CHARLES UNIVERSITY
Faculty of Pharmacy
in Hradec Králové

Adhesive and rheological properties
of chitosan-based mixtures in media of different pH

Diploma Thesis

Department of Pharmaceutical Technology

Hradec Králové 2020   Alaa Omar

Statement of originality

I confirm that this diploma thesis is my own work and I worked on it by myself. Literatures and sources that I used are listed in the literature list and are properly cited.

Date: 31/05/2020   Alaa Omar

Acknowledgments

I am really grateful and I would like to express my deep gratitude to my supervisor PharmDr. Eva Šnejdrová, Ph.D. for her help, guidance, encouragement and patience. Thanks to the consultant Mgr. Juraj Martiška for his helpful advice and technical assistance.

Thanking the lord for giving me the strength, the power and the ability to focus to put 100% effort in my work.

To all my friends and family for helping me survive through the stress and not letting me give up.

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Abstract

Title of thesis:

Adhesive and rheological properties of chitosan-based mixtures in media of different pH

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The aim of the diploma thesis is the study of rheological and adhesive properties of tableting materials for matrix tablets based on chitosan. The theoretical part describes in detail the materials used to prepare the matrix tablets, which were chitosan, sodium alginate and hypromellose. The experimental section was focused on the flow and adhesive properties of the chitosan-based mixtures after exposing them to a media of different pH. The flow tests were done on an absolute rotational rheometer. Obtained viscosity curves were analysed by Power law model. Viscosity at 10 s^{-1} and Power Law model coefficients were used to evaluate and compare the flow behaviour of dispersions with different concentrations of retarding component in different media. The test of adhesion was carried out using a pull away test on a rotational rheometer and evaluated as maximal detachment force. The remarkably high viscosity of 5% dispersions at pH 1.2 is due to the dissolution of chitosan, as sodium alginate is not soluble in acidic media. The increase in viscosity with the concentration of the retarding component is insured by hypromellose. A 20% dispersion of tablet mixtures in a medium is more suitable for testing. Higher concentrations better reflect the conditions in the intestine where there is less fluid. In subsequent tests, it will be desirable to first expose the tablets to an acidic environment, immediately to bring them to pH 6.8 and only then measure the viscosity and adhesion.

Keywords: matrix tablet, chitosan, sodium alginate, hypromellose, viscosity, adhesion

Aim of the diploma thesis

The aim of this diploma thesis is to test and compare the rheological and adhesive properties of chitosan-based mixtures for matrix tablet in different media.

In summary, this thesis includes:

- Testing of the rheological behaviour employing absolute rotational rheometer. Choice of suitable geometry, sequence for testing, variable parameters and method of evaluation of the results.

- Testing of the adhesivity employing the suitable tensile test in software f-Space for Kinexus. Choice of suitable variable parameters of the test and method of evaluation of the results.

- Use of water, hydrochloric acid buffer pH 1.2 and phosphate saline buffer pH 6.8 for hydration of two types of hypromellose and chitosan-based mixtures for matrix tablets with different contents of retarding components made of sodium alginate and hypromellose.

- Evaluation of the effect of the type of medium and the composition of the tested chitosan-based mixtures for matrix tablets on flow behaviour and adhesion.

Abbreviations

BAC	Benzalkonium chloride
F10	Chitosan-based mixture for matrix tablet made of chitosan and 50 % of SA and MC100 in ratio 1:1
F8	Chitosan-based mixture for matrix tablet made of chitosan and 30 % of SA and MC100 in ratio 1:1
F9	Chitosan-based mixture for matrix tablet made of chitosan and 40 % of SA and MC100 in ratio 1:1
HCl	Hydrochloric acid buffer
HOP	Hydroxypropoxy
HP	Hydroxypropyl
HPMC	Hypromellose
HTCC	N-(2-Hydroxyl) propyl-3-trimethyl ammonium chitosan chloride
MC	Methocel
MC100	Methocel K100M
MC15	Methocel K15M
MO	Methoxyl
PEC	Polyelectrolyte complex
PSB	Phosphate saline buffer
SA	Sodium alginate

1   Introduction

Tableting mixtures for matrix systems presented in this study are based on chitosan, a cationic linear polysaccharide exhibiting a pH-sensitive behaviour due to the large quantities of amino groups on its chain. It dissolves easily at low pH while it is insoluble at higher pH ranges. Sodium alginate used as a retarding component is an anionic polysaccharide soluble in neutral or alkaline solutions but insoluble in acidic ones. The principle of action of the mixture of these polymers is that at low pH chitosan is protonated, i.e. soluble, but sodium alginate, not. At pH 6.8, sodium alginate begins to dissolve. Its dissociated carboxyl groups react with the amino groups of chitosan and crosslink these chains. A polyelectrolyte complex is formed between chitosan and sodium alginate, which brings considerable advantages, such as the ability to release in a controlled manner, but also to reduce the pH dependence. Hypromellose is added as an excipient to increase viscosity, adhesion, and also as a retardant.

The diploma thesis deals with the study of rheological and adhesive properties of tableting mixtures for the formulation of matrix tablets for targeting a drug to the intestine. The rheological and adhesive properties after exposure to media of different pH were determined by rotational and tensile tests using absolute rheometer.

2 Theoretical section

2.1 Matrix tablets

Matrix tablets are systems that are used for controlling the release of drugs. The story behind such theory was to control the drug release in our body by optimization of the plasma level of the medicine, since the most used route for the ingestion of drugs is by mouth. Such systems are of several types, such as: the modified release type, the extended and the delayed release type.[1] Matrix systems can either be controlled by diffusion, dissolution, or erosion, all of which are used to control the release of the medicine in a manner that is continuous.[2]

Figure 1. Types of matrix systems [3]

Hydrophobic matrix   Swellable matrix   Erodible matrix (size reduction)
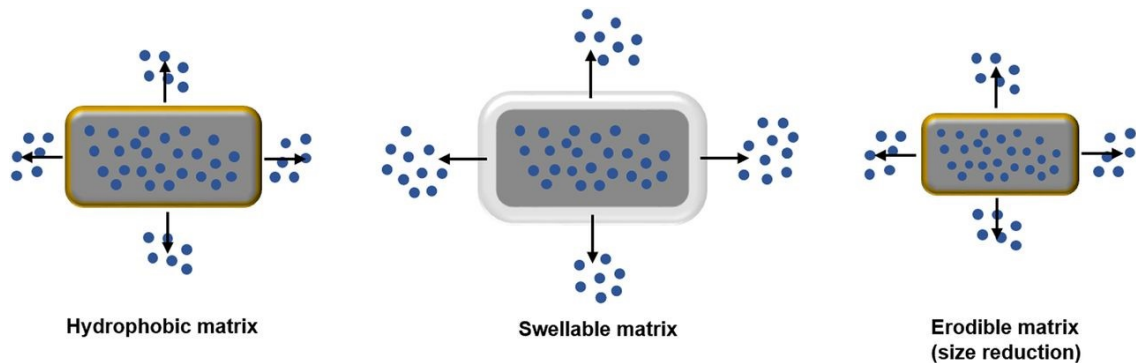
Matrix systems can be classified into several types:[4]
- Hydrophilic: which is mostly water soluble, for e.g.: Eudragit L30D.
- Hydrophobic: which are mostly made of fatty acids or waxes, for e.g.: stearic acid.
- Lipid: which are made mostly of lipids, for e.g.: Carnauba wax with stearic acid.
- Biodegradable: which can be both, synthetic or natural, for e.g.: proteins or esters.
- Mineral: which are usually made from seaweed, for e.g.: Alginic acid.

Matrix systems can also be classified based on their porosity:[4,5]
- Macro-porous: the diffusion of the drug occurs through pores and the pores are larger than the molecule.
- Micro-porous: the diffusion of the drug occurs slightly through pores and the pores are a bit larger than the molecule.

- Non-porous: pores are non-existent and diffusion happens through a mesh of network.

Nowadays, matrix tablets are widely used as they have a lot of advantages. They provide higher stability of drugs since the drugs don't undergo changes or don't get hydrolysed in the stomach. They reduce the number of doses since the release of the drug is over a longer time which makes it cost effective as well as side effects are reduced and offer better safety for drugs with a large potency, which makes it very useful for patients that have to take multiple drugs, have multiple diseases or have chronic diseases and forget to take their medicine on time because of high number of doses, thus resulting in a very good patient compliance.[6]
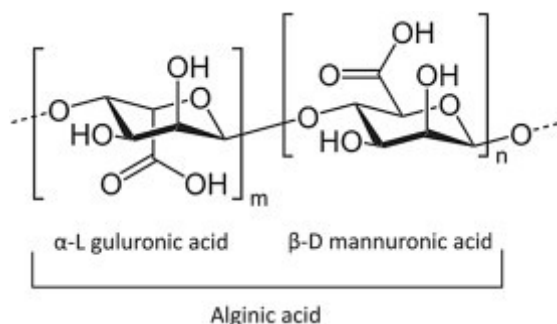
2.2 Alginate

Alginate is a hydrophilic polysaccharide and a natural polymer. It is found in algae, brown seaweed and it can consist of multiple cations such as Ca, Na. It's derived from alginic acid, which swells in water forming insoluble derivatives. It has relatively low toxicity and is quite cheap, which is a reason for why it's used in so many applications, orally or even parentally.

Alginate gels can be formed by the reaction with cations, only, the divalent ones. However, alginate is quite sensitive to pH changes. Alginate doesn't work at low pH such as the pH of the stomach acid whereas in high pH, it's converted to a soluble form such as in the intestines. Alginate allows bio-adhesion meaning it is muco-adhesive, which allows drug delivery to the mucosal areas.[7]

It's biocompatible meaning it has low toxicity and is not harmful to the tissues and are widely used as emulsifiers, thickeners and stabilizers. Moreover, Alginates can entrap and release proteins, proteins like heparin and haemoglobin.[8,9] The entrapment theory is based on preparing a solution of sodium alginate containing the protein and the release theory is based on a couple of mechanisms; diffusion and degradation. However, the charge of the protein plays an important influence on its release, therefore, if it's negative, it's immediately released while if it's positive, it will firstly interact with the negative charge thus slowing down the release.

Figure 2. Alginic acid structure showing its glucuronic and mannuronic acid linkage [10]

α-L guluronic acid   β-D mannuronic acid

Alginic acid

Alginate is prepared by extracting it from its sources i.e. brown algae, then treated with alkaline solutions such as sodium hydroxide. Then it's filtered thoroughly and one of the following salts, either calcium or sodium chloride will be added to it to allow precipitation to occur. After this process, hydrochloric acid is added and several steps like conversion and purification are performed to give us the alginate powder.[11]

2.2.1 Applications of Alginate

Alginates are widely used in the pharmaceutical field since they are very good stabilizers, emulsifiers and thickeners, which makes them useful in controlled release preparations. Alginates can also help in delivering drugs with low molecular weight[12] and if an amphiphilic gel is prepared, it can help in controlling the release of drugs that don't absorb water i.e. hydrophobic.[13] However, studies were performed around beads incorporation into alginates which formed oxidized alginates to a partial extent. This turned out to be successful since it was possible to use it for the delivery of cytostatic drugs. [14]

In addition, alginates can be used to treat wounds. It does so by being incorporated in wound dressings i.e. gauze, which could keep the wound pretty dry and protect the wound from the access of any type of pathogens. The gels of alginate are very promising in medicine since they can replace organs or tissues for patients affected by diseases. [15]

Figure 3. Actions of dressings with alginate fibres in wounds [15]
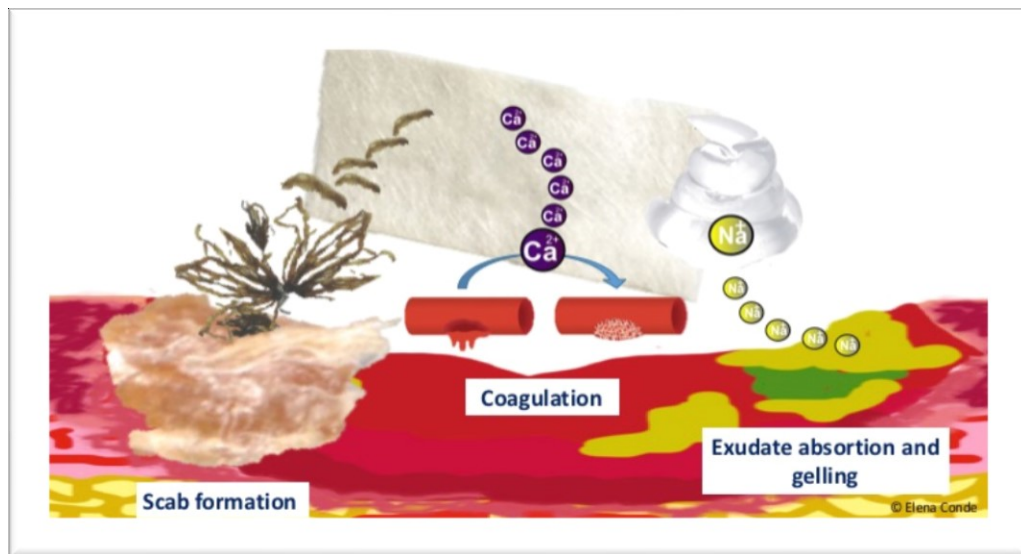
2.2.2 *Alginate hydrogels*

Alginate is often used as a hydrogel rather than powder. The hydrogel form of alginate is often used in most of the applications mentioned above. Hydrogels have a very high water content which gives it the structure of a 3D network.[16] Hydrogels can be prepared by several methods such as:

- **Ionic cross linkage:** Hydrogels prepared by this method include two steps; mixing the aqueous solution of an alginate with a bivalent cation such as calcium together, which will result in the formation of a hydrogel.

- **Covalent cross linkage:** Hydrogels prepared by this method include adding stress to previously formed ionic cross linked hydrogel which will lead to the escape of water and as water escapes, it leads to the formation of a covalently cross linked hydrogel.[17]

- **Cell cross linkage:** Hydrogels prepared by this method include adding cells to an alginate solution that is modified which will lead to the formation of the cross linked network.[18]

Figure 4. Calcium alginate hydrogel [19]
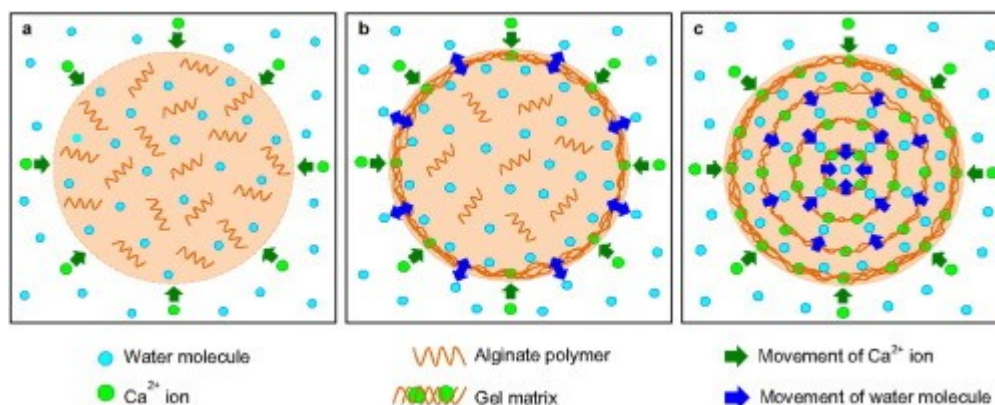
2.2.3 Alginate modifications

Alginate can be modified into several forms and by several methods.[20] Firstly, the thiolated alginate, which is done by covalently linking cysteine to an alginate. This modified type clearly shows positive effects on the properties of muco-adhesivity of alginate.[21]

Secondly, the hydrophobic alginate, which is done by linking wide alkyl groups on the ester group of a sodium alginate derivative. This modified type was very useful in extracting microparticles.[22]

Lastly, the polyelectrolyte complex, which is done by mixing two solutions of polymers with different charges, which has resulted in the formation of a PEC such as the alginate-chitosan complex which is useful in so many applications nowadays such as delivering drugs of protein nature.[23]
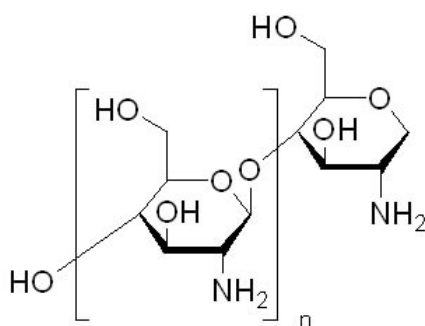
2.3   Chitosan

BP: Chitosan hydrochloride.

Ph.Eur.: Chitosan hydrochloride.

Chemical name: Poly-β-(1,4)-2-amino-2-dexoy-D-glucose.

Typical properties:

- pH: 4.0-6.0.

- Density: 1.35-1.40 g/cm^3

- Moisture content: It adsorbs moisture from the surroundings.

- Solubility: Insoluble in ethanol of 95% and solvents with a pH above 6.5 but not acidic solvents. In acidic solvents, it's quite soluble and the amino groups become protonated.

- Stability: It's quite stable. [24]

Figure 5. Chitosan structure [25]

Chitosan is a linear polysaccharide that is produced by deacetylation to a partial extent. It's a natural polymer that's cationic and it attaches to negatively charged surfaces. It has great surface area and porosity. After it's dried, it's a hygroscopic powder. Its gels can be prepared by acetic acid and sodium hydroxide solution. An interesting fact about chitosan is that, its respective gels can be formed without any addition of a cross linking product or an organic solvent.

It can be found in various animals (crustaceans) such as: crabs, prawns, lobsters. It can also be found in several insects and fungi. The α-chitosan, is the most common type of chitosan, which is extracted from crab and prawn shells. After the extraction, it exists in the form of chitin, which would then be treated by alkali/acid, then the respective chitosan is formed. However, the β-chitosan also exists, it can be found in squids and certain fungi, but is of less importance, since it's quite rare.

Chitosan was found to be non-toxic to the tissues i.e. biocompatible. It can adhere and deliver drugs to mucosal surfaces i.e. muco-adhesive and can be broken down by bacteria i.e. biodegradable. Moreover, chitosan has been seen to improve the bioavailability and absorption of drugs across membranes i.e. absorption enhancer.[26] It does best so for peptide drugs. This is due to the positive charges that exist in chitosan and can interact with membranes and broaden the tight junctions of the membranes making it easier for drugs to pass through.[27]

Chitosan, however, is quite sensitive to pH changes. At low pH, such as in the stomach acid, it's quite soluble. At high pH, such as the intestines, it's quite insoluble.[28] It has been observed that if chitosan is added with a protein, it forms a solution and a chemical bond would be formed between them, if a certain product was added, which is known as a cross linking agent. For example, tripolyphosphate (TPP). The end product that would be formed by this reaction is a chitosan gel. Lastly, there is a good feature about chitosan that it can be easily modified chemically because of its free amino groups.[29,30]

2.3.1 Applications of Chitosan

Chitosan may not only be used in the pharmaceutical field but also in non-medical applications, for example, cosmetics, food, agriculture, water and beverages.[31] Its respective gels that are formed without any organic solvent or cross-linking agent, can be used in transplantation. It can be used also as an enzyme immobilizer, a binder; in fat plus paper and can be used in biosensors too.

If chitosan is mixed with alginate, it can immobilize antibodies. Chitosan can help in the adhesion of compounds to the surfaces i.e. adsorbent. It can remove substances with undesired effects from solutions. It's used as implants in surgeries and by doctors to stitch wounds during surgeries, it's also contained in wound dressings i.e. gauze. It causes bleeding to stop and facilitates wound healing.[32]

In the pharmaceutical field, it has been seen that chitosan is widely used in controlled release preparations for drugs and can stop the growth of tumour cells by its ability to activate macrophages.[33] In addition to its usage as a coating material, it helps in coating other products i.e. encapsulation.[31,34]

Figure 6. Schematic representations of the benefits of chitosan wound dressing [35]
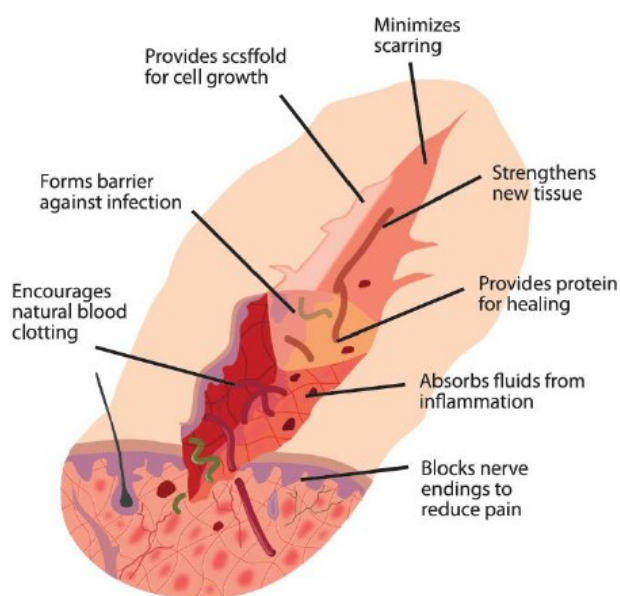
2.3.2 *Chitosan modifications*

Chitosan can be modified into several forms and by several methods. Firstly, the thiolated chitosan, which is done by fixing or resting thiol groups of chitosan.[36] Secondly, the trimethylated chitosan, which is done by methylating chitosan in a reduction type of reaction.[37] Thirdly, carboxymethyl chitosan, which is done by the addition of a carboxylic acid group to an alcohol group on chitosan.[38] Fourthly, cationically modified chitosan, N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC), which is done by reacting chitosan with methyl ammonium chloride thus resulting in a water soluble chitosan derivative. Lastly, the polyelectrolyte complex (PEC) such as chitosan-alginate complex or chitosan-pectin complex.[39]

Figure 7. Preparation of HTCC [39]
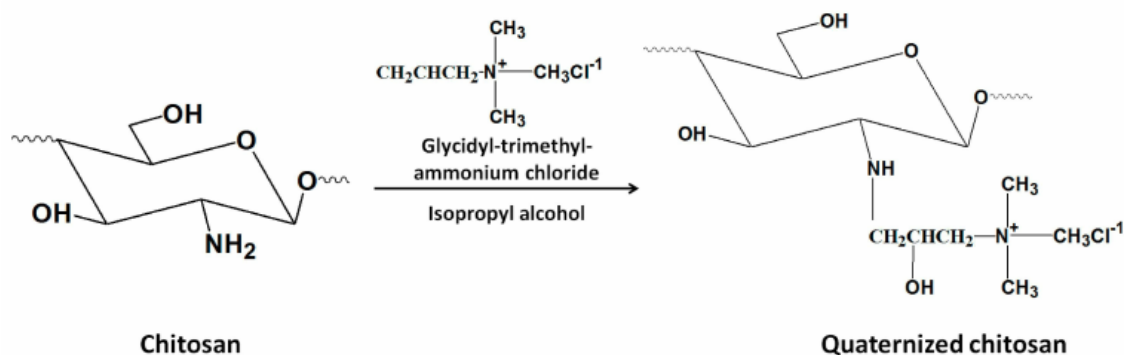
2.4   Combination of Alginate-Chitosan

Combining alginate and chitosan together has shown great success due to its possible usage in delivering drugs of protein nature. When combined together, a complex is formed and the theory behind such complex formation is due to the presence of the carboxyl groups in alginate which interact with the free amino groups of chitosan. In another words, combining chitosan and alginate, result in such polyelectrolyte complex(PEC).

Figure 8. Scheme of polyelectrolyte complex [40]
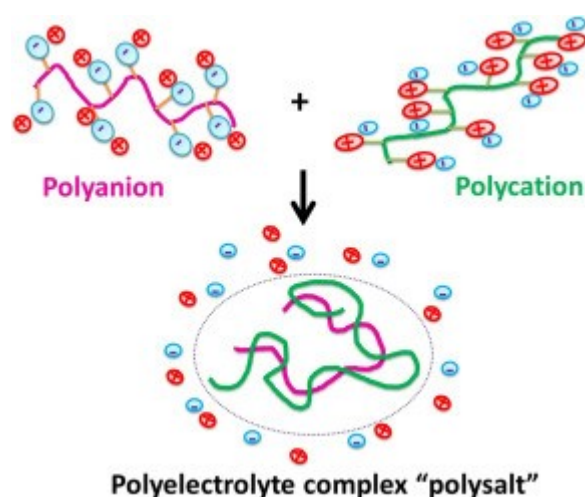
Such complex may be quite useful in reducing any leakage from drugs that are encapsulated. However, this complex had some limitations. As mentioned above, alginate was seen to be insoluble in the stomach acid whereas as chitosan was quite soluble, so the presence of alginate helped in the prevention of chitosan's instability in the stomach low pH. Such way is also observed for the opposite pH, as in, alginate was quite soluble in the intestines whereas chitosan was insoluble, so the presence of chitosan prevented alginate's instability in the intestine pH.[41,42,43]

Figure 9. Alginate-chitosan cross linking interaction [44]
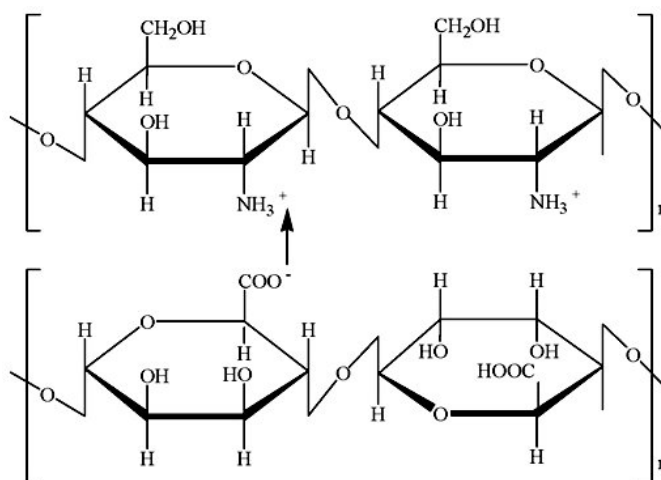
2.5   Hypromellose

Ph.Eur.: Hypromellose.

JP: Hypromellose.

BP: Hypromellose.

Chemical name: Ce llulose hydroxypropyl methyl ether.

Typical Properties: It's a white synthetic polymer. It's without any taste nor smell.

- **pH**: 5.0-8.0.

- **Density**: 1.326 g/cm^3

- **Melting point**: It has a glass transition temperature at 170-180 ℃, it gets a tan colour at 190-200 ℃ and chars at 225-230 ℃.

- **Moisture content**: It's absorbing from the surroundings any moisture.

- **Solubility**: It forms a viscous colloidal solution in cold water whereas in hot water, ethanol (95%), ether and chloroform- it's pretty insoluble. Whenever, a mixture of ethanol is prepared with another solvent, it becomes soluble.

- **Stability**: It's quite stable at pH 3-11. For long term storage, aqueous solutions are prepared and stored because of enzyme resistance activity and high stability.

Hypromellose is a polysaccharide from the family of cellulose ethers. It's mostly used as a binder and in film coated tablets. It shows hygroscopic behaviour after drying. An interesting feature of Hypromellose is that upon heating it at 75-90 °C, it forms a gel which can reverse back to a solution, which is the term known as: reversible sol-gel transformation. It can retain water, which is pretty useful in coatings, ceramics as well as it can lower friction in ceramics or rubber. It's widely used in food since they don't increase the number of calories, so they are of a neutral function in food. It's non-toxic to tissues i.e. biocompatible and can be broken down by bacteria i.e. biodegradable.[45,46]

Figure 10. Hypromellose structure [47]

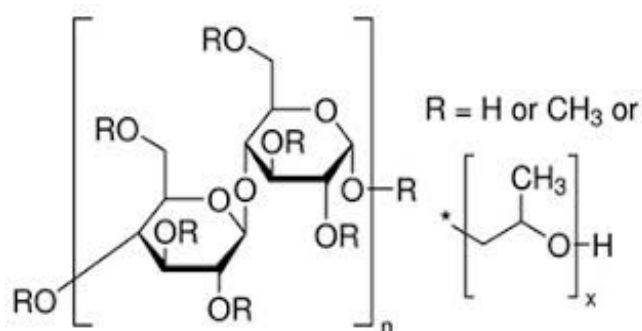Table 1. HPMC substitution types [47]

Substitution	MO percent	HOP percent
1828	16,5 to 20,0	23,0 to 32,0
2208	19,0 to 24,0	4,0 to 12,0
2906	27,0 to 30,0	4,0 to 7,5
2910	28,0 to 30,0	7,0 to 12,0

2.5.1 *Preparation of HPMC aqueous solution*

Firstly, HPMC is going to be hydrated. This hydration is achieved by the addition of about 20-30% water. HPMC will then be added to the water and stirred when it's going to be heated at around 80-90 °C. When everything is mixed thoroughly, some cold water is added to reach the desirable volume. However, such solution is susceptible to microbial attack and so antimicrobial preservative should be added. For e.g. when HPMC solutions are prepared, they are sometimes used in eye preparations, in such a preparation, a preservative like BAC is added.[46]

2.5.2 *Applications of Hypromellose*

HPMC is widely used for binding tobacco papers. It has the ability to prevent the oil absorption in food such as potatoes, when they are fried since it has resistance against oil and fats. It can be used to prepare films that can be used to cover food, in order to persevere it and make it live longer since Hypromellose has shown resistance against bacteria which gives it the property of being anti-microbial. It's widely used in other fields such as cosmetics, paints, cleaners and in agriculture as well. It's often used in eye preparations to prevent dry eye problems due to its ability to lubricate the eye as well as its possible use in contact lenses to moisten them. It has been used also in nasal, oral and topical applications.[45]

Summary of uses of HPMC:[46]
- Bioadhesive material
- Coating, suspending and film forming agent
- Controlled, sustained and extended release agent
- Dissolution enhancer
- Viscosity increasing and thickening agent
- Tablet binder
- Solubilizing and foaming agent
- Mucoadhesive

2.5.3 Methocel®

Methocel® is a trademark of The Dow Chemical Company for a line of cellulose ether products. Methocel® cellulose ether products are available in two basic types: methylcellulose and hydroxypropyl methylcellulose. Both types of Methocel® have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units. An initial letter identifies the type of cellulose ether. "A" identifies methylcellulose products. "E", "F", "J", and "K" identify different hydroxypropyl methylcellulose products. (Figure 11). The numbers in the name (e.g. 15 and 100) provides us with information about their viscosities measured at 20 ⁰C in water, and the letter 'M' represents the number 1,000.

Figure 11. Typical Chemical Structures of Methocel® products
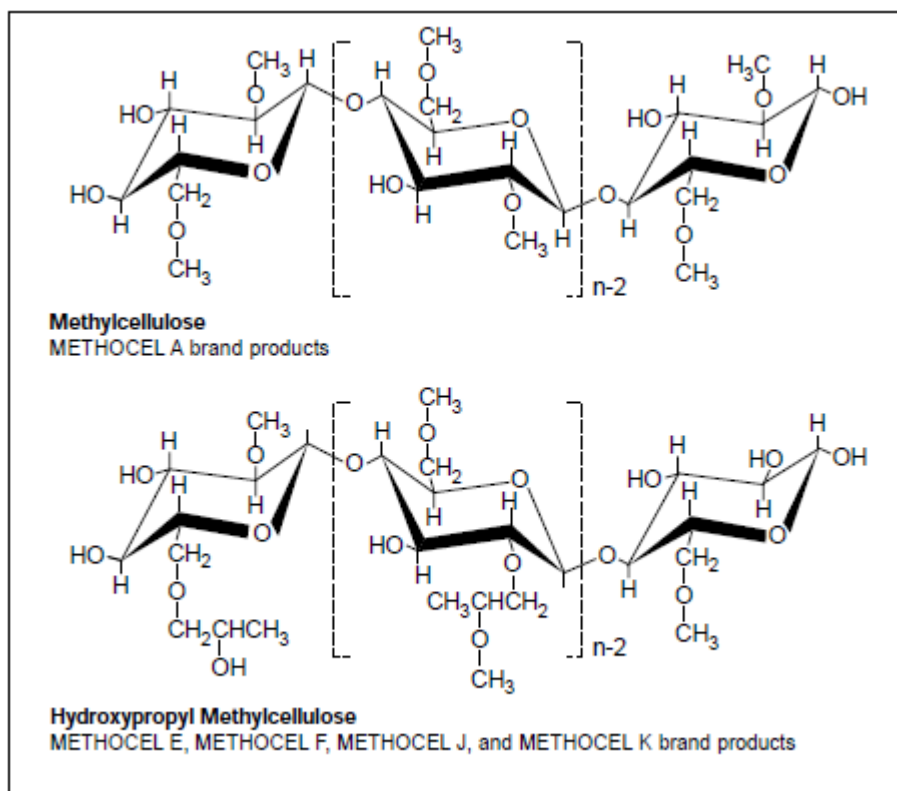
Such ethers are without any ionic charge therefore it doesn't form any precipitates nor salts. They have a huge pH stability ranging from 3 to 11. If they are added to an aqueous solution, they have a property of acting as a surfactant. Methocel is quite resistant to microbes. But sometimes if a solution is prepared, microbes could grow and so preservatives would be required. They can be powders or granules. In addition to that, their surfaces can be treated or non-treated. In order to decrease its solubility, they are chemically treated until they become insoluble in cold water. If the rate of dissolving is to be increased, this can be achieved by altering its pH to an alkaline pH and if added to a neutral pH, the following powders will earn complete hydration. Such techniques are useful in preparing solutions of Methocel.

Methocel solutions can result in a shear thinning property which is also known as a pseudoplastic behaviour meaning it its viscosity will decrease with higher shear rate i.e. non-Newtonian fluid. Such property can increase with higher molecular weight or concentration and that is because they are quite sensitive and are influenced by molecular weight, solutes, temperature and concentration. However, at lower shear rate, they behave as a Newtonian fluid.

There is no sharp solubility limit such as the one that occurs in the dissolution of ionizing salts. Solutions of low-viscosity products can be made at 10 to 15% concentration. High-viscosity products find a normal limit at 2 to 3% concentration. Methocel solutions can be prepared by adding the Methocel powder to hot water or other solvents such as vegetable oil, by mixing it with dry products before the addition of a solvent and by adding it to a concentrated salt solution followed by the addition of cold water. This last technique is useful for the preparation of solutions using both treated and un-treated Methocel powders.[45]

Dispersion in hot water is often called the "hot/cold" technique. This method takes advantage of the insolubility of Methocel cellulose ethers in hot water. The powder is first dispersed by mixing thoroughly with 1/5 to 1/3 of the total required volume of water that has been heated to above 90 °C (194 °F). Mixing continues until all particles are thoroughly wetted.

Figure 12. Dispersion of Methocel® in hot water - *hot/cold* technique

1/3 of 90 °C water	Add Methocel®	Agitate	Add cold water or ice	Agitate for at least 30 min
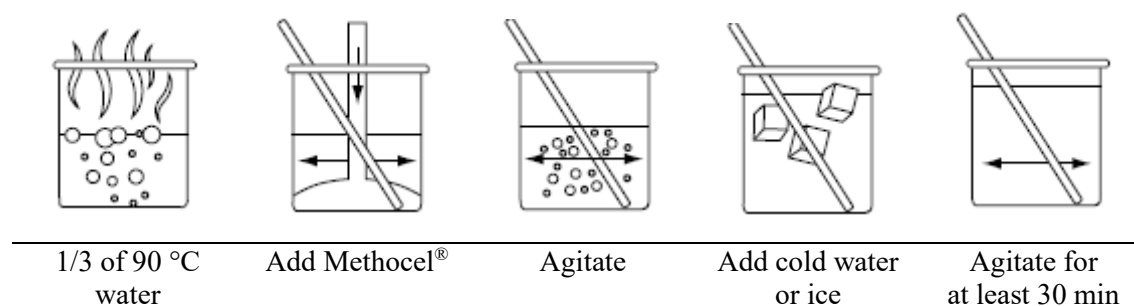
Methocel has a wide range of applications and has quite a lot of benefits. In the pharmaceutical area, it can be used as a coat for tablets since it has the ability to maximize stability and minimize friability. It's used also as a binder in several granulation processes.

Methocel is useful in preparing controlled release products, this can be achieved by several ways, either by incorporating it in a capsule or in hydrophilic matrix tablets. For single matrix tablets production, Methocel can be heated and added to a plasticiser. They are often incorporated in oral and topical products since they have thickening properties, don't allow moisture to escape, provide moisturising effects and enhance stability. Due to its moisturising effects, it's incorporated in many creams, lotions and shampoos.

Outside the pharmacy field, they can be used in inks for printer's, although only water-based ones. They can also be used in textiles, paints, detergents and to produce papers. In agriculture, it's used in fertilizers and in sprays for plants to help attach nutrients to the plant seeds. In food, it's used in bakery products such as in pies, frozen sweets, whipped cream to improve the look of it and in salad dressings. It's not added only for its good properties such as for better stability or texture but also because it increases the life of such products.[48]

Table 2. Methocel® applications [48]

Application	Grades	Benefits
Tablet Coating	Methocel LV Premium Methocel VLV Premium	Glossing coating that is printable, hypo-allergenic, non-tacky, compatible with dyes
Hard-shell capsules	Methocel LV Premium	Vegetarian, has good mechanical properties that enable high quality & robust product
Wet granulation	Methocel LV Premium Methocel VLV Premium	Binding and adhesive properties during granulation for immediate release tablets
Controlled-release-matrix tablets	Methocel Premium Methocel Premium CR	Deliver consistent drug release
Controlled-release matrix-tablets, direct compression	Methocel Premium DC2	Improved flow properties, faster processing speed, consistent drug release profile

3 Experimental section

3.1 Materials

Chitosan (Sigma-Aldrich, USA)

Hydrochloric acid (Kulich Pharma, CR)

Methocel K100M (Colorcon, Germany)

Methocel K15M (Colorcon, Germany)

Potassium dihydrogen phosphate (Sigma-Aldrich, USA)

Purified water (Faculty of Pharmacy, Hradec Kralove)

Sodium alginate (Sigma-Aldrich, USA)

Sodium chloride (Kulich Pharma CR)
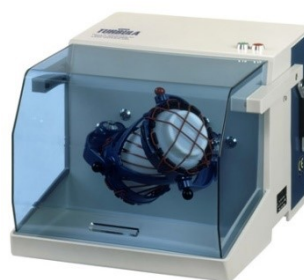
Sodium hydroxide (Kulich Pharma CR)

3.2 Instrument

Kinexus Pro+ Rheometer (Malvern instruments Ltd, UK)

Turbula (Bachofen AG, Switzerland)

Figure 13. Kinexus rheometer [49]   Figure 14. Turbula [50]

3.3 Methods

3.3.1 Preparation of mixtures

Tableting mixtures of composition according to Table 3 were prepared by homogenizing the individual components. 10 grams of each mixture was prepared. Calculated amount of each excipient was weighed on a paper card on an analytical balance. They were then added to plastic jars and they were homogenised together using the Turbula instrument. Following this, they were transferred to glass bottles and labelled.

Table 3. Composition of the mixtures for matrix tablets

	Retardant component		Labeled as
Chitosan 70 %	15 % SA	15 % MC 100	**F8**
Chitosan 60 %	20 % SA	20 % MC 100	**F9**
Chitosan 50 %	25 % SA	25 % MC 100	**F10**

3.3.2 Preparation of buffers

For the preparation of hydrochloric acid buffer, firstly 11.69 g of NaCl was dissolved in water and diluted to 1000 mL. Then, from the NaCl solution, 250 mL of it was taken, 425 mL of HCl was added and diluted to 1000 mL. For the phosphate saline buffer, 250 mL of potassium dihydrogen phosphate and 112 mL of NaOH were added, then diluted to 1000 mL with water. The respective mass taken from them was, 16.0 g and 19.0 g from each, to hydrate the excipients or tableting mixtures for performing the viscosity and adhesion test.

3.3.3 Preparation of samples for viscosity and adhesivity measurements

Dispersions of Methocels in water were prepared by controlled swelling realised by the change of water temperature during the solubilization method known as *hot/cold* technique.[45] Approximately, half of the required amount of water was poured in a beaker and heated to approx. 90°C. A given amount of MC 15 (resp. MC 100) powder was weighed on a paper card on an analytical balance and sprinkled on the surface of the hot water. The mixture was agitated until the particles are thoroughly wetted and dispersed. The remaining amount of cold water was added, and agitation was continued until particles of MC is dissolved. It was made to the total mass with purified water.

Samples of tableting mixtures were prepared at ambient temperature. A given amount of the powder was weighed on a paper card on an analytical balance. It was placed into the porcelain mortar and a specific amount of the medium was added to it. Then, the mixture was stirred slowly to avoid air bubbles until it's a homogenous dispersion.

Samples at a concentration of 5 % or 20 % were in three media (water, HCl pH 1.2; PBS pH 6.8) and were prepared in a final mass of 20.0 g. They were added to jars and were covered by a film to prevent evaporation. List of samples tested is shown in Table 4.

Table 4. List of tested samples

Sample	Medium	Powder mixture concentration	
Methocel 15M	HCl	5 %	-
	PSB	5 %	-
	water	5 %	-
Methocel 100M	HCl	5 %	-
	PSB	5 %	-
	water	5 %	-
F8	HCl	5 %	20 %
	PSB	5 %	20 %
	water	5 %	20 %
F9	HCl	5 %	20 %
	PSB	5 %	20 %
	water	5 %	20 %
F10	HCl	5 %	20 %
	PSB	5 %	20 %
	water	5 %	20 %

3.3.4 Starting up the rheometer

Before turning on the device, the air and pressure supply were checked. Then, the computer and Kinexus device were switched on and a green light on the Kinexus device would pop, when they were connected together. After, they were connected, the device had to stabilize for 5 minutes. Then, the r-Space software for Kinexus on the computer is started and by clicking Next, the device was initialized. The upper geometry had to be chosen according to the type of the test and was inserted. By clicking next, the zero gap was set and the upper geometry would go down and meet the lower one and then when they are separated, the instrument was ready to use, and the sample could be loaded after choosing the respective sequence.

3.3.5   *Test for flow properties*

From the favourite's toolbar, the sequence required for this test was chosen. Then, the shear rate range was inserted, and the sample was loaded after the Load icon appeared on the software. The sample would be loaded on the lower geometry using a plastic spatula and not a metal one, so scratching of the instrument could be avoided. Following that, the test had to be named according to the excipient type, concentration and type of medium (e.g. F8 water 20 %).

Then after loading, a Next icon would appear and by clicking it, the upper geometry goes down on the loaded sample. If there was any excess of the sample, it was trimmed off using the spatula. The hoods had to be placed and by clicking next, the temperature, followed by the samples per decade and shear rate had to be inserted.

When the measurement started, stabilization for 5 minutes follows. When the test ended, the hoods were removed, the sample was unloaded, and the data was saved. However, when loading the following sample, the upper and the lower geometry had to be cleaned using water and ethanol.

Flow behaviour of the samples was evaluated by the course of the viscosity curves, and value of viscosity at shear rate of 10 s^{-1} (η_{10}). Viscosity curves were analysed by the Power law model, and coefficients of Power law equation, *K* and *n*, were used for comparison of the samples. The consistency index *K* ($Pa \cdot s^n$) numerically equals to the viscosity measured at $1s^{-1}$, and power law index *n* (-) ranges from zero for very shear thinning materials to one for Newtonian materials.

All the measurements were done in a triplicate and an average and standard deviation were calculated.

Parameters for measurement

Sequence:

  Toolkit_V005 Shear Rate Ramp - Alternative Flow Curve

  Analyse_0004 Power law model for viscometry

Shear rate range: 0.1 – 100 s^{-1}

Upper geometry: CP 2/20

Temperature: 25 °C

Samples per decade: 10

3.3.6 *Test for adhesive properties*

From the favourite's toolbar, the sequence required for this test was chosen. By clicking next, the temperature and the working gap were inserted. The sample then had to be loaded on the lower geometry using a plastic spatula and the test would be named according to the excipient type, concentration, and type of medium (e.g. F9 water 5 %). The upper geometry then would go down on the loaded sample and any excess would be trimmed off using the spatula. Then, the hoods would be placed. When the measurement starts, waiting for stability for 5 minutes follows. During the measurement, the force/time curve was recorded. When the test ends, the hoods were removed, and the upper geometry was separated from the lower one. Then, the data would be saved. When loading the following sample, the upper and lower geometry had to be cleaned with water and ethanol. The adhesive properties of the samples were evaluated as the peak in normal force F_{max} (N). All the measurements were done five times, the average and SD were calculated.

Parameters for measurement

Sequence: rSolution_0020 Evaluating tackiness and adhesion using a pull away test

Upper geometry: PU20

Temperature: 37 °C

Working gap: 0.2 mm

Gapping speed: 10 mm/s

Final gap: 100 μm

4 Results

4.1 Flow properties of hypromellose
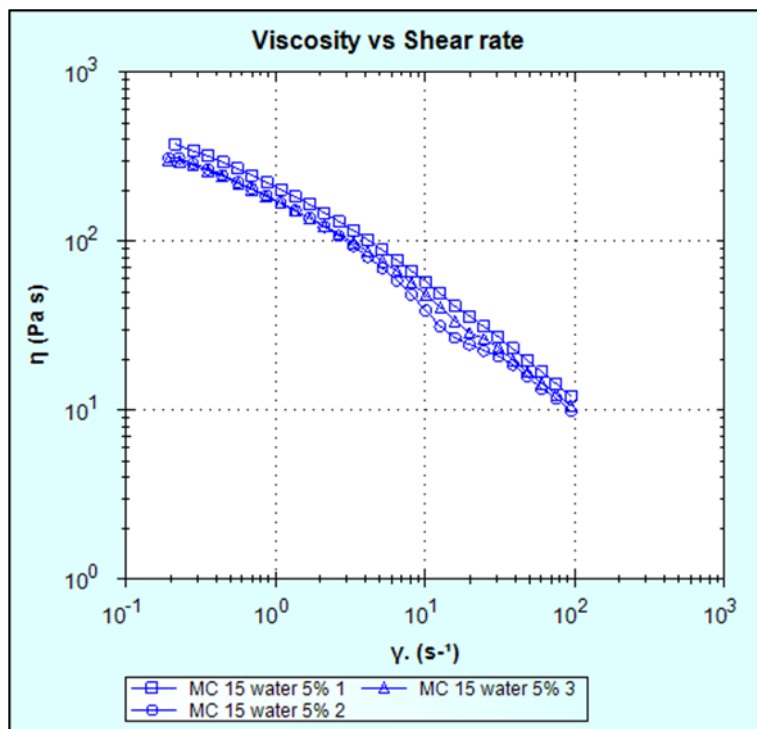
Figure 15. Viscosity curves of 5 % Methocel K15M in water

Table 5. Power law model fit of 5 % Methocel K15M in water

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	90.31	311.2	0.4207	0.9872
2	97.01	329.8	0.4205	0.9871
3	89.02	297.9	0.4338	0.9859
AVRG	92.11	313.0	0.4250	
SD	4.29	16.0	0.0076	

Figure 16. Viscosity curves of 5 % Methocel K15M in HCl 1.2
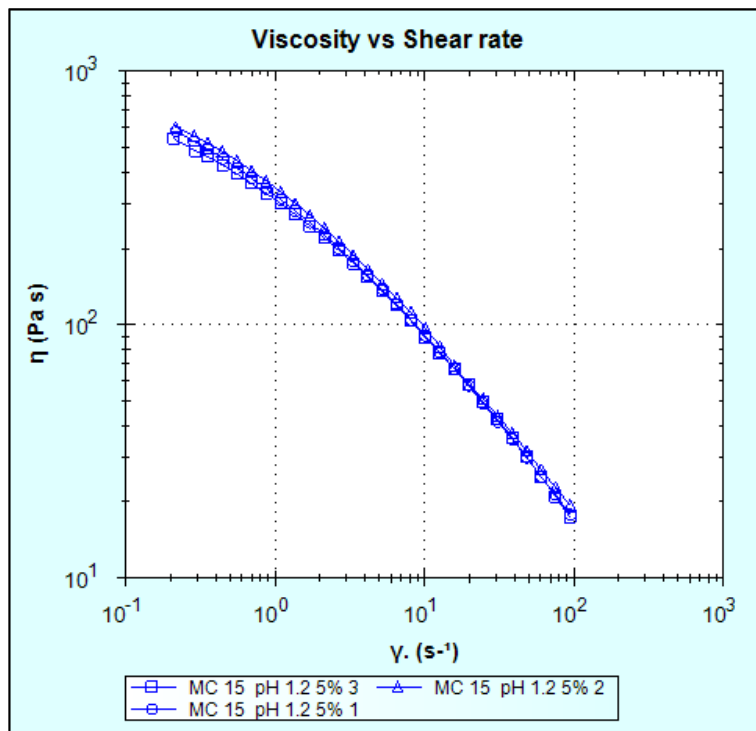
Table 6. Power law model fit of 5 % Methocel K15M in HCl 1.2

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	57.75	200.7	0.4236	0.9891
2	38.82	158.70	0.4114	0.9868
3	48.20	161.90	0.4418	0.9881
AVRG	48.26	173.77	0.4256	
SD	9.47	23.38	0.0153	

Figure 17. Viscosity curves of 5 % Methocel K15M in PSB 6.8
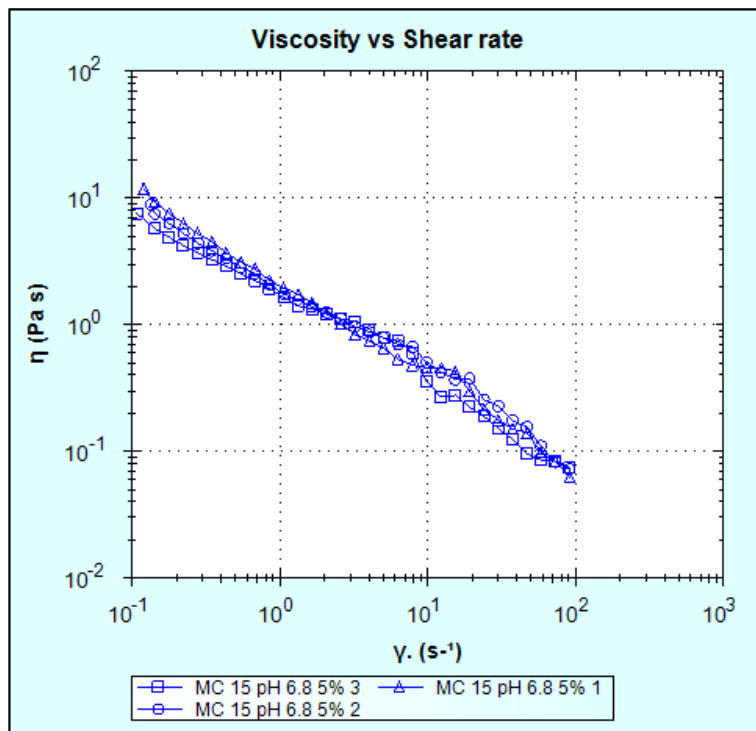
Table 7. Power law model fit of 5 % Methocel K15M in PSB 6.8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	92.43	355.9	0.3521	0.9895
2	94.17	403.4	0.3811	0.9922
3	83.08	393.2	0.3552	0.9902
AVRG	89.89	384.2	0.3628	
SD	5.96	25.0	0.0159	

Figure 18. Viscosity curves of 5 % Methocel K100M in water
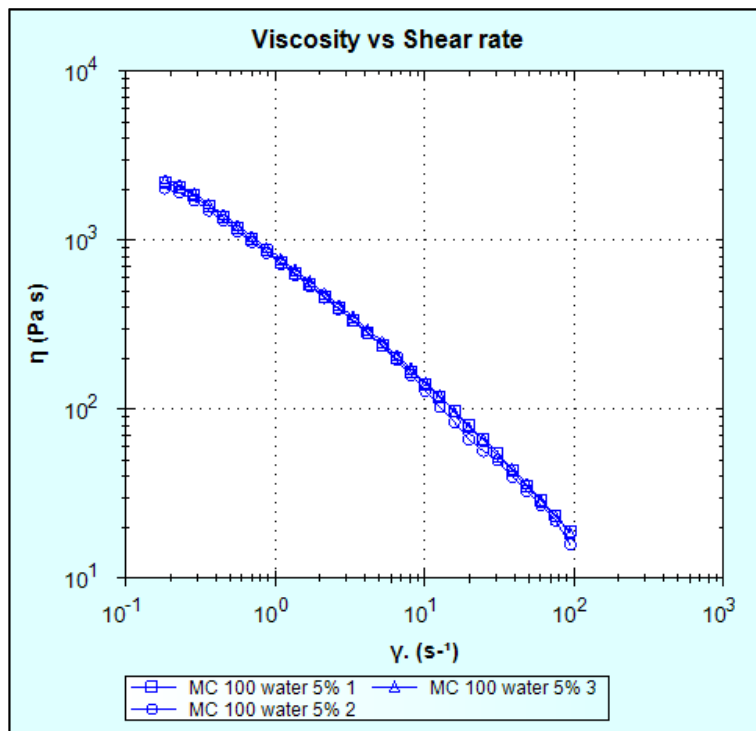
Table 8. Viscosity curves of 5 % Methocel K100M in water

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	114.40	494.3	0.3138	0.9710
2	110.30	559.2	0.2607	0.9734
3	116.70	604.5	0.2497	0.9863
AVRG	113.80	552.7	0.2747	
SD	3.24	55.4	0.0343	

Figure 19. Viscosity curves of 5 % Methocel K100M in HCl 1.2
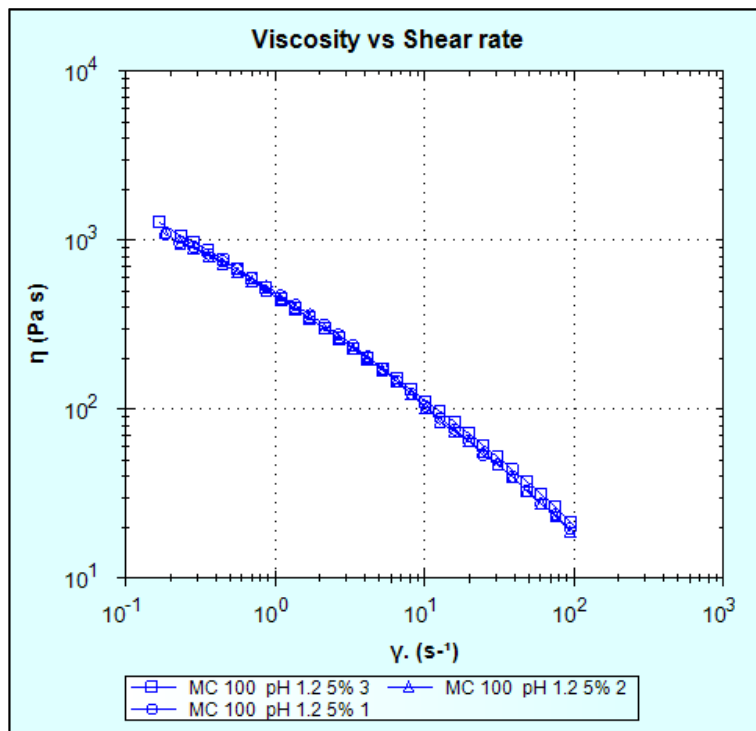
Table 9. Power law model fit of 5 % Methocel K100M in HCl 1.2

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	104.1	458.5	0.3421	0.9860
2	101.8	443.3	0.3475	0.9892
3	111.6	467.3	0.3597	0.9951
AVRG	105.8	456.4	0.3498	
SD	5.1	12.1	0.0090	

Figure 20. Viscosity curves of 5 % Methocel K100M in PSB 6.8
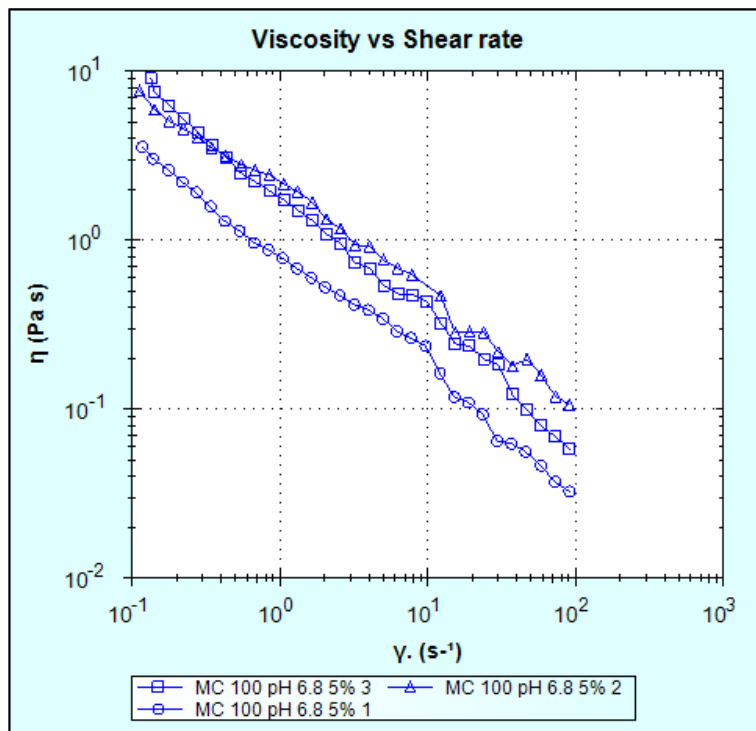
Table 10. Power law model fit of 5 % Methocel K100M in PSB 6.8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	140.8	764.1	0.2310	0.9739
2	128.1	727.4	0.2173	0.9568
3	143.4	792.5	0.2213	0.9663
AVRG	**137.4**	**761.3**	**0.223**	
SD	**8.2**	**32.6**	**0.007**	

4.2   Flow properties of tableting mixtures

4.2.1 5% dispersions of tableting mixtures in water
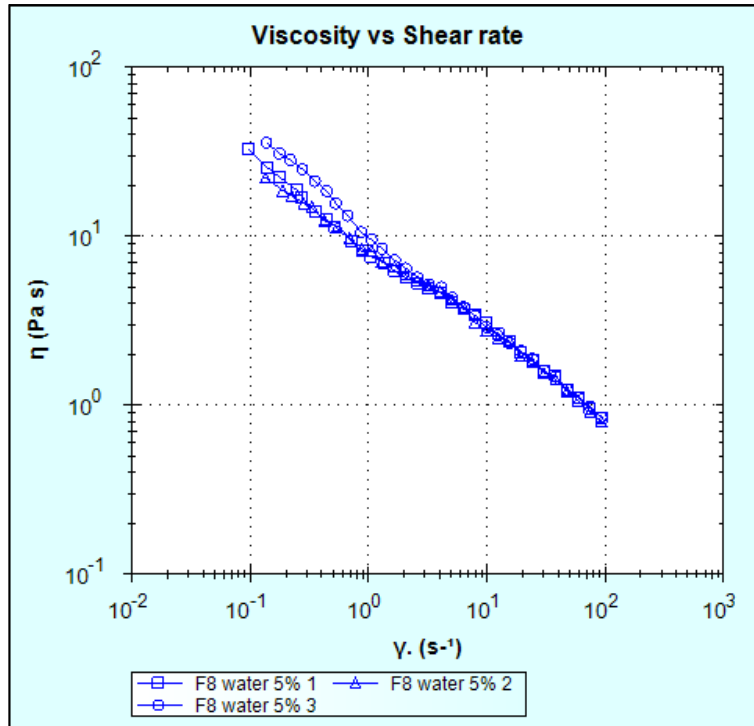
Figure 21. Viscosity curves of F8

Table 11. Values of viscosity and Power law model coefficients of F8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	3.052	8.765	0.4988	0.9974
2	2.761	8.463	0.5059	0.9984
3	2.896	10.870	0.4329	0.9969
AVRG	**2.903**	**9.366**	**0.4792**	
SD	**0.146**	**1.311**	**0.0403**	

Figure 22. Viscosity curves of F9
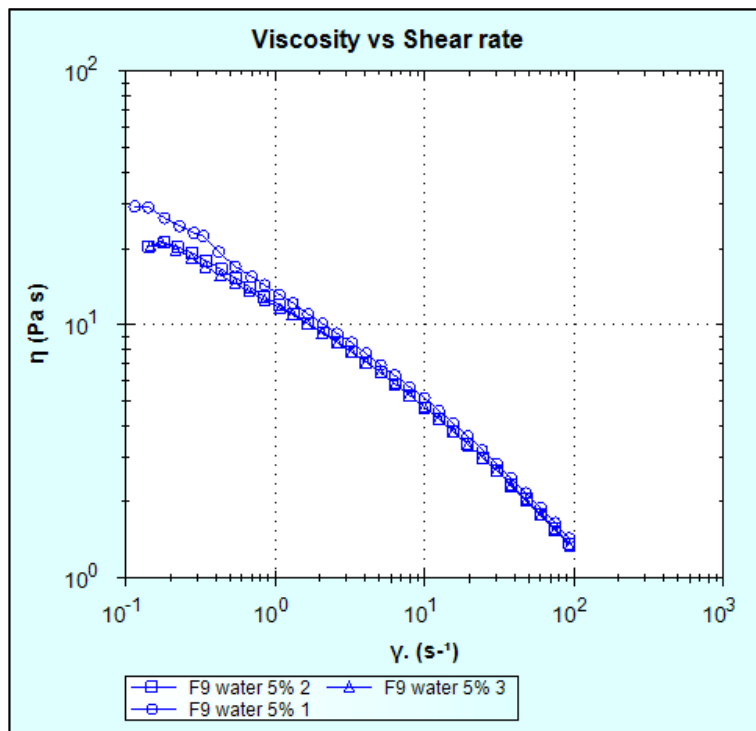
Table 12. Values of viscosity and Power law model coefficients of F9

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	5.142	13.22	0.5504	0.9975
2	4.714	11.64	0.5721	0.9960
3	4.722	11.40	0.5767	0.9958
AVRG	4.859	12.09	0.5664	
SD	0.245	0.99	0.0140	

Figure 23. Viscosity curves of F10
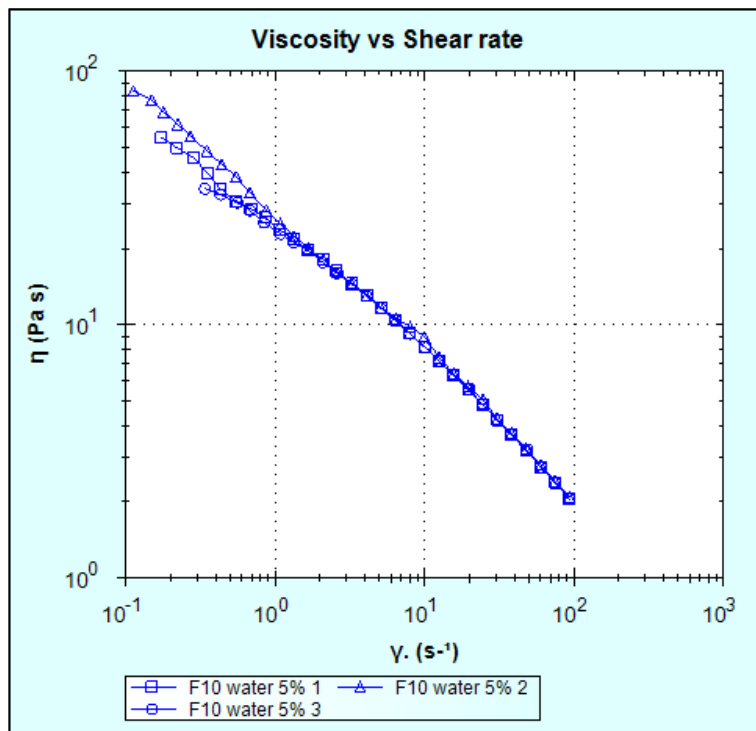
Table 13. Values of viscosity and Power law model coefficients of F10

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	8.150	24.52	0.4879	0.9968
2	8.975	27.35	0.4578	0.9984
3	8.153	24.12	0.4920	0.9946
AVRG	8.426	25.33	0.4792	
SD	0.475	1.76	0.0187	

4.2.2 5% dispersions of tableting mixtures in HCl buffer pH 1.2
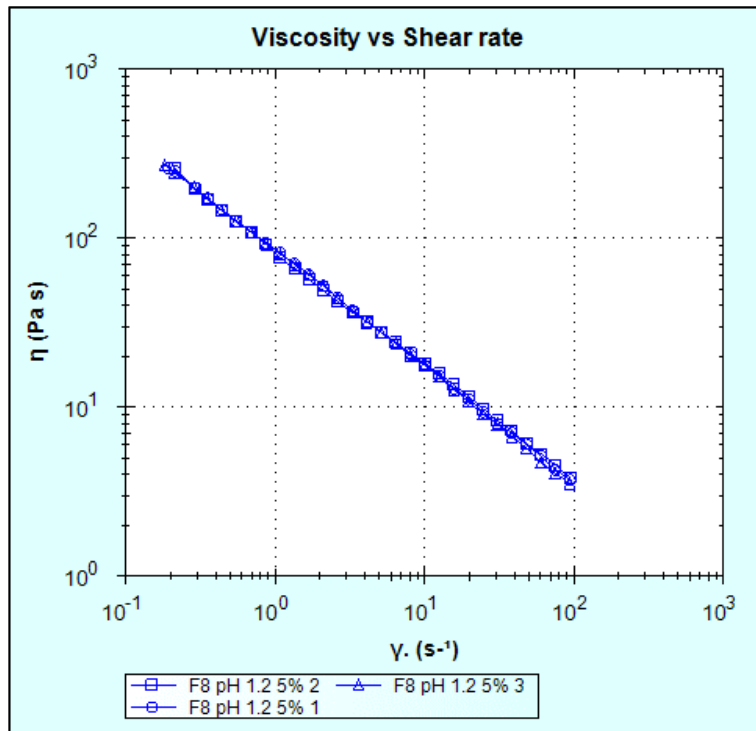
Figure 24. Viscosity curves of F8

Table 14. Values of viscosity and Power law model coefficients of F8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	18.18	85.26	0.3132	0.9997
2	17.65	84.06	0.3251	0.9988
3	17.62	84.82	0.3048	0.9992
AVRG	17.82	84.71	0.3144	
SD	0.32	0.61	0.0102	

Figure 25. Viscosity curves of F9
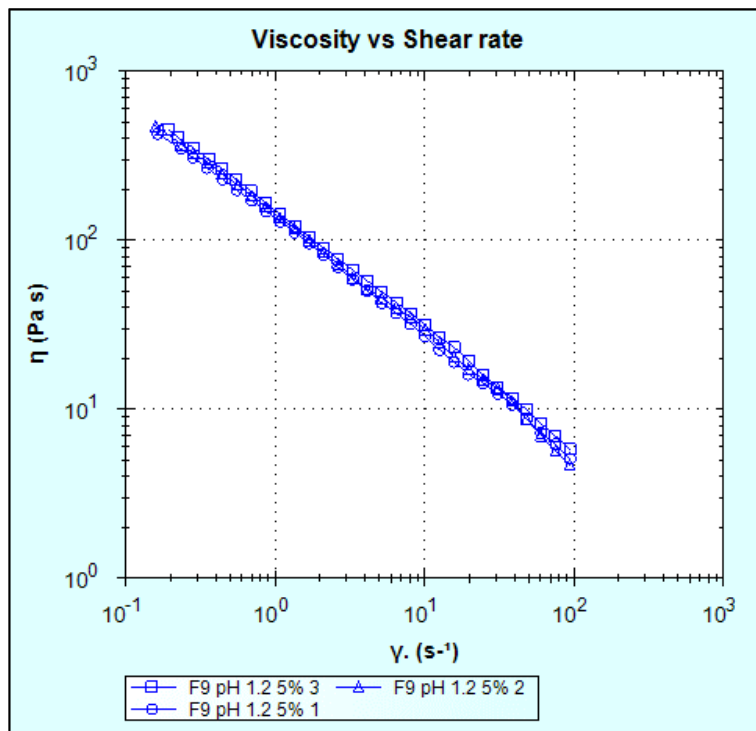
Table 15. Values of viscosity and Power law model coefficients of F9

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	27.11	132.2	0.3019	0.9979
2	29.79	140.5	0.2911	0.9935
3	31.34	150.4	0.3020	0.9981
AVRG	29.41	141.0	0.2983	
SD	2.14	9.1	0.0063	

Figure 26. Viscosity curves of F10
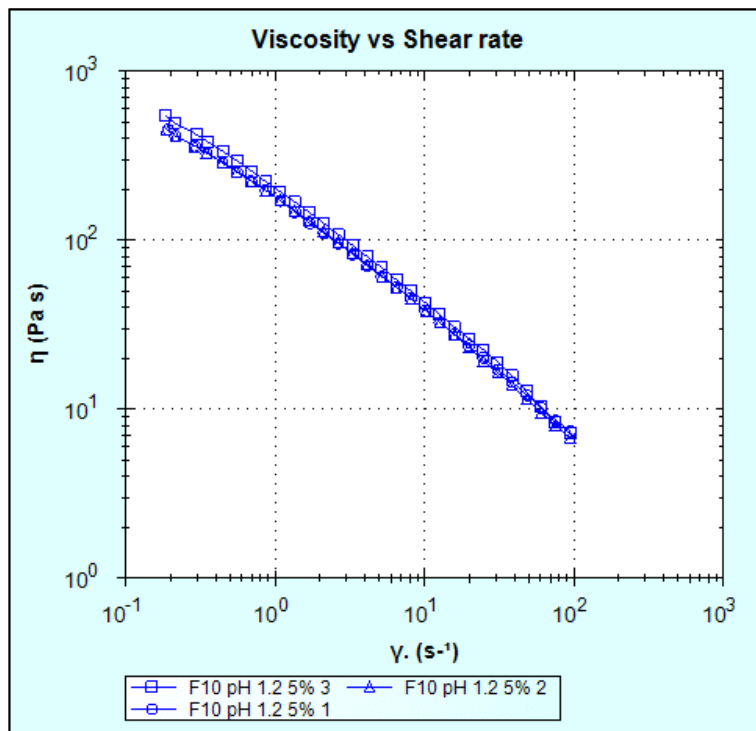
Table 16. Values of viscosity and Power law model coefficients of F10

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	38.36	171.0	0.3323	0.9945
2	38.43	172.4	0.3197	0.9900
3	42.85	197.6	0.3085	0.9898
AVRG	39.88	180.3	0.3202	
SD	2.57	15.0	0.0119	

4.2.3   5% dispersions of tableting mixtures in PSB pH 6.8

Figure 27. Viscosity curves of F8
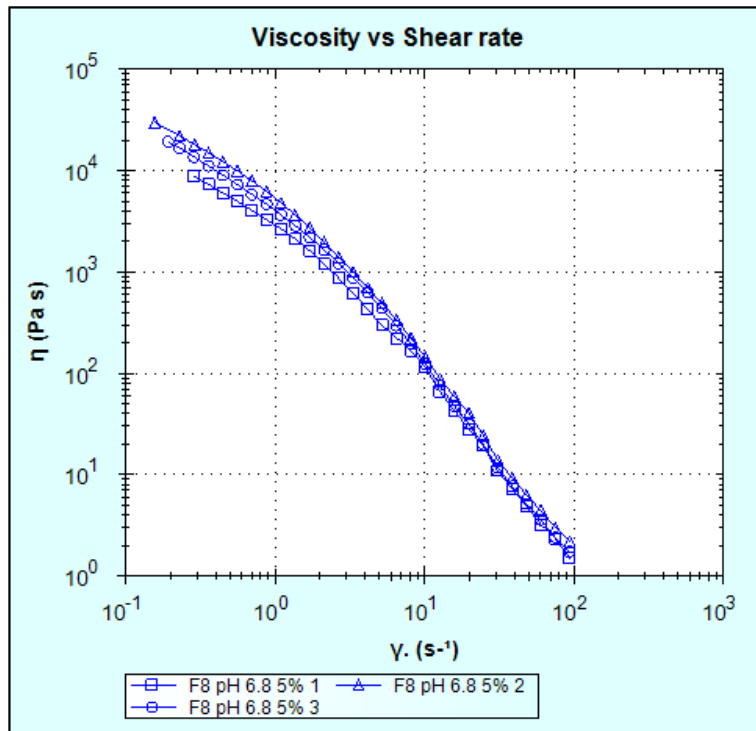
Table 17. Values of viscosity and Power law model coefficients of F8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	114.0	2692	0.5452	0.9859
2	113.8	2141	0.5698	0.9879
3	123.9	2305	0.5587	0.9575
AVRG	**117.2**	**2379**	**0.5579**	
SD	**5.8**	**727**	**0.0123**	

Figure 28. Viscosity curves of F9
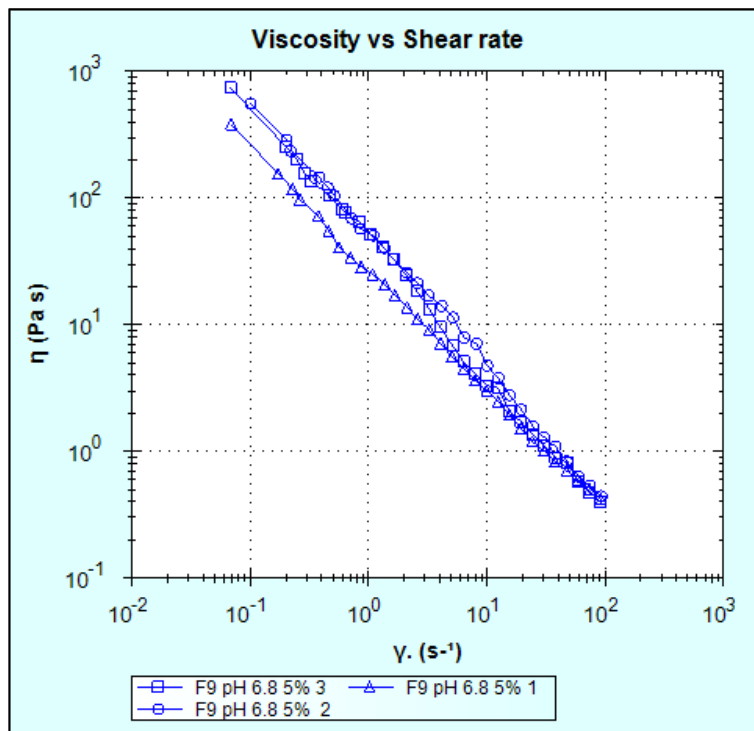
Table 18. Values of viscosity and Power law model coefficients of F9

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1*	3.016	27.14	0.0489	0.9636
2	4.476	53.33	0.0591	0.9538
3	4.247	45.76	0.0796	0.9937
AVRG	4.362	49.545	0.0694	
SD	0.162	5.353	0.0145	

Figure 29. Viscosity curves of F10
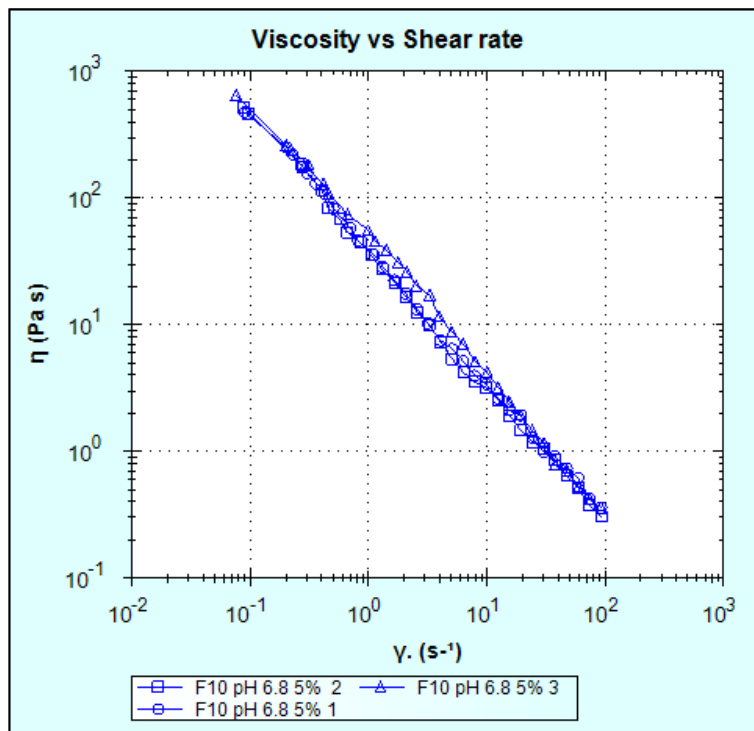
Table 19. Values of viscosity and Power law model coefficients of F10

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	3.401	39.86	0.0627	0.9921
2	3.319	37.45	0.0766	0.9506
3	4.247	49.94	0.0910	0.9716
AVRG	3.656	42.417	0.0768	
SD	0.514	6.626	0.0142	

4.2.4 20 % dispersions of tableting mixtures in water

Figure 30. Viscosity curves of F8
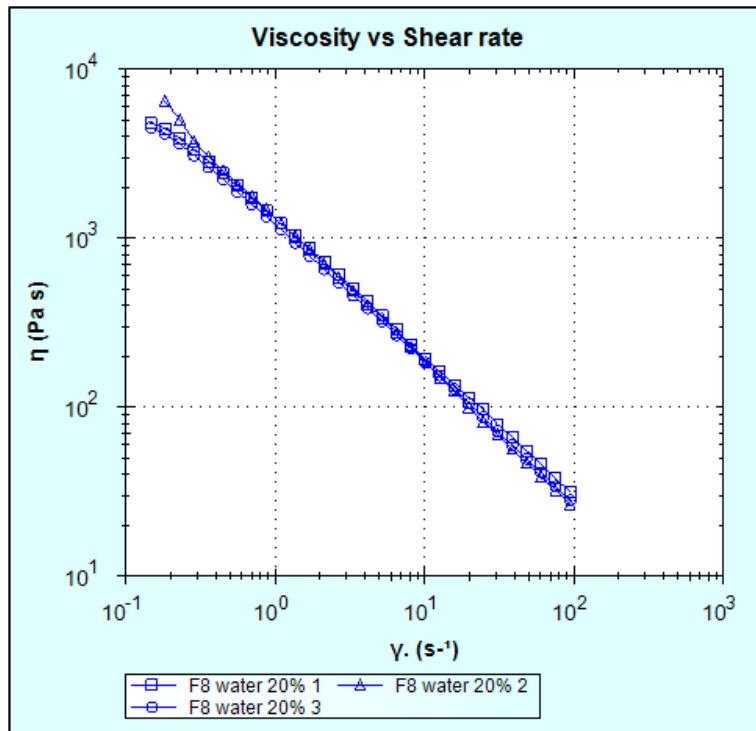
Table 20. Values of viscosity and Power law model coefficients of F8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	192.2	1253	0.2011	0.9913
2	186.5	1341	0.1371	0.9893
3	183.5	1156	0.1963	0.9917
AVRG	187.4	1250	0.1782	
SD	4.4	93	0.0356	

Figure 31. Viscosity curves of F9
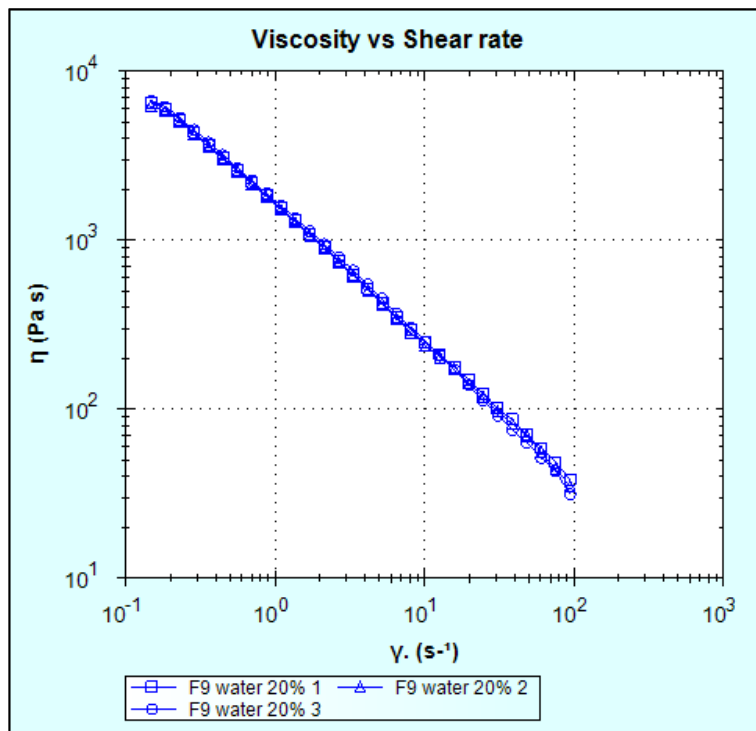
Table 21. Values of viscosity and Power law model coefficients of F9

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	264.4	1609	0.1960	0.9950
2	236.7	1564	0.1908	0.9915
3	250.1	1652	0.1674	0.9976
AVRG	250.4	1608	0.1847	
SD	13.9	44	0.0152	

Figure 32. Viscosity curves of F10
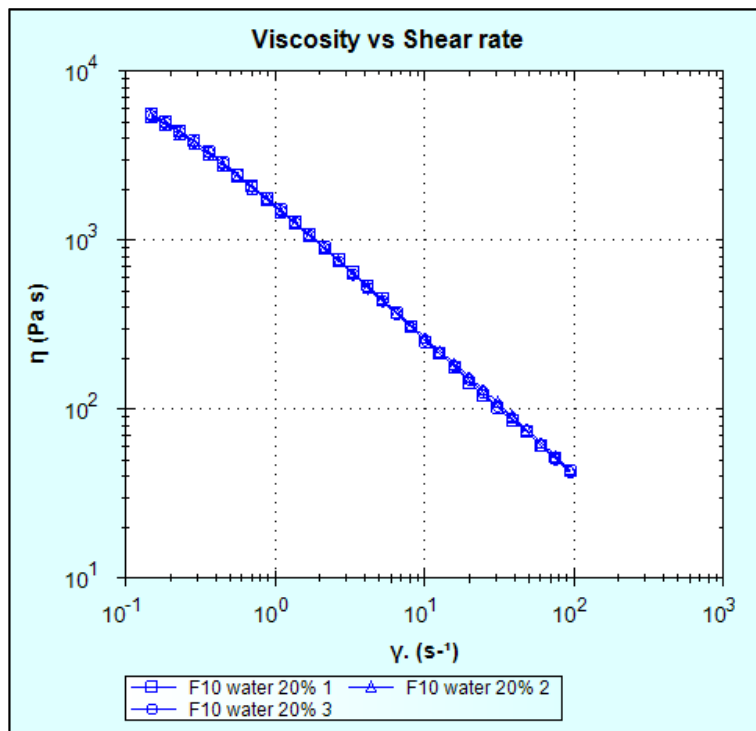
Table 22. Values of viscosity and Power law model coefficients of F10

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	250.5	1525	0.2339	0.9902
2	262.9	1419	0.2425	0.9929
3	256.1	1504	0.2292	0.9918
AVRG	256.5	1483	0.2352	
SD	6.2	56	0.0067	

4.2.5 20 % dispersions of tableting mixtures in HCl buffer pH 1.2

Figure 33. Viscosity curves of F8
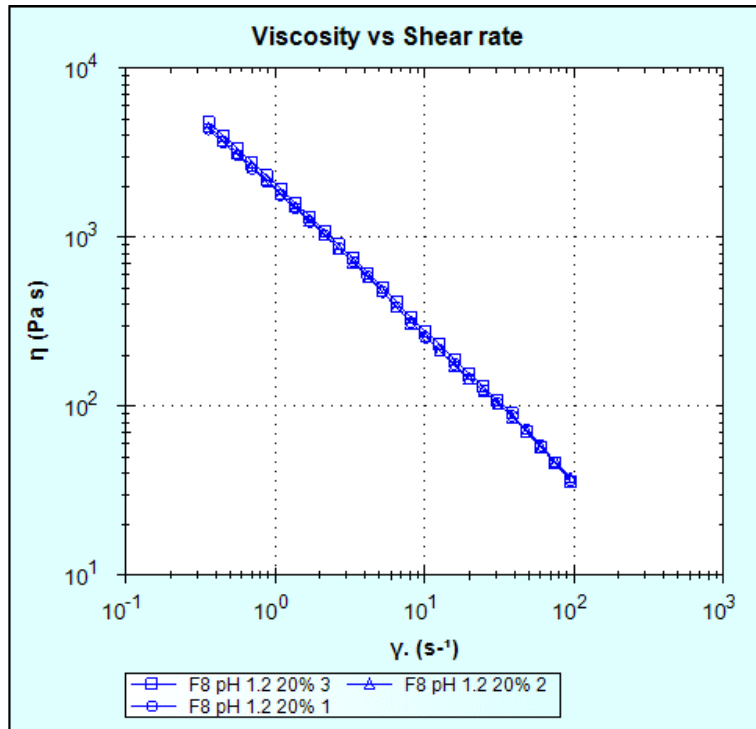
Table 23. Values of viscosity and Power law model coefficients of F8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	255.5	1896	0.1484	0.9926
2	256.9	1932	0.1418	0.9937
3	278.1	2077	0.1287	0.9983
AVRG	263.5	1968	0.1396	
SD	12.7	96	0.0100	

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Figure 34. Viscosity curves of F9
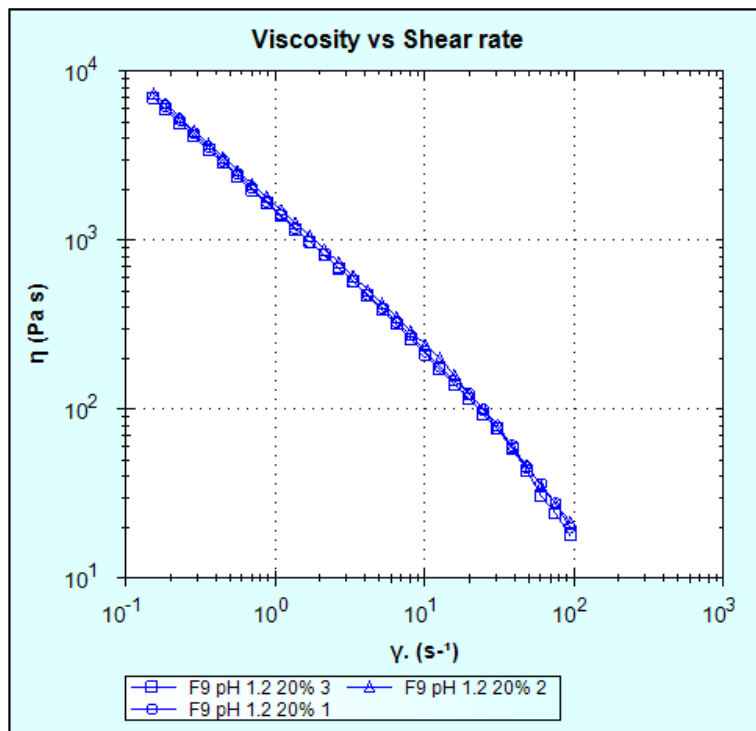
Table 24. Values of viscosity and Power law model coefficients of F9

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	220.5	1539	0.1141	0.9866
2	240.7	1609	0.1144	0.9788
3	211.2	1485	0.1080	0.9540
AVRG	224.1	1544	0.1122	
SD	15.1	62	0.0036	

Figure 35. Viscosity curves of F10
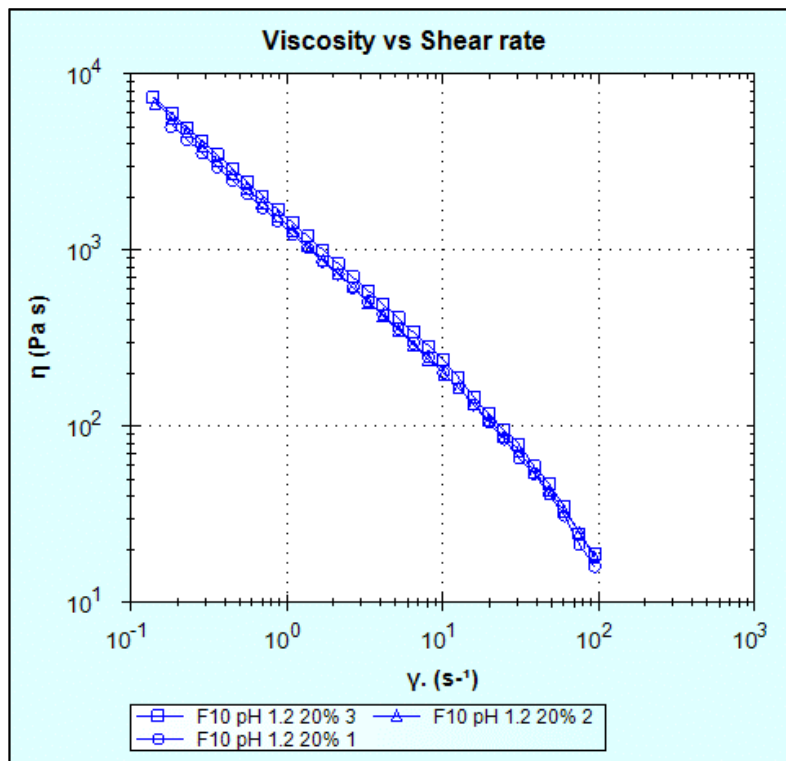
Table 25. Values of viscosity and Power law model coefficients of F10

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	201.8	1310	0.1224	0.9583
2	198.6	1378	0.1183	0.9603
3	236.6	1518	0.1188	0.9602
AVRG	212.3	1402	0.1198	
SD	21.1	106	0.0022	

4.2.6 20 % dispersions of tableting mixtures in PSB pH 6.8

Figure 36. Viscosity curves of F8
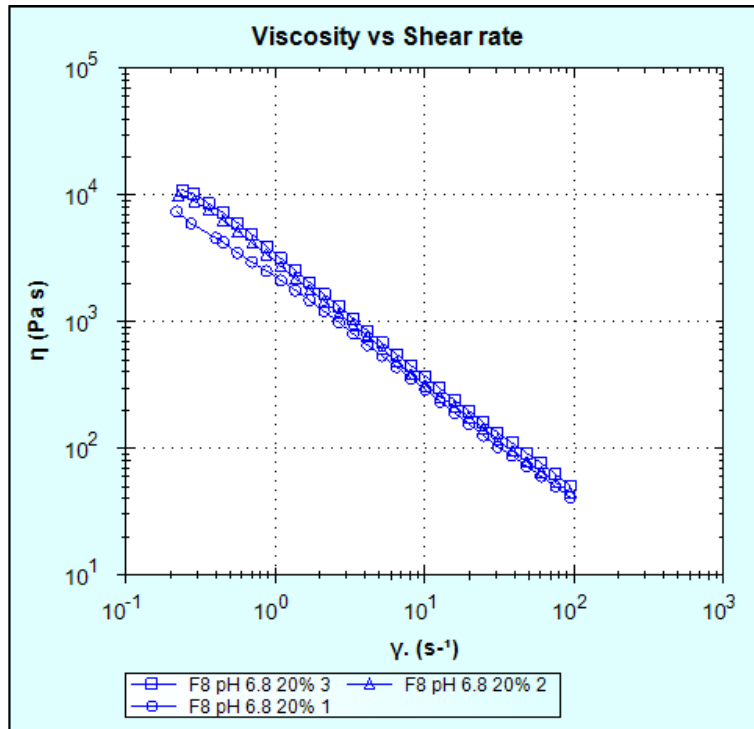
Table 26. Values of viscosity and Power law model coefficients of F8

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	324.5	2774	0.0704	0.9871
2	313.3	2870	0.0714	0.9546
3	369.4	3281	0.0712	0.9529
AVRG	335.7	2975	0.0710	
SD	29.7	269	0.0005	

Figure 37. Viscosity curves of F9
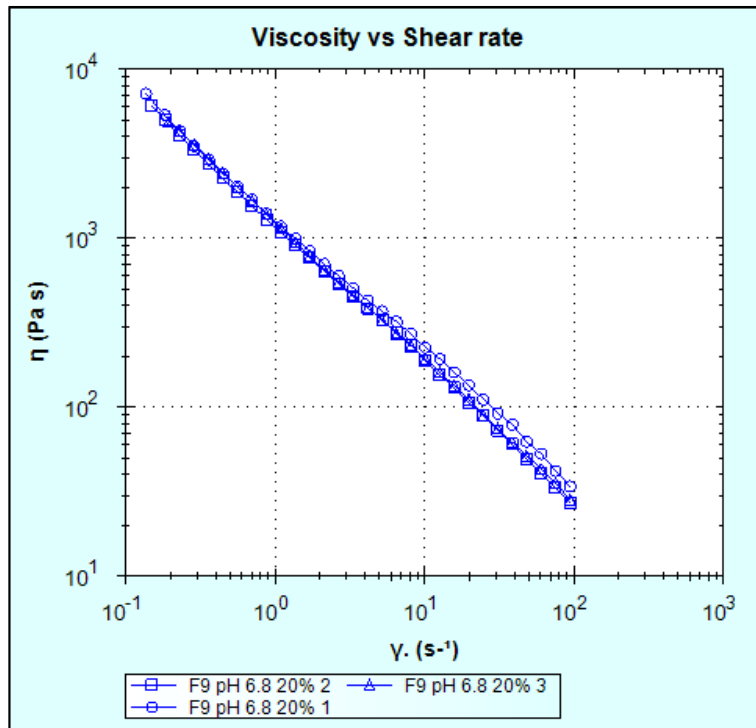
Table 27. Values of viscosity and Power law model coefficients of F9

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	202.0	1267	0.1739	0.9929
2	188.5	1210	0.1792	0.9945
3	192.4	1259	0.1760	0.9978
AVRG	194.3	1245	0.1764	
SD	6.9	31	0.0027	

Figure 38. Viscosity curves of F10
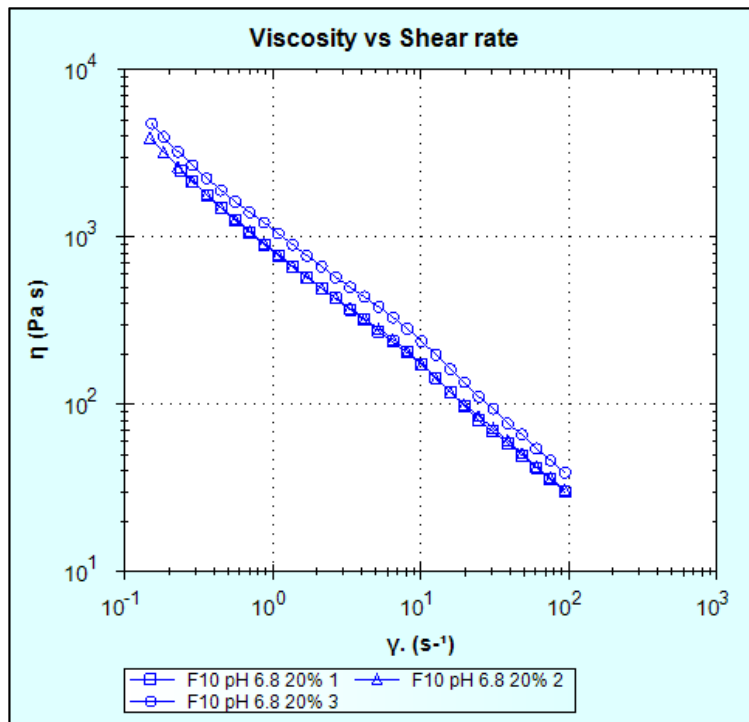
Table 28. Values of viscosity and Power law model coefficients of F10

	η_{10} (Pa·s)	K (Pa·s^n)	n (-)	corr
1	173.0	859.0	0.2714	0.9961
2	174.7	882.6	0.2695	0.9958
3	181.0	901.4	0.2658	0.9930
AVRG	176.2	881.0	0.2689	
SD	4.2	21.2	0.0028	

4.3   Adhesive properties of tableting mixtures

4.3.1   5% dispersions of tableting mixtures in different media

Table 29. 5 % dispersion of tableting mixtures in water

Sample	Normal force (N)		
	F8	F9	F10
1	0.8131	0.5104	1.101
2	0.8175	0.5071	1.108
3	0.8295	0.5277	1.117
AVRG	0.8200	0.5151	1.109
SD	0.0085	0.0111	0.008

Table 30. 5 % dispersion of tableting mixtures in HCl buffer pH 1.2

Sample	Normal force (N)		
	F8	F9	F10
1	1.256	1.878	2.458
2	1.331	1.792	2.027
3	1.364	1.861	2.759
AVRG	1.317	1.844	2.415
SD	0.055	0.046	0.368

Table 31. 5 % dispersion of tableting mixtures in PSB pH 6.8

Sample	Normal force (N)		
	F8	F9	F10
1	1.021	0.139	0.156
2	1.413	0.140	0.153
3	1.088	0.145	0.161
AVRG	1.174	0.141	0.157
SD	0.210	0.003	0.004

4.3.2 20% dispersions of tableting mixtures in different media

Table 32. 20 % dispersions of tableting mixtures in water

Sample	Normal force (N)		
	F8	F9	F10
1	15.88	19.29	18.33
2	16.16	19.04	18.14
3	15.47	19.19	18.99
AVRG	15.84	19.17	18.49
SD	0.35	0.13	0.45

Table 33. 20 % dispersion of tableting mixtures in HCl buffer pH 1.2

Sample	Normal force (N)		
	F8	F9	F10
1	10.100	8.506	10.06
2	10.275	8.155	10.51
3	10.890	9.423	10.25
AVRG	10.422	8.695	10.27
SD	0.415	0.655	0.23

Table 34. 20 % dispersion of tableting mixtures in PSB pH 6.8

Sample	Normal force (N)		
	F8	F9	F10
1	8.860	5.720	6.692
2	6.260	5.620	6.243
3	7.750	6.110	8.067
AVRG	7.623	5.817	7.001
SD	1.305	0.259	0.950

5   Discussion

Tableting materials for matrix systems tested in this diploma thesis are based on chitosan, a linear polysaccharide composed of randomly distributed β-(1→4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). As a cationic polymer, chitosan exhibits a pH-sensitive behaviour due to the large quantities of amino groups on its chain. It dissolves easily at low pH while it is insoluble at higher pH ranges. Therefore, it has only limited ability for controlling the release of incorporated drugs.[51] The chitosan at acidic pH levels possesses high charge density, and thus reveal an adhesion to mucous,[52] which is consistent with the electrostatic theory of mucoadhesion.[53]

Sodium alginate and hypromellose, excipients used as retarding components in presented thesis, perfectly meets the general requirements for mucoadhesivity, which are as follows: a strong hydrogen-bonding groups (-OH, -COOH), strong anionic charges, high molar weight, sufficient chain flexibility. [54]

Hypromellose dissolves in cold water by swelling and subsequent hydration. Although the viscosity of solution is generally stable over a wider pH range, outside the range of pH 3 to 11, however, there may be a gradual loss of viscosity at higher temperatures, especially with high-viscosity solutions. Solutions of hypromellose in acidic or in strong alkaline media will decrease in viscosity.[45]

On the other hand, alginate, a linear polysaccharide composed of alternating blocks of 1–4 linked α-L-guluronic and β-D-mannuronic acid residues, is an anionic polymer with carboxyl end groups. It is not soluble in acidic media, subsequently into the higher pH of the intestinal tract, it is converted to a soluble viscous and adhesive layer.

Drug release from matrix tablets and consequently the final effect of the medicinal product targeted to the intestine is influenced by rheological and adhesive properties of the polymeric carriers after treatment of physiological fluids in the GIT. The intraluminal pH is rapidly changed from highly acidic in the stomach to about pH 6 in the duodenum. The pH gradually increases in the small intestine from pH 6 to about pH 7.4 in the terminal ileum. The pH drops to 5.7 in the caecum, but again gradually increases, reaching pH 6.7 in the rectum.[55]

The viscosity and adhesion of the tableting mixtures after exposure to water, hydrochloric acid buffer pH 1.2; and PBS pH 6.8 were studied to find the optimal compositions for targeting the drug to the intestine and drug release profile.

5.1 Flow properties

The flow properties of the samples listed in Table 3 in different concentrations plus different pH were measured, and as we know, concentration plus pH influence the viscosity. The samples were then measured in their respective concentrations, first 20 % concentration was measured, later also 5 %. The higher concentration better reflects the lower content of water medium in intestine. However, a problem with the homogeneity and measurability of some samples arised. It was obvious that higher viscosities will be obtained in the respective 20 % concentrations.

The courses of the viscosity-shear rate curves of the tested samples clearly demonstrate typical shear-thinning behaviour as viscosity drops with increasing shear rate (Fig. 21-38). The linear sections of viscosity curves were fitted by Power law model, and the correlation coefficients are a good measure of how well the model fits the data with a value as close to unity as possible preferable. For all the samples the values were above 0.95 (Tab. 11-28) indicating good correlation between measured and predicted data.

The coefficients of Power law were used for comparison of the rheological behaviour of the studied materials. The consistency index K, numerically equal to the viscosity at $1s^{-1}$, serves as a good measure of a zero-shear viscosity (or at-rest-viscosity) for comparative purposes, and the index of non-Newtonian behaviour n expresses the sensitivity of the material to a stress. Viscosity at shear rate 10 s^{-1} η_{10} was chosen as a characteristic reflecting the flow behaviour of chitosan-based matrix tablets in the intestine where there is only a low stress exposure.

5.1.1 Flow properties of hypromellose

A hypromellose of the trade name Methocel® was used as a component of tableting mixtures. Dispersions of 5 % Methocel® K15M or Methocel® K100M in water, hydrochloric acid buffer pH 1.2 or PBS pH 6.8 were prepared by controlled swelling based on the change of water temperature during the solubilization. Hydrochloric acid buffer was heated only to approx. 60 °C. The number in the designation of Methocel means viscosity in millipascal-seconds (mPa·s) of that product measured at 2% concentration in water at 20°C with Ubbelohde viscometer. The letter "M" is used to represent 1000.

Figure 39 shows the comparison of viscosities η_{10} of hypromellose dispersions at different media. However, the higher difference between the viscosities of MC15 and M100 was expected. Regarding the effect of pH, the lowest values of viscosity were observed at pH 1.2, higher in water and at pH 6.8. It is clearly visible particularly in case of consistency indexes K in Figure 40. These findings could be expected and correspond to the declared Methocel® pH stability in the range from 3 to 11.

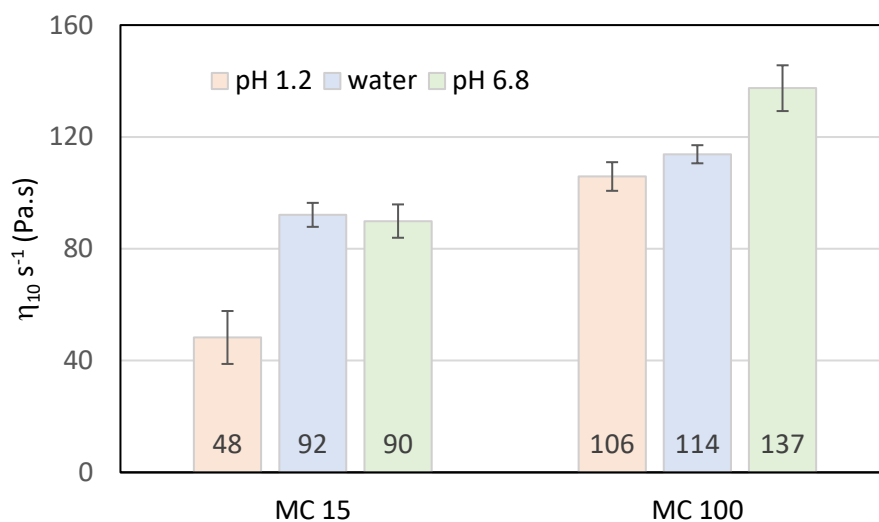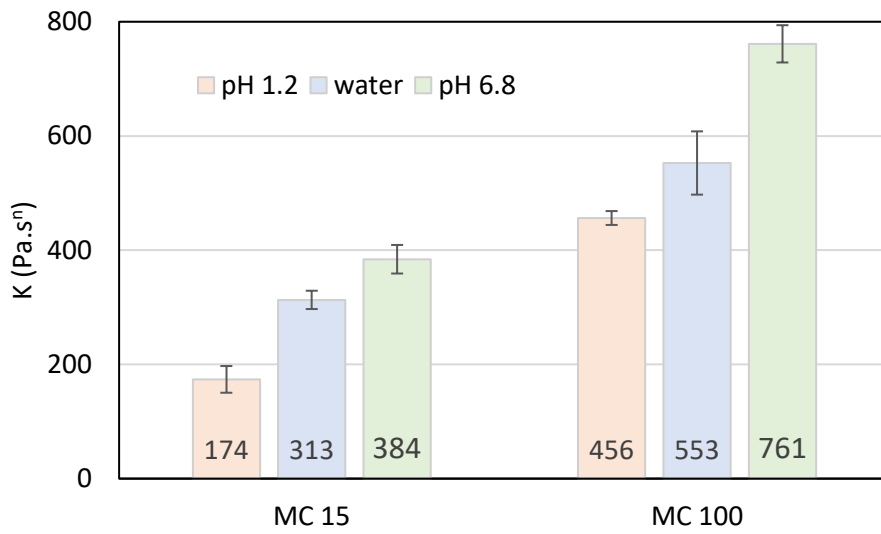Figure 39. Viscosity η_{10} of 5 % Methocel® K15M and K100M at different media

Figure 40. Consistency index K of 5 % Methocel® K15M and K100M at different media

The power law index n as a measure of non-Newtonian behaviour or sensitivity to a shear was used to compare the extent of shear thinning of the hypromellose dispersions. Considering that n equals one for Newtonian materials, then it can be established that the measured samples are fairly shear thinning having the values of n in the narrow range of 0.22 to 0.43 (Figure 41). This is consistent with the values of K, which means that a more viscous or stiff gel is more sensitive to shearing.

Figure 41. Power law index n of 5 % Methocel® K15M and K100M at different media
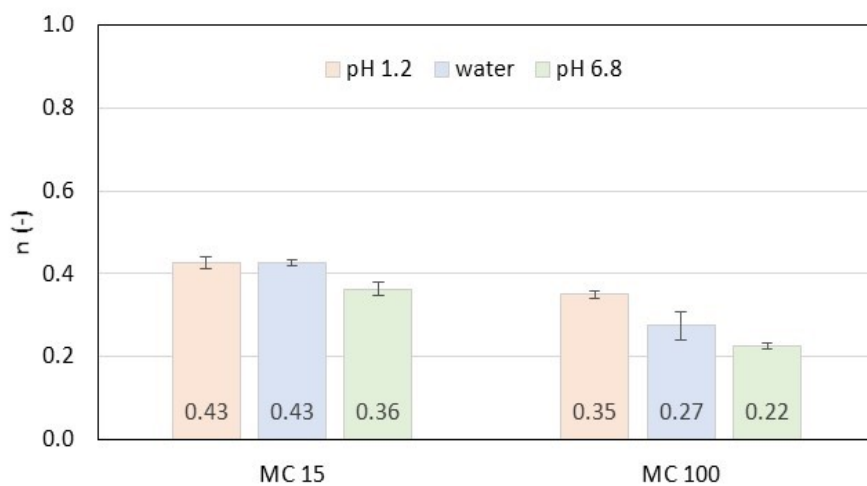
### 5.1.2 Flow properties of chitosan-based tableting mixtures

The influence of the concentration of retarding component in chitosan based on tableting mixture and on the type of medium used on flow behaviour is showed in Figures 42 and 43. The mixture of Methocel® K100M and sodium alginate in ratio 1:1 was used as a retardant. The viscosity depends on the solubility of the individual components at different media. The highest viscosities measured at pH 1.2 are insure probably by dissolution of chitosan. As sodium alginate is not dissolved at acidic medium, the increase of viscosity with concentration of retardant is caused by hypromellose.

Figure 42. Viscosity at 10 s^{-1} of 5 % tableting mixtures at different media
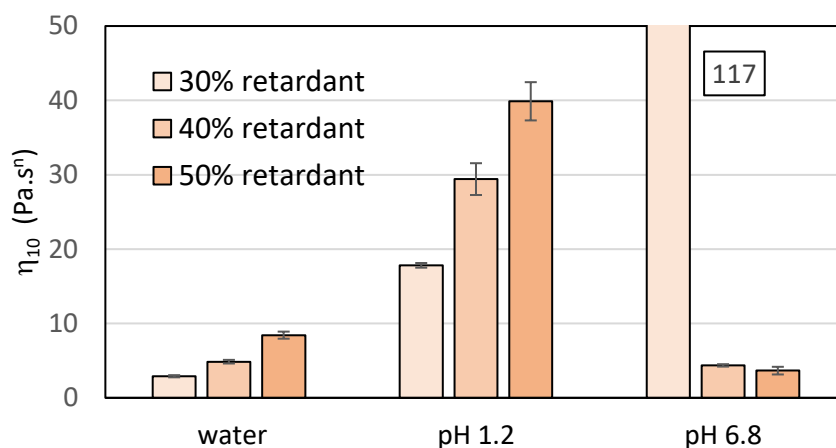
It was problematic to measure the viscosity at pH 6.8. A high viscosity value was found at 30 % concentration and unexpectedly low values at 40 % and 50 % retardant concentration even in a repeat test. A major problem and practically the impossibility of performing the test was the inhomogeneity of the samples. Sodium alginate and hypromellose at pH 6.8 formed a very stiff gel while chitosan was not dissolved. Repeated testing will be necessary and great attention will have to be paid to the preparation of dispersions and to wait long enough for the components to dissolve completely.

Figure 43. Consistency index *K* of 5 % tableting mixtures at different media
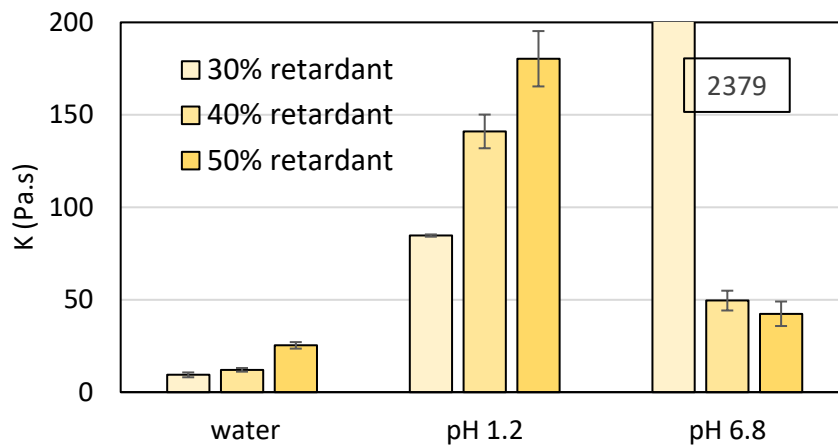
Comparison of the consistency coefficients *K* (Figure 43) and viscosities η_{10} (Figure 42), it showed approximately four times higher values of *K* as a measure of "*at rest*" viscosity or "consistency" of a material. The values of *n* are consistent with this statement as shown in Figure 44. Besides, the values of Power law indexes at pH 6.8, the values range from 0.3 to 0.6 approximately meaning quite stiff gels. A gel very sensitive to stress has a value of *n* even ten times lower. Unreliable values at pH 6.8, confirm the problems during the testing.

Figure 44. Power law index *n* of 5 % tableting mixtures at different media
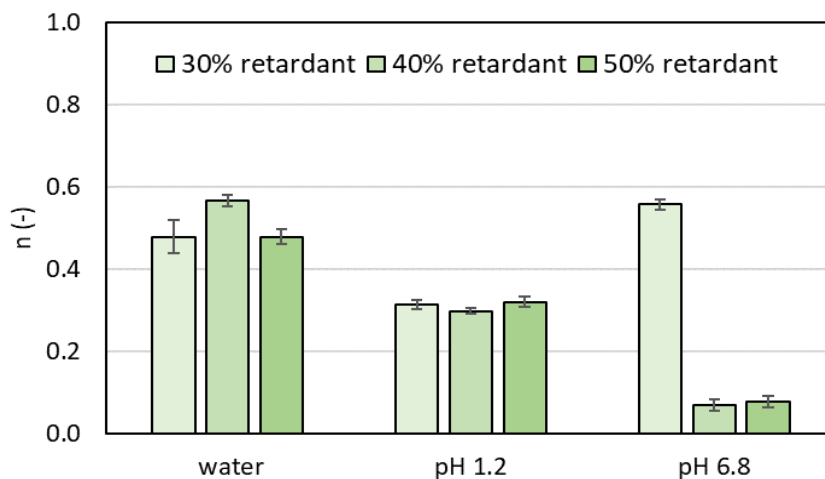
Figures 45-47 show the flow behaviour of the 20% dispersions of tableting mixtures in different media. This higher concentration better reflects conditions in the intestine where there is less fluid. Compared to 5% dispersions, the viscosity values were two orders of magnitude higher and as well as the difference between the viscosity η_{10} (Figure 45) and K (Figure 46) was about one order of magnitude. Thus, these gels are therefore highly viscous, but at the same time very sensitive to shear, as evidenced by the values of n in most cases less than 0.2 (Figure 47).

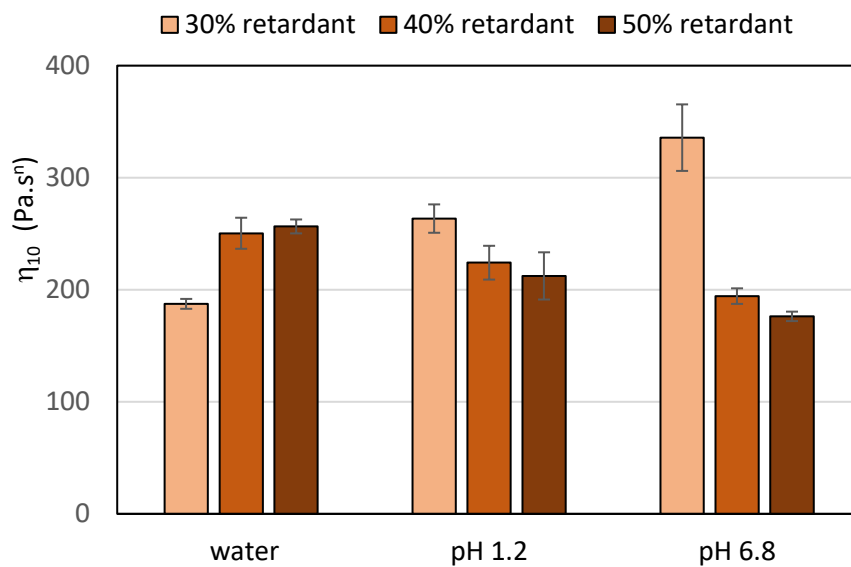Figure 45. Viscosity at 10 s^{-1} of 20 % tableting mixtures at different media

Figure 46. Consistency index K of 20 % tableting mixtures at different media
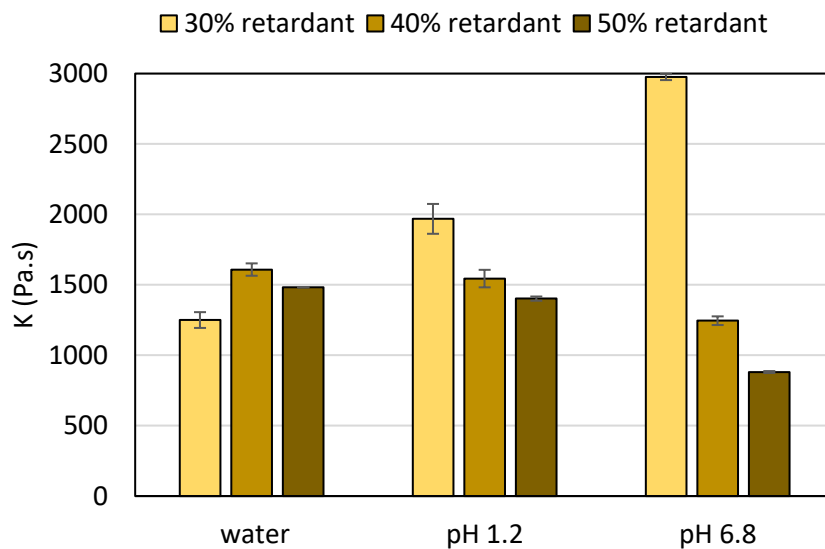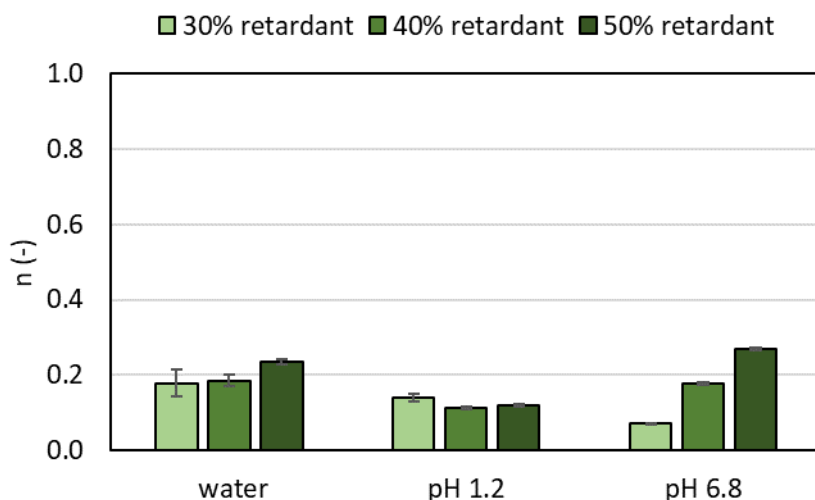
Figure 47. Power law index *n* of 20 % tabling mixtures at different media

At 20% concentration, there was less effect of retardant concentration and pH of medium. Dispersions in pH 6.8 buffer in this concentration were measurable with no problem with homogeneity. Figure 45 and 46 shows that when water was used, a higher concentration of retardant caused a higher viscosity, although there is no significant difference between 40% and 50%. The opposite dependence was observed for dispersion in media of pH 1.2. This can be explained by the solubility of chitosan in an acidic medium and the insolubility of sodium alginate and Methocel. Thus, the higher the concentration of chitosan and less concentration of retardant (i.e. sodium alginate and hypromellose) the higher the viscosity. However, the same results were measured at pH 6.8, which is interesting but difficult to explain.

5.2   Adhesive properties

Adhesive properties of chitosan-based tableting mixtures were evaluated based on measuring of detachment force F_{max} of the 5% or 20% dispersions in different media. In general, adhesion correlates with viscosity but there is no direct relationship. At very low viscosity, and at very high viscosity, adhesion can be insufficient. Possible reasons can be weak electrostatic interactions of polymer chains in case of low viscous dispersions, resp. a poor spreadability of a stiff gel. For a given polymer, there is a specific range of viscosity values providing optimal adhesion.

As shown in Figure 48, the highest adhesion of the 5% dispersions was found in the acidic medium and increased with the concentration of the retarding component. This corresponds to the measured viscosity values (see Figure 42).

Figure 48. Adhesive properties of 5% tableting mixtures in different media
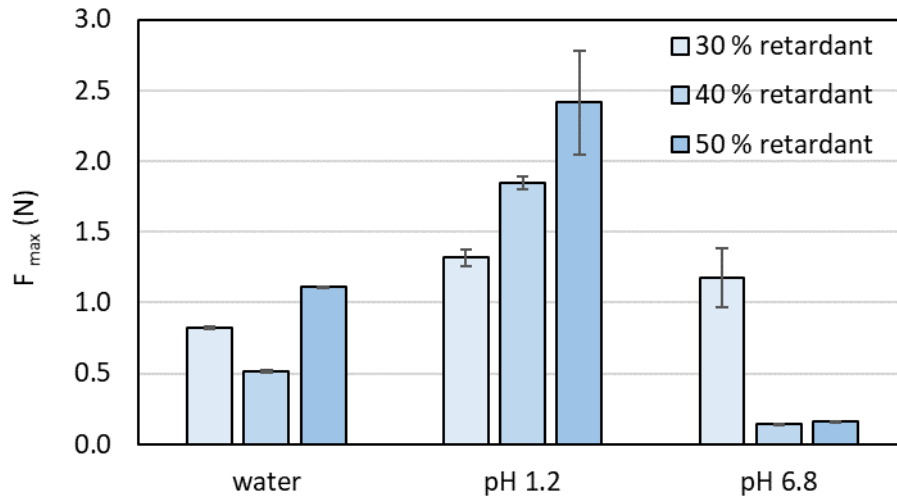
Dispersions of 20% chitosan-based tableting mixture revealed higher adhesion, even very stiff, high-viscosity gels could spread on the lower plate of the rheometer and were measurable. No effect of increasing concentration of retardant on adhesion was observed. The highest adhesion was measured in water, lower at pH 1.2 and lowest but still sufficient at pH 6.8.

Figure 49. Adhesive properties of 20% tableting mixtures in different media
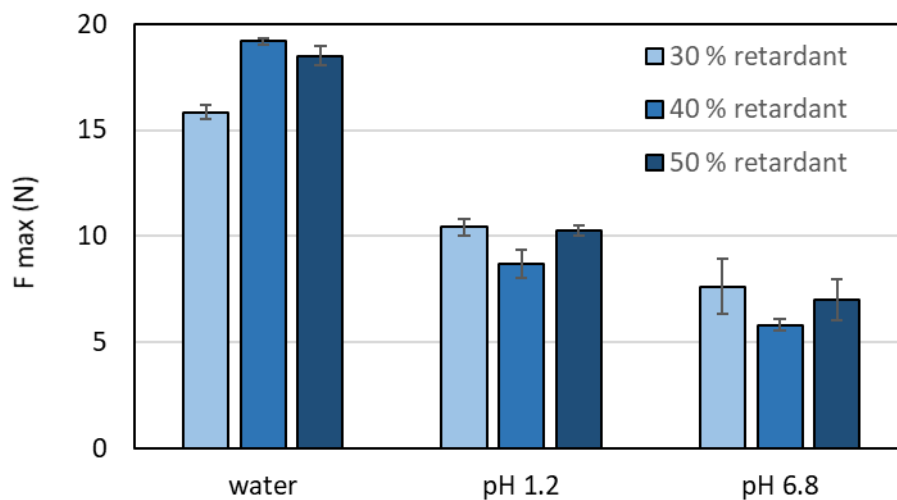
6   Conclusion

From all the studies performed in this diploma thesis, such points can be concluded:

- The courses of viscosity-shear rate curves of all tested samples clearly demonstrate typical shear-thinning behaviour. A good correlation of the measured data and the prediction by Power law model was found.

- Hypromellose showed a decrease in viscosity in acidic medium. However, the higher difference between the viscosities of Methocel® K15M and Methocel® K100M was expected.

- The remarkably high viscosity of 5% dispersions at pH 1.2 is due to the dissolution of chitosan, because sodium alginate is not soluble in acidic media. The increase in viscosity with the concentration of the retarding component is insured by hypromellose.

- A 20% dispersion of tablet mixtures in a medium is more suitable for testing. Higher concentrations better reflect the conditions in the intestine where there is less fluid.

- Unreliable viscosity values obtained at pH 6.8 may be due to inhomogeneity of very rigid gels and slippage during rotational tests. Great attention will have to be paid to the preparation of the samples and to the use of serrated geometries.

- 20% dispersions of chitosan-based tablets revealed high adhesion. No effect of increasing retardant concentration was observed. The highest adhesion was measured in water, lower in an acidic environment and lowest, but still sufficient at pH 6.8.

- In subsequent tests, it will be desirable to first expose the tablets to an acidic environment, to immediately bring them to pH 6.8 and only then measure the viscosity and adhesion.

7   Literature

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