w/w) each. The presence of the first and second coating layers was certified by the Scanning electron microscopy (SEM) studies. Releasing profiles were evaluated at two pHs of 1.2 and 7.4. At pH=1.2 no release was observed while at 7.4 the dissolution was improved by adding the pectinase enzyme in the dissolution media. 62.62 % of the drug was released without pectinase while when pectinase was used 77.01 of API was released [4].

Ethylcellulose (EC) was used as a film-forming agent taking into consideration its advantages such as reduced swelling of SPS fact that implies a leaching reduction in two important compartments represented by: stomach and small intestine. As expected, the incorporation of SPS in the EC matrix conducted to a smaller tensile strength in comparison to the films that contained only EC. The tensile strength was three times lower when SPS was incorporated in the EC matrix [4].

The lag time for different coating agents and APIs was studied to establish a composition that conducts to increased lag times. As it can be noticed in Table I, the combination of EC-SPS and Eudragit conducted to the highest lag time, a fact that might be useful in the future in developing new pharmaceutical formulation with pulsatile release in the colon with different APIs. Even if in some studies the *in vivo* and *in vitro* lag times tend to be similar there are cases where differences might occur [39].

Soy polysaccharides therapeutic effects

SPS has been intensively studied regarding its therapeutic effect. The primary disease that has been taken into consideration when using SPS was diarrhea. The results regarding their effect on diarrhea and different other fecal parameters can be found in Table II.

SPS tends to improve the stool consistency, and usually, the aqueous consistency lasts less in the case of patients where SPS was used [40,41]. Also, parameters such as cholesterol, HDL cholesterol, TG levels, are not usually influenced by the SPS intake. A review study conducted by Akhlaghi and its collaborators where the influence of SPS and the isoflavones found in SPS were studied showed that the isoflavones might have a different impact on weight status, as isoflavones might decrease the bodyweight whilst

Table I. The lag time for different colon drug delivery formulations with various APIs

Nr.	Composition	Active pharmaceutical ingredient (API)	Lag time (h)	Ref.
1	EC, SPS, Eudragit©100	Chlorpheniramine maleate	9	4
2	Eudragit© RSPO, Guar gum and Hypromellose (HPMC)	Theophylline	7.5	33
3	Eudragit©, superdisintegrants (SSG or CCS)	Mesalazine	5	34
4	Eudragit© S100, starch polysaccharides	Diethylenetriaminepentaacetic acid	7.2	35
5	Pectin, chitosan, HPMC	Diethylenetriaminepentaacetic acid	7	36
6	Amylose, $HPMC_{15LV}$	Paracetamol	4	37
7	Amylose, $HPMC_{4M}$	Paracetamol	8	37
8	Chitosan microspheres	Meloxicam	4.7	38
9	Hypromellose acetate succinate L and M grade (HPMCAS-LG, MG)	Theophylline	4	39
10	$HPMCAS_{LG, MG}$	Antipyrine	2	39
11	$HPMCAS_{LG, MG}$	Paracetamol	4	39

Table II. Clinical studies where the SPS effect on fecal and blood parameters were studied

Nr.	Objective	Patients	Observations	Conclusion	Ref.
1	The effect of SPS on severity, duration, and nutritional outcome at patients with diarrhea	34 patients Ages: 2-24 months 2 groups: G1: 19 – received SPS G2: 15 – did not receive SPS	Liquid stool after hospitalization 43 h at patients who received SPS and 163 h at the patients who did not receive SPS	4 patients from G1 and 2 from G2 failed therapy. The absorption of macronutrients and changes in anthropometrics were not affected. The liquid stool duration was reduced in the first group where SPS was used.	40
2	The influence of tube-feeding with SPS on stool weight, stool consistency, fecal nitrogen, and diarrhea incidence	9 head-injured patients	Incidence of diarrhea was higher in subjects who had albumin levels higher than 37g/L.	SPS-tube feeding did not affect the stool weight and mean fecal nitrogen. Slightly positive influences on SPS-tube-feeding on stool consistency.	41
3	The influence of SPS on perceived hunger, body weight, lipids, and fecal parameters.	30 adults 1 male 29 females 2 groups – a fiber group and placebo group	Participants from both groups received crackers. The first groups received 6.76 g of SPS while the second one received low fibers crackers 30 minutes before each meal.	Subjects that consumed fiber crackers felt less hungry. The weight loss was insignificant in both groups. Total cholesterol, High-Density lipoprotein cholesterol - HDL, triglycerides - TG, blood glucose, hemoglobin, hematocrit levels did not change during the 14 weeks study. Insignificant changes regarding the fecal parameters were observed.	42

in some cases SPS conducted to an increased weight (which was insignificant from a statistic point of view). Usually, the isoflavones tend to decrease the bodyweight in the cases of low-ages women participants [43].

In a study conducted by Kraemer et al., the effects of soy and whey protein supplementation were studied on Acute Hormonal Responses in ten resistance-trained men. This study highlighted the fact that SPS does not obstruct the anabolic signaling post-exercise (the concentration of estradiol did not increase and the testosterone serum levels remain the same) [44].

Kalman showed in his research called *Effect of protein source and resistance training on body composition and sex hormones* that no significant differences occurred between a placebo group and a group that received SPS. Also, the total body mass and the percentage of body fat were not altered [45].

Conclusions:

SPS represents a useful excipient that might be utilized in developing fast dissolving tablets since in concentration between 4-8% improves the disintegration behavior of the final matrix. The main advantage of the SPS is represented by the fact that it can be included in the class of natural excipients whilst the other superdisintegrants widely used in the pharmaceutical market are included in the artificial class of superdisintegrants. EMCS represents an excipient that might be used in the future to formulate dietary supplements taking into consideration the fact that is a natural excipient. Besides its superdisintegrant effect, SPS has been considered a good excipient for colon drug delivery with better or comparable lag time in comparison with consecrated excipients, but it must be specified that it was used in combination with two other excipients that are widely used in the colon drug delivery pharmaceutical formulation (EC and Eudragit© S100). SPS can be considered as a double-faceted excipient. Also, the nutritional and the therapeutic effect should not be forgotten, SPS presenting good results in stool consistency in patients with gastrointestinal diseases.

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Author Contributions

R-AV: Conceptualization, Formal analysis, Resources, Data curation, Writing - original draft preparation, Visualization, Project administration, Funding acquisition, Writing- Reviewing and Editing
AP: Methodology, Resources, Writing-original draft preparation, Writing- Reviewing and Editing
EMR: Methodology, Resources
MB: Software, Writing - original draft preparation
D-LM: Conceptualization, Data curation, Supervision, Project administration
NT: Resources, Writing-original draft preparation.
A T: Formal analysis, Resources, Data curation, Writing-original draft preparation
AC: Conceptualization, Methodology, Resources, Data curation, Writing-original draft preparation, Supervision, Project administration

Conflict of interest

None to declare.

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