Universidade de Lisboa

Faculdade de Farmácia

Flowable liquid retention potential of Neusilin US2 and Chitosan mixtures

André Cruz Nogueira de Carvalho

Mestrado Integrado em Ciências Farmacêuticas

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ABSTRACT

This thesis is focused on the preformulation studies of the innovative formulation known as liquisolid systems (LSS) that are capable of improving the dissolution profile and bioavailability of poorly water-soluble drugs. A liquisolid system is formulated by the sorption of a liquid drug or a drug in a liquid state onto a carrier with a high adsorption capacity. The main aim was to evaluate the flowable liquid retention potential of carrier's mixtures intended for the formulation of liquisolid systems with the targeted drug delivery. Chitosan is a polysaccharide and has been investigated for colon specific drug release. Colon targeted drug delivery could be used for the treatment of colonic diseases and to increase the systemic absorption of peptides and proteins through the colon. Liquisolid powders were prepared using Neusilin® US2 and Chitosan as carriers in different ratios (100:0, 75:25, 53.3:42.7 and 50:50) and increasing amounts of polyethylene glycol 200 as a non-volatile solvent. In order to establish a flowable liquid retention potential, conventional pharmacopeia's test, as well as the angle of slide, were employed. From the evaluation of liquisolid powder mixtures, it could be implied that 1g of Neusilin® US2 can retain 1.06 of PEG 200 according to the conventional angle of slide method, while maintaining an acceptable flow character. However, the addition of Chitosan decreased the flowable liquid retention potential of the liquisolid mixtures. Results confirm the high flowable liquid retention potential of Neusilin® US2, making it a suitable carrier for liquisolid system formulation. Whereas, the values for the mixtures did not imply any dependence on the ratio of Chitosan of the liquisolid mixture.

KEYWORDS Neusilin, Chitosan, Angle of Slide, Liquisolid Systems, Flowable liquid retention potential.

RESUMO

Esta tese centra-se nos estudos de pré-formulação de sistemas inovadores conhecidos como Liquisolid Systems (LSS) que permitem melhorar o perfil de dissolução e de biodisponibilidade de princípios ativos pouco solúveis em meio aquoso. A formulação de um sistema sólido-líquido tem por base a absorção de um fármaco líquido ou um fármaco no seu estado líquido num transportador com uma capacidade de absorção elevada. O objetivo principal era avaliar o potencial de retenção de líquidos escoáveis de várias misturas de transportadores destinadas à formulação de sistemas sólido-líquidos com a libertação localizada de uma determinada substância ativa. O quitosano é um polissacárido e tem sido investigado para a utilização na libertação localizada de fármacos especificamente no cólon. A libertação localizada de fármacos no cólon pode ser usada no tratamento de doenças no cólon bem como na administração de péptidos e proteínas no cólon para uma melhor absorção sistémica. Os pós sólido-líquidos foram preparados usando neusilina ® US2 e quitosano como transportadores em diferentes ratios (100:0, 75:25, 57.3:42.7 e 50:50) e com quantidades crescentes de polietilenoglicol 200 como solvente não volátil. De forma a estabelecer um potencial de retenção de líquidos escoáveis, avaliações convencionais provenientes da Farmacopeia, tais como o ângulo de deslizamento foram executados. Através da avaliação das misturas de sólido-líquido é possível observar que 1g de neusilina ® US2 consegue reter 1.06g de PEG 200 de acordo com o método convencional de determinação do ângulo de deslizamento enquanto apresenta caraterísticas de fluxo aceitáveis. No entanto, a adição de quitosano diminuiu o potencial de retenção de líquidos escoáveis das misturas sólido-líquidos. Os resultados confirmam o elevado potencial de retenção de líquidos escoáveis da neusilina ® US2, fazendo deste um transportador adequado na formulação de sistemas sólido-líquidos. No entanto, os valores do potencial de retenção de líquidos escoáveis das misturas de neusilina ® US2 e quitosano não permitiram concluir nenhuma relação com a quantidade de quitosano presente na mistura.

PALAVRAS-CHAVE: Neusilina, Quitosano, Ângulo de deslizamento, Sistemas sólido-líquido, Potencial de retenção de líquidos escoáveis.

AGRADECIMENTOS/DEDICATÓRIAS

A todos vós que me ajudaram a concluir estes cinco anos, que de uma maneira ou de outra participaram na minha vida e certamente deixaram uma marca. Pai e mãe, espero que continuem tão orgulhosos como desde o primeiro dia em que embarquei nesta aventura, isto é para vocês. Rita e Zé que vos sirva de exemplo, a nunca desistir e a fazer tudo por tudo sem nunca esperar uma recompensa. À Jéssica e ao Marcelino por toda a paciência que tiveram de ter para aturar esta personagem e obrigado por todas as palavras de apoio, de carinho e de amor. A um círculo de amigos forte que resiste a tudo: a mudanças de curso e demais peripécias que são demasiado peculiares para mencionar num documento tão sério. Obrigado do fundo do coração e agora sei que isto não teria sido possível sem a vossa companhia. Vamos agora ao que interessa e mostrar ao mundo do que somos feitos!

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INTRODUCTION

1.1. LIQUISOLID SYSTEMS: AN INNOVATIVE DOSAGE FORM TO INCREASE ORAL BIOAVAILABILITY

Modern active pharmaceutical substances often exhibit poor bioavailability after oral administration. Drug bioavailability depends on multiple factors such as drug permeability, aqueous solubility, dissolution rate, first-pass effect, and presystemic metabolism, and susceptibility to efflux mechanisms. The parameter that most influence orally administered drugs is solubility which is the achievement of a required concentration in systemic circulation necessary for the desired pharmacological response (1). Monitoring these parameters could potentially lead toward a sustained-release oral dosage form that allows for a reduction in the drug administration's frequency (2). For this reason, a promising area of pharmaceutical technology is now focused on improving drug solubility especially for solid dosage forms designated for oral administration. There are several different techniques reported in the scientific literature for this challenging aspect (such as the preparation of self-emulsifying drug delivery systems (3), enhancing the drug's dissolution rate via lyophilization (4), using surfactants (5) and reducing particle size via micronization (6)).

From all the approaches available, liquisolid systems (LSS) represents one of the most promising methods for improving the *in vivo* bioavailability of poorly soluble drugs. According to the biopharmaceutical classification system (BCS), a poorly water-soluble drug with a low dissolution rate drug belongs to the class II: low solubility and high permeability. Formulations based on liquisolid systems are prepared by, first, the absorption of the liquid drug or a drug in a liquid state (emulsion, suspension, solution) into the interior structure of the carrier (7). After the carrier's interior is saturated, a liquid layer is formed on the surface of the carrier, which is immediately absorbed by the coating materials. Consequently, a dry, free-flowing, easily compressed and nonadherent powder mixture is formed (8). One important advantage of these systems is that, afterward, the dry powder blend can be converted into conventional solid dosage forms (compressed into tablets and filled into capsules). This liquisolid technique has recently been attempted to be used in order to minimize the influence of pH deviations on the drug's dissolution (9) and to improve drug photostability (10).

A liquisolid system is expected to exhibit acceptable compressible and flowable properties. This can be achieved by calculating the appropriate quantities of coating material and carrier a concept using a mathematical model. Flowable liquid retention potential (Φ value) and compressible liquid retention potential (ψ value) are both fundamental powder properties

that are the basis for this model. These values of a powder express the maximum capacity of the powder bulk to retain a liquid vehicle without compromising flowability and compressibility (11).

LSS provides other advantages in avoiding systemic side effects and improving local therapeutic efficiency, e.g. colon targeted delivery systems, in patients with chronic inflammatory disorders (such as Chron's diseases, ulcerative colitis, colorectal cancer, and amebiasis). The liquisolid technique can be used to formulate colon targeted drug delivery systems. The additional step in this method is the use of bacterial degradable polysaccharides such as chitosan, sodium alginate, guar gum and pectin as carriers (12). The presence of bacterial enzymes in the colon deteriorates the carrier polymer allowing the content's release for localized or systemic absorption (13). For that reason, this thesis is focused on the evaluation of a possible polysaccharide-based carrier in mixtures of different ratios for its potential use in the formulation of LSS.

1.2. A STABLE SOLVENT FOR IMMEDIATE RELEASE

The first stage of preparing a liquisolid system is to transform the solid drug to a liquid state. Therefore, the liquid vehicle should be non-volatile, orally safe, not highly viscous, inert and preferably water-miscible organic solvent must be used (e.g. liquid polyethylene glycols, polysorbates, propylene glycol). The drug release rate could be influenced by its solubility in a non-volatile solvent: the fraction of molecularly dispersed drug (F_M) is correspondingly higher to the drug solubility, which leads to an improvement of the dissolution rate (14). As previously investigated and demonstrated different non-volatile solvents were successfully used in the preparation of a liquisolid technique by sustaining and increasing the release of the drug (15,16). In a low concentration, the compactness of liquisolid tablets could be explained by the binder function which a liquid vehicle can have. The presence of hydroxyl groups in the molecular structure of the liquid vehicle will lead to a hydrogen bond between solvents and excipients. Thus, in conclusion, polyethylene glycol (e.g. PEG200), a hydrophilic surfactant, fulfills all the criteria for a good non-volatile solvent which main advantage towards other solvents remains on its low molecular weight group regarding low grades of PEG (17).

1.3. MAGNESIUM ALUMINOSSILICATE AS A CARRIER

The selection of the powder carriers depends on its properties such as liquid absorption capacity, flowability, compressibility and specific surface area (SSA) (2). SSA and liquid absorption capacity are the most limiting properties therefore if both are high it would be possible for the carrier to retain a higher quantity of solvent. Microcrystalline cellulose (MCC) is the current most commonly used carrier having three different grades (i.e. PH 101, 102, and 200). MCC PH101 has qualifying properties for a carrier due to its suitable compressibility, flowability, and dissolution profile, but with rather low SSA of 1.18 m^2/g. Low SSA values imply a higher amount of carrier for the conversion of liquid drugs into the powder mixture.

Alternatively, magnesium aluminosilicates (Pharmsorb®, Neusilin®, Veegum®) are versatile excipients for a wide variety of applications. For example, Neusilin®, a newly-developed carrier, is available in 11 amorphous grades (commercially in 4 grades), differing from each other according to its forms (granules, powder), pHs (alkaline pH 8.5-10.0 and neutral pH 6.5-8.0), water content, particle sizes and bulk densities (18). It can be used as a coating material or carrier depending on its form: a powder or a granulate. This carrier material has a very large SSA (up to 300 m^2/g), high liquid adsorption capacity (up to 3.4 mL/g) [12] and flow enhancing properties. Therefore, it is possible to incorporate a superior amount of drug in a liquid state in comparison to microcrystalline cellulose (MCC), which allows for preparing liquisolid tablets with a lower weight. In pharmaceutical technology, they have been given multiple uses in order to enhance the formulation stability and dissolution (19). Recent experiments have shown that Neusilin® US2 is the most commonly used carrier for LSS formulations as 1g of this carrier can retain 1.00 g of propylene glycol (PG), 1.16g of PEG 400 or 1.48g of PEG 200, without affecting negatively the flow properties (20).

1.4. CHITOSAN: NATURAL POLYSACCHARIDE

An early dissolution in the gastrointestinal tract (GIT) is the most limiting step during drug absorption and that is why polysaccharides are used. Certain biodegradable polysaccharides (inulin, pectin, chitosan) are only digested by the bacterial enzymes of the colon and by protecting the selected drug with them it is possible to achieve a localized drug delivery.

Chitosan is a derivative of chitin and the second most abundant polysaccharide found in nature (21). Its structure with amino and hydroxyl groups (Figure 1) gives the possibility to

modify their chemical structures, including solubility (22). Due to chitosan's high specific surface area and high porosity, there is a very promising future to biomedical and pharmaceutical applications such as surgical sutures and controlled release of drugs for animals and humans, for example (23).

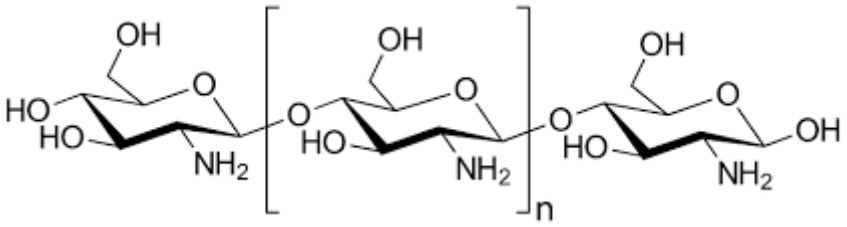

Figure 1 - Chemical structure of Chitosan

Chitosan is soluble in dilute acidic solutions below pH 6.0 and precipitates at a pH above 7.0. These low pH ranges emphasise the need for coating (e.g Eudragit RLPO) the chitosan to protect it against the stomach's acidity and enable the formulation to reach the colon.

The selection of a suitable carrier depends on the functional groups of the drug molecule and is also influenced by the drug's stability and physicochemical nature. It is very important an optimal proportion of the hydrophilic and hydrophobic parts as well as the quantity of free hydroxy groups in the molecule. As one of the natural polysaccharides which have long been used in colon targeted drug delivery for being resistant to enzymes of the upper part of the GIT by human digestive enzymes (24). It has some good biological properties such as non-toxicity, biocompatibility, and biodegradability complemented by being widely approved as a food ingredient, which could lead towards its acceptability as an innovative excipient for oral administration (25).

A controlled drug release mechanism is applied in a colon-specific drug delivery system. In this system, different technologies have been attempted using pH-dependent, prodrugs or colonic microflora-activated approaches. Among these approaches, microbially activated delivery systems hold promise. It operates on the colon's anaerobic bacteria's ability to recognize diverse substrates and to degrade them with their enzymes. With a specific colon drug carrier, it is possible to produce a hydrostatic pressure in the design of microflora triggered colon targeted drug delivery (MCDDS). Studies have shown that bacterial enzymes of the colon's microflora were able to degrade chitosan and that the concentration of chitosan was directly proportional to the drug release from MCDDS. So it has been proven that a mixed film with Chitosan/Eudragit RLPO coating can achieve a desired gastrointestinal protection and a controlled drug release in the colon at the same time (26).

A rapid dissolution in a gastric cavity could also have been a real obstacle in incorporating chitosan in a colon delivery system. Crosslinking chitosan with aldehydes has been an alternative to overcome this problem (27) but the aldehydes' toxicity itself revealed to be a major limitation (28). However, chitosan salified with different acids using a spray drying technique is a suitable supporting material for the preparation of colon-specific drug delivery systems (29). Depending on the final objective of the liquisolid system, a suitable acid should be selected. For a higher drug release rate, β-glucosidase was found to be the appropriate acid as its solubility enhances enzyme-polymer interactions.

2. MATERIALS AND METHODS

2.1. MATERIALS

Magnesium aluminometasilicate (Neusilin® US2) (Fuji Chemical Industry Co., Ltd., Japan) and Chitosan (Sigma-Aldrich, Germany) were used as carrier materials. Polyethylene glycol 200 (Dr. Kulich Pharma, Hradec Králové Czech Republic) was used as a non-volatile solvent.

2.2. METHODS

2.2.1. Preparation of Liquisolid Powders

Liquisolid powders were prepared by simple blending of the carrier with a non-volatile solvent in the mortar with pestle. The composition of the initial mixtures is shown in Table 1. The whole mixture was subsequently sieved using a 1 mm mesh size sieve, homogenized using a Cube Mixer (Erweka KB 20 S) for 10 minutes and sieved again. The mixture of carriers without any liquid vehicle and all liquisolid mixtures were evaluated by determining flow through an orifice, angle of repose, bulk and tapped densities, angle of slide and pycnometric density. Subsequently, 1 g of PEG 200 was added followed by homogenization and evaluation of flow properties as described above. When the value of the angle of slide achieved an optimal value of 33° (30) or if its value starts to increase, at least two further additions of PEG 200 were performed.

Table 1 The composition of the initial mixtures.

Mixture (Proportion of Neusilin® US2: Chitosan)	Neusilin® US2 (g)	Chitosan (g)
50:50	25	25
75:25	37.5	12.5
100:0	50	0

2.2.2. Determination of Angle of Slide

According to the scientific literature (31), the angle of slide is the preferred method for the determination of the flowability of liquisolid powders. In this experimental work, there were used two methods for this determination measured with a prototype containing a metal plate

with a polished area (Figure 1). These methods differ in the sample (10g of a measured powder) placement on the polished plate: line or fine layer.

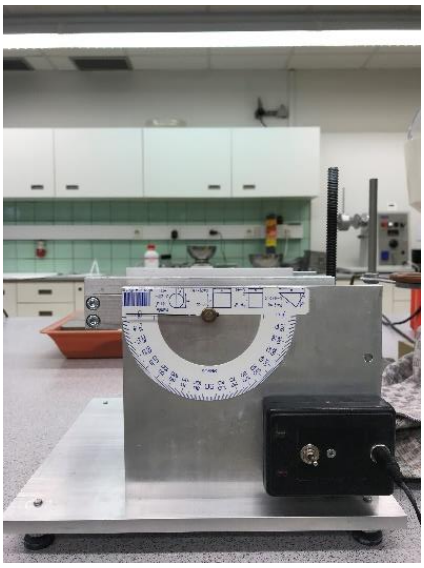

Figure 2 - The equipment used for evaluating the angle of slide.

2.2.2.1. Standard fine layer method

In the "fine layer method," the mixture covers most of the metal plate area as a fine layer: the powder is slowly laid down using a spoon and a fine layer is formed by gently moving the equipment horizontally. Then, one end of the plate is raised in a controlled and continuous action until the powder is about to slide in an even thinner layer. The measurement was repeated five times and the average value and standard deviation were calculated.

Figure 3 - Method for evaluating the angle of slide described as fine layer method.

2.2.2.2. A new approach to this evaluation: line method

In this method, the powder was set up using only a spoon and displayed in a narrow triangular layer which can be observed in Figure 2. Then, one end of the plate is raised in a controlled and continuous action until the powder starts to slide and forms an equally dispersed layer. The measurement was repeated five times and the average value and standard deviation were calculated.

Figure 4 - Method for evaluating the angle of slide described as line method.

2.2.3. Angle of Repose

There are various methods to evaluate the angle of repose which will lead to different results. In this thesis, it was measured using an Erweka Granulate & Powder Flow Tester, Type GTB where different parameters such as the orifice's diameter should be previously inserted.

The sample (25g of a measured powder mixture) was measured after flowing through an orifice and a cone of powder is formed. Then the equipment measures the height of the cone of powder and the angle of repose is calculated. This determination was performed with three orifices with different diameters (10 mm, 15 mm and 25 mm) and repeated 5 times each.

2.2.4. Density

2.2.4.1. Bulk Density

The bulk density of a powder is dependent on the particle packing and changes as the powder consolidate. It is measured in a graduated cylinder according to the Determination of bulk and tapped density of powders (32). Bulk density was determined by introducing the powder (20g) into a dry 100 mL cylinder without compacting and the unsettled apparent volume V_0 is found. This measurement should be slow and careful in order to minimize dust and loss of sample. Using the formula m/V_0, bulk density is calculated. The bulk density evaluation was repeated five times.

2.2.4.2. Tapped Density

Tapped density is obtained by mechanically tapping a graduated measuring cylinder containing the powder sample. Once the bulk volume is determined, on the same powder sample is carried out 10, 50 and 1250 taps and read the volumes V_{10}, V_{50} and V_{1250}. Compressibility Index (CI) and Hausner Ratio (HR) were calculated from bulk and tapped volumes values as follows:

$$CI = 100 \text{ x } \frac{V_0 - V_f}{V_0}$$

$$HR = \frac{V_0}{V_f}$$

Each measurement was performed five times and the average and standard deviation were calculated. According to Table 2, it is possible to describe the Flow Character of the different powder mixtures of Chitosan: Neusilin® US2 measured during this experimental work.

Table 2 - Scale of flowability [20].

Compressibility Index (%)	Flow Character	Hausner Ratio
1-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21.25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

2.2.4.3. Pycnometer Density

A gas displacement technique using a helium pycnometer (AccuPyc II 1340 Series Pycnometer) was used to evaluate the pycnometer density of all samples (Figure 5). In a previously calibrated pycnometer, a weighed, clean and dry test cell was filled with a given mass of the mixture. The test cell was inserted and sealed in the pycnometer. After at least 20 minutes of analysis, density and its standard deviation were recorded. For each powder mass, the helium pycnometer displays 5 different densities and the mean value, as well as the standard deviation, were calculated.

Figure 5 - AccuPyc II 1340 Series Pycnometer.

2.2.5. Flow through an orifice

A direct method was used to determine the flow through an orifice or flowability by using also the Erweka Granulate & Powder Flow Tester, Type GTB. In this method, the sample (25g of a measured powder mixture) was introduced in a dry stainless hopper with the bottom opening closed (33). This measurement was performed with three different hoppers with three different diameters: 10mm, 15mm, and 25mm. Automatically, the bottom opening was unblocked and measured manually how much time the sample took to flow out of the funnel. Five measurements were performed and the average and standard deviation were calculated.

2.2.6. Determination of the flowable liquid retention potential (Φ-value)

The liquisolid blend containing an increasing amount of PEG 200 was formulated as described previously. The Φ-value is defined as the weight of carrier that can retain a maximum weight of the non-volatile solvent while maintaining acceptable flow properties. The flowable liquid retention potential of mixtures is calculated (Equation 1) with the amount of solvent that produced an angle of slide value closest to 33°.

$$\Phi_{CA} = \frac{m_{\max}}{Q} \quad (1)$$

3. RESULTS

3.1. EVALUATION OF THE CARRIERS' PROPERTIES

Chitosan and Neusilin were subjected through all experimental methods so it would be clearer how the addition of PEG 200 influenced their flow properties. From this experimental work, we were able to draw some conclusions regarding both substances.

3.1.1. Chitosan

In the case of Chitosan, it was possible to carry out only bulk and tapped volumes measurement and the pycnometer density (Table 3). The Compressibility Index (CI) with values of 28.23 ± 0.96% and Hausner Ratio (HR) are 1.39 ± 0.03 were calculated using the values of tapped and bulk densities. For the evaluation of gas density using the previously established pycnometer was found a 1.45365 ± 0.00034 g/cm³ result. The remaining measurements were not possible to perform due to the insufficient flow properties of Chitosan.

Table 3 - Flow properties of Chitosan.

CI [%]	SD	HR	SD	Pycnometer Density [g/cm³]	SD
28.23	0.96	1.39	0.03	1.45365	0.00035

3.1.2. Neusilin ® US2

On the other hand, the evaluation of Neusilin® US2 (Table 4) showed that Compressibility Index (CI) and Hausner Ratio (HR) values were 12.60 ± 0.89% and 1.14 ± 0.01, respectively, revealing a "good" flow character (34). The angle of repose which could suggest a worse degree of flowability (values of 35.90 ± 0.59° with a 10mm orifice and of 38.5 ± 0.12° with a 15mm orifice) suggest a "fair" classification. However, the Angle of Slide's results were able to reach a very close value to the optimal described in the literature (33°): 33.1 ± 1.93° with the line method and 42.7 ± 1.44° with the layer method. Flow through an orifice was the method for measuring flowability resorting to orifices of 10 mm, 15 mm and 25 mm with these results: 44.59 ± 0.67 s/25g, 12.72 ± 0.7 s/25g and 1.79 ± 0.24 s/25g, respectively. Pycnometer density of Neusilin was 2.1346 ± 0.0096 g/cm³.

Table 4 - Flow properties of aluminometasilicate carrier Neusilin® US2. The orifices' diameter is displayed below the parameter evaluated.

Angle of Repose [°]				Flowability [s/25g]						CI [%]	SD	HR	SD	Angle of Slide [°]				Pycnometer Density [g/cm³]	SD
10mm	SD	15mm	SD	10mm	SD	15mm	SD	25mm	SD					Line	SD	Layer	SD		
35.90	0.59	38.50	0.12	44.59	0.67	12.72	0.70	1.79	0.24	12.60	0.89	1.14	0.01	33.1	1.93	42.7	1,44	2.1346	0.0096

3.2. DETERMINATION OF FLOWABLE LIQUID RETENTION POTENTIAL

3.2.1. Neusilin® US2 and PEG200

Results obtained from the evaluation of Neusilin® US2 with an increasing amount of PEG 200 are presented in Table 5 and Figure 6. Evaluation of the Angle of slide was carried out through two methods: layer method and line method. In the first method, it is possible to observe (Figure 4) that Neusilin® US2 itself had an Angle of slide of 42.7 ± 1.6°. On the other method, the Angle of slide had values of 33.1 ± 2.2°. The angle of slide of the sample containing 20g of PEG 200 was 38.0 ± 0.5° using the layer method and 31.3 ± 0.6° using the line method. In both methods, the addition of 1g of the solvent made the Angle of Slide increase up to 40.4 ± 1.1° and 32.7 ± 0.6°. In the layer method, the closest value to an optimal Angle of Slide of 33° was achieved with an amount of 53g of PEG 200: 33.4 ± 0.5°. On the other angle of slide method, it was only necessary 22g of PEG 200 to reach a lower angle of slide: 32.9 ± 0.7°. Furthermore, the remaining measurements performed in order to evaluate the mixture's flow character such as Flowability (2.80 ± 0.27 s/25g), Angle of Repose (41.75 ± 1.14°), CI (19.91 ± 2.33%), HR (1.25 ± 0.04) and Pycnometer Density (1.540 ± 0.099 g/cm³) also corresponded to powders with "fair" flow properties (34).

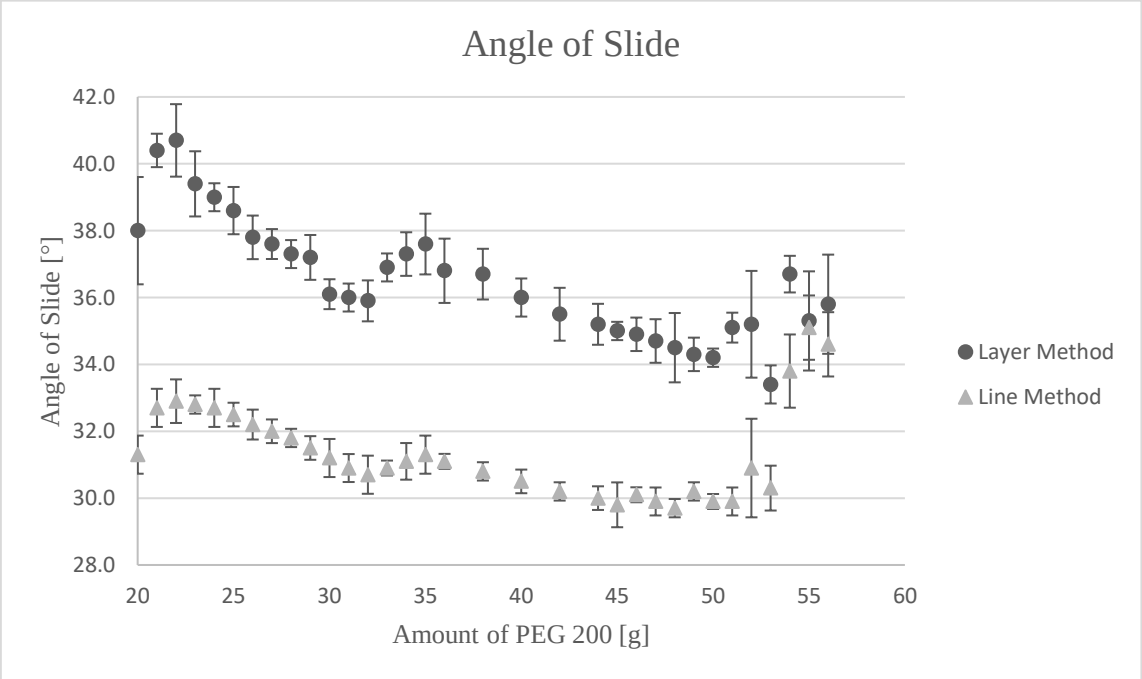

Figure 6 - Evaluation of the Angle of Slide of the mixture with Neusilin® US2 (50g) and PEG200 using the line method and the layer method.

Neusilin® US2 itself had an Angle of Repose of 38.54 ± 0.13° and a Flow rate of 1.79 ± 0.27 s/25g. After the first addition of 20g of PEG 200, both values increased to 38.88 ± 1.02°

and 2.08 ± 0.14 s/25g respectively. The addition of more liquid vehicle increased values of Angle of Repose up to a maximum value of 43.96 ± 0.12° (with an orifice diameter of 10 mm and 24g of PEG 200) and to a maximum value of 43.14 ± 1.70° (with an orifice diameter of 15 mm and 32g of PEG 200). Evaluation of flowability also indicated a decrease in its values when the amount of PEG 200 increased, in comparison to Neusilin® US2 itself. The mixture containing 22g of PEG 200 registered the maximum value of 4.65 ± 0.67 s/25g (orifice diameter of 25 mm). As Table 5 indicates, values of flowability decreased reaching a minimum of 1.81 ± 0.22 s/25g (a mixture containing 50g of PEG 200) which represented a flow rate enhancement. The pycnometer density of the liquisolid mixture (minimal value of 1.405 ± 0.0004 g/cm^3) was lower in comparison to Neusilin® US2 itself (2.1346 ± 0.0080 g/cm^3).

The determination of parameters such as the Compressibility Index (CI) and Hausner Ratio (HR) was not revealing any dependence on the amount of liquid added. In spite of the lack of evidence, the results fulfill the criteria for powders with fair flow properties (34).

The flowable liquid retention potential (Φ-value) of Neusilin® US2 mixed with PEG 200 was calculated (Equation 1) for both methods used to determine the Angle of slide. In the layer method, the ratio was calculated with 53g of PEG 200 and 50g of mixture and is equal to 1.06 (Table 5). Whereas in the line method the closest measurement to 33° was achieved with 22g of liquid producing a Φ-value of 0.44 (Table 5).

Table 5 - Flow properties and pycnometer densities of Neusilin® US2 (50g) and PEG 200 mixtures. The orifices' diameter is displayed below the parameter evaluated.

Amount of PEG 200 [g]	Φ-value	Angle of Repose [°] (10mm)	Angle of Repose [°] (15mm)	Flowability [s/25g] (15mm)	Flowability [s/25g] (25mm)	CI [%]	HR	Angle of Slide [°] (Line)	Angle of Slide [°] (Layer)	Pycnometer Density [g/cm³]
0	0	35.90	38.54	12.72	1.79	12.60	1.14	33.1	42.7	2.135
20	0.4	37.90	38.88	10.78	2.08	15.44	1.18	31.3	38.0	1.726
21	0.42	42.36	41.82	18.94	3.42	16.98	1.21	32.7	40.4	1.706
22	0.44	43.70	42.28	23.18	4.65	16.94	1.20	32.9	40.7	1.691
23	0.46	42.22	42.28	21.03	3.49	18.47	1.23	32.8	39.4	1.687
24	0.48	43.96	42.50	21.12	4.05	18.97	1.23	32.7	39.0	1.668
25	0.5	43.26	41.72	19.71	3.89	19.48	1.24	32.5	38.6	1.661
26	0.52	43.66	41.88	18.61	4.16	20.13	1.25	32.2	37.8	1.637
27	0.54	43.28	41.52	18.30	3.87	19.81	1.25	32.0	37.6	1.625
28	0.56	42.68	42.08	17.59	4.11	20.79	1.26	31.8	37.3	1.627
29	0.58	43.08	41.34	16.15	3.34	21.61	1.28	31.5	37.2	1.617
30	0.6	41.46	41.58	14.08	3.61	21.88	1.28	31.2	36.1	1.606
31	0.62	41.94	40.90	15.32	3.54	21.09	1.27	30.9	36.0	1.583
32	0.64	42.00	43.14	12.88	3.48	20.85	1.26	30.7	35.9	1.572
33	0.66	43.18	42.56	11.29	3.15	20.51	1.26	30.9	36.9	1.563
34	0.68	41.76	42.00	11.87	3.10	21.41	1.27	31.1	37.3	1.556
35	0.7	42.08	42.18	10.18	2.83	20.04	1.25	31.3	37.6	1.564
36	0.72	42.22	41.60	9.63	2.66	20.91	1.26	31.1	36.8	1.528
38	0.76	43.34	42.22	9.08	2.66	24.43	1.32	30.7	36.7	1.516
40	0.8	41.86	41.38	7.19	2.15	21.05	1.27	30.5	36.0	1.499
42	0.84	41.48	41.54	7.01	2.43	22.56	1.29	30.2	35.5	1.484
44	0.88	40.82	40.92	6.45	2.09	22.14	1.29	30.0	35.2	1.473
45	0.9	41.26	41.28	-	2.31	22.08	1.28	29.8	35.0	1.468
46	0.92	41.40	42.12	-	1.98	20.59	1.26	30.1	34.9	1.459
47	0.94	42.82	42.44	-	1.98	21.58	1.28	29.9	34.7	1.454
48	0.96	40.52	41.40	-	1.97	20.30	1.25	29.7	34.5	1.450
49	0.98	41.28	41.02	-	1.90	20.78	1.26	30.2	34.3	1.443
50	1	42.08	41.14	-	1.81	18.07	1.22	29.9	34.2	1.439
51	1.02	40.68	40.28	-	1.83	21.19	1.27	29.9	35.1	1.432
52	1.04	43.08	41.78	-	1.92	21.73	1.28	30.9	35.2	1.424
53	1.06	43.58	42.26	-	1.95	19.97	1.25	30.3	33.4	1.424
54	1.08	42.70	42.26	-	1.96	16.90	1.20	33.8	36.7	1.417
55	1.1	43.28	42.64	-	2.25	14.79	1.17	35.1	35.3	1.409
56	1.12	42.10	42.96	-	1.90	13.64	1.16	34.6	35.8	1.405

3.2.2. An even proportion of Neusilin® US2 and Chitosan (50:50)

The flow properties of a liquisolid mixture of Neusilin® US2 and Chitosan (50:50 ratio) and PEG 200 was evaluated and displayed in Table 6 and Figure 7. The addition of Chitosan to this mixture implied an increase in the initial values of the measurements. For example, the Angle of slide of the blend with only Neusilin® US2 and Chitosan was 43.50 ± 2.10° and 44.0 ± 3.95° through the line method and the layer method, respectively. However, the addition of liquid vehicle, PEG 200, decreased substantially these values to 36.90 ± 1.11° and 41.00 ± 0.84°. Further additions of solvent lead to a minimum value of 33.1 ± 0.58° and 35.3 ± 0.24° in a mixture containing 26g of PEG 200 which was the closest to the desired value of 33°. (Figure 7).

Table 6 - Flow properties of Neusilin® US2 (25g), Chitosan (25g) and PEG 200 mixtures. The orifices' diameter is displayed below the parameter evaluated.

Amount of PEG 200 [g]	Φ-value	Angle of Repose [°] (10mm)	Angle of Repose [°] (15mm)	Flowability [s/25g] (10mm)	Flowability [s/25g] (15mm)	Flowability [s/25g] (25mm)	CI [%]	HR	Angle of Slide [°] (Line)	Angle of Slide [°] (Layer)	Pycnometer Density [g/cm³]
0	0	39.66	39.20	35.81	16.13	3.72	17.94	1.22	43.5	44.0	1.7414
20	0.4	40.68	39.70	23.15	10.76	3.03	21.17	1.27	36.9	41.0	1.5072
21	0.42	-	40.10	-	13.01	3.02	22.56	1.29	35.2	39.6	1.4994
22	0.44	-	41.40	-	13.77	4.14	21.29	1.27	34.5	38.0	1.4912
23	0.46	-	41.10	-	-	4.10	22.78	1.30	33.6	36.9	1.4855
24	0.48	-	41.50	-	-	3.07	22.19	1.29	33.1	35.8	1.4699
25	0.5	-	40.60	-	-	3.96	22.76	1.30	33.2	35.2	1.4643
26	0.52	-	42.30	-	-	5.25	22.27	1.29	33.1	35.3	1.4568
27	0.54	-	42.60	-	-	-	23.03	1.30	34.3	38.6	1.452
28	0.56	-	43.68	-	-	-	22.86	1.30	34.5	36.4	1.448
29	0.58	-	43.70	-	-	-	23.10	1.30	35.4	38.5	1.4408

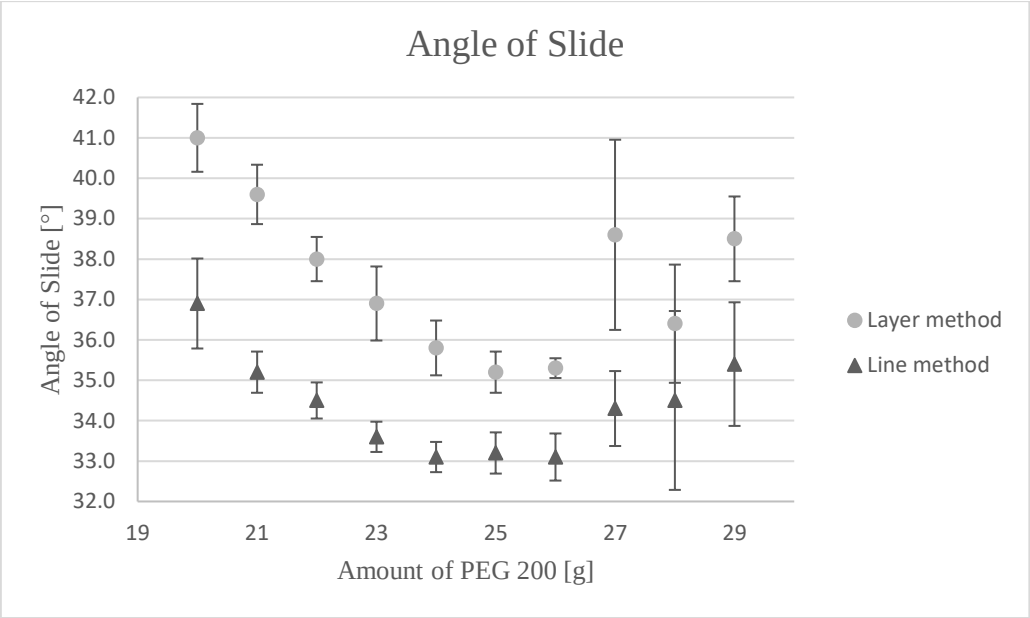

Figure 7 - Evaluation of the Angle of Slide of the mixture with Neusilin® US2 (25g), Chitosan (25g) and PEG200 using the line method and the layer method.

Other measurements of this liquisolid mixture such as Angle of Repose and Flow through an orifice indicated that increasing the amount of PEG 200 would increase its values. With no solvent, the Angle of repose was 39.20 ± 0.36° and flowability was 3.72 ± 0.30 s/25g. The Angle of repose increased with the continuous additions of solvent reaching a maximum of 43.70 ± 0.93° (orifice diameter of 15 mm) that corresponded to a mixture with 29g of PEG 200. The flow properties of the mixture changed from fair to passable (34). However, evaluation flowability indicated that increasing the amount of liquid vehicle improved the flow properties of the blend. The lowest value of flowability (3.07 ± 0.2 s/25g) was registered in the presence of 24g of liquid (orifice diameter of 25 mm).

From the values of the Compressibility Index (CI) and Hausner Ratio (HR) registered it was possible to observe the worsening of the flow properties (changed from fair to passable) (34). The Compressibility index of the initial mixture was 17.94 ± 0.56% and the addition of 1g of the liquid vehicle increased to 21.17 ± 1.10%. From this addition, CI continued to increase until a maximum of 23.10 ± 0.49%. Hausner Ratio was subjected to the same phenomenon during its measurement. After the addition of the initial 20g of PEG 200, the HR increased from 1.22 ± 0.01 to 1.27 ± 0.02° and kept increasing (Table 6).

The values of the pycnometer density of the liquisolid blend decrease with the addition of a liquid vehicle. Initially, a value of 1.7414 ± 0.0020 g/cm³ was observable, though by adding a solvent, pycnometer density decreased to 1.5072 ± 0.0010 g/cm³. Further additions decreased values of pycnometer density to 1.4408 ± 0.0005 g/cm³.

The Φ-value for this ratio of Neusilin® US2 and Chitosan was calculated (Equation 1) and it differs accordingly with the method used to determine the Angle of slide. With the standard fine layer method as the ratio weight of PEG 200 (25g) and amount of carrier (50g) and is equal to 0.5. In Table 6 it is also possible to observe that in the line method the Φ-value is calculated using 24g as the amount of liquid and 50g as the amount of carrier and it is equal to 0.48.

3.2.3. An intermediate ratio of Neusilin® US2 and Chitosan (57.3:42.7)

From Figure 6, it is possible to observe that the Angle of slide decreases with the addition of PEG 200 in this liquisolid mixture. The sample without the liquid vehicle has values of this measurement of 40.0 ± 1.52° with the line method and 41.4 ± 0.58° with layer method. Evaluation of angle of slide implied that the addition of 1g of solvent decreased its value to 31.3 ± 0.40° and 35.5 ± 0.84°, respectively. In the line method, the closest to the optimum value 33° was achieved with the blend containing 27g of PEG 200: 33.3 ± 0.93° (line method). On the other method, it was necessary 24g of a liquid vehicle (36.5 ± 0.77°) to achieve the desired angle of slide (33°).

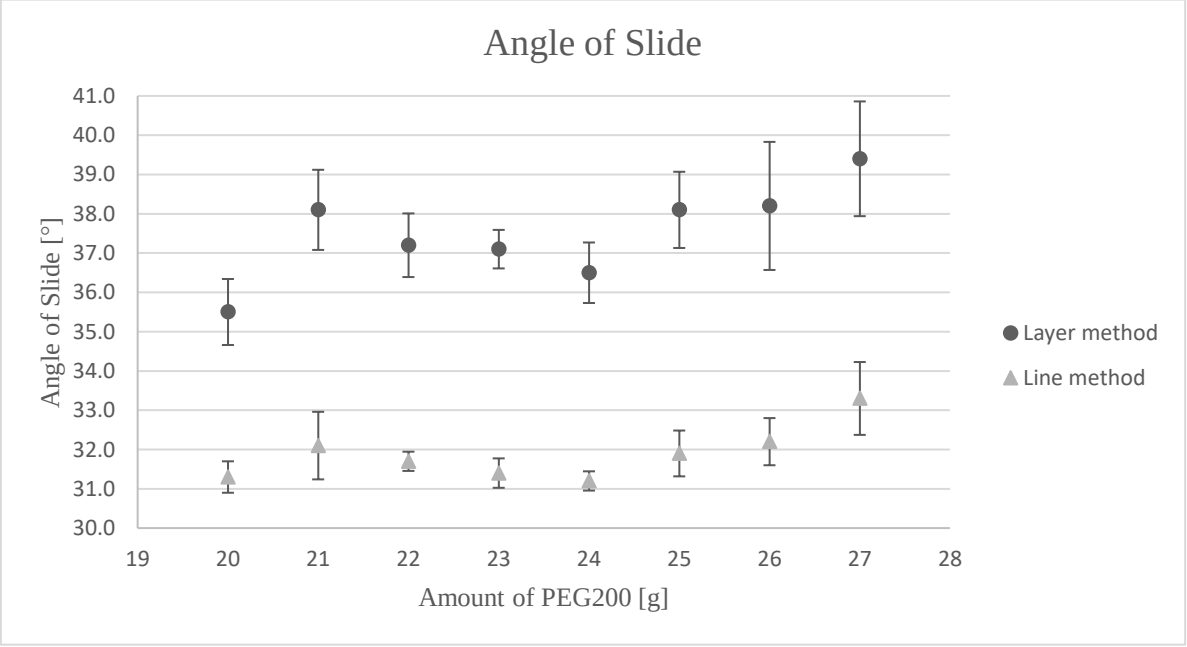

Figure 8 - Evaluation of the Angle of Slide of the mixture with Neusilin® US2 (28.65g), Chitosan (21.35g) and PEG200 using the line method and the layer method.

In Table 7, it is displayed all other measurements used to evaluate the flow properties of this carrier blend, such as flowability (3.42 ± 0.22 s/25g), angle of repose (42.90 ± 0.51°), CI (22.62 ± 1.96%), HR (1.29 ± 0.03) and pycnometer density (1.4934 ± 0.0006 g/cm³) fulfilling

the requirements for powders with passable flow properties (34). Evaluation of the Angle of repose did not imply any dependence on the amount of liquid vehicle added to the carrier (Table 6).

Table 7 - Flow properties of Neusilin® US2 (28.65g), Chitosan (21.35g) and PEG 200 mixtures. The orifices' diameter is displayed below the parameter evaluated.

Amount of PEG 200 [g]	Φ-value	Angle of Repose [°] (10mm)	Angle of Repose [°] (15mm)	Flowability [s/25g] (10mm)	Flowability [s/25g] (15mm)	Flowability [s/25g] (25mm)	CI [%]	HR	Angle of Slide [°] (Line)	Angle of Slide [°] (Layer)	Pycnometer Density [g/cm³]
0	0	41.26	39.90	48.24	17.11	3.68	17.23	1.21	40.0	41.4	1.7967
20	0.4	41.20	39.90	21.29	9.42	2.72	18.44	1.23	31.3	35.5	1.5309
21	0.42	42.32	41.90	-	13.83	3.47	20.25	1.25	32.1	38.1	1.5149
22	0.44	41.56	39.10	-	-	3.56	20.69	1.26	31.7	37.2	1.5109
23	0.46	41.06	42.70	-	-	3.53	20.52	1.26	31.4	37.1	1.4989
24	0.48	43.00	42.90	-	-	3.42	22.62	1.29	31.2	36.5	1.4934
25	0.5	41.10	42.70	-	-	3.60	22.69	1.29	31.9	38.1	1.4891
26	0.52	43.26	41.70	-	-	5.69	23.86	1.31	32.2	38.2	1.4792
27	0.54	42.16	42.00	-	-	4.76	22.35	1.29	33.3	39.4	1.4702

Mixing Neusilin® US2 and Chitosan with an increasing amount of PEG 200 implied the improvement of the flow rate through an orifice (orifice diameter of 25 mm). The values of this parameter decreased from 3.68 ± 0.05 s/25g to 2.72 ± 0.26 s/25g with the addition of 20g of liquid vehicle Further additions of the solvent increased the value to 3.56 ± 0.24 s/25g (mixture with 22g of PEG 200). The results from pycnometer density decreased from 1.7967 ± 0.0014 g/cm³ to 1.5309 ± 0.0004 g/cm³ with the addition of solvent. The increasing amount of liquid vehicle leads to a continuous decrease of pycnometer density of the mixture, reaching a minimum of 1.4702 ± 0.0004 g/cm³ (blend containing 27g of PEG 200).

Previous to the addition of the liquid phase, the admixture is considered to have a fair flow character (34) with a CI of 17.23 ± 0.36% and an HR of 1.21 ± 0.01. After the addition of 1g of PEG 200, values increased to 18.44 ± 1.53% and 1.226 ± 0.023, respectively. Continuous additions of 1g of PEG 200, the values kept increasing until a maximum value of 23.86 ± 0.97% (CI) and 1.31 ± 0.02 (HR) that was measured in the blend containing 26g of liquid vehicle.

The flowable liquid retention potential (Φ-value) for this liquisolid mixture was calculated (Equation 1) as the proportion of the amount of non-volatile solvent (27g) and the amount of carrier (50g) and was equal to 0.54 (using the line method for the Angle of Slide evaluation). However, the Φ-value for this same mixture based in the layer method with the proportion of the amount of liquid (24g) and weight of carrier (50g) was calculated and equal to 0.48.

3.2.4. Decreasing the initial amount of Chitosan by half (75:25)

Evaluation of the parameters of this liquisolid powder initially containing 37.5g of Neusilin® US2 and 12.5g of Chitosan (ratio of 75:25) are displayed in Table 8. The increasing quantity of polyethylene glycol 200 improves the mixture's flow properties by decreasing the Angle of Slide that is measured with two different methods (Figure 7). The sample with no PEG 200 has its value of 36.6 ± 0.97° using the line method and 45.3 ± 1.16° using the layer method. The addition of the liquid vehicle (20g) decreased the Angle of slide to 31.2 ± 0.6° and 35.8 ± 1.83° respectively. In the line method, the blend containing 25g of PEG 200 has its value (32.8 ± 0.5°) closest to 33°. In the other method, it was only necessary an amount of 24g of liquid to achieve 35.0 ± 0.63° that was the closest to the optimum value.

Table 8 - Flow properties of Neusilin® US2 (37.5g), Chitosan (12.5g) and PEG 200 mixtures. The orifices' diameter is displayed below the parameter evaluated.

Amount of PEG 200 [g]	Φ-value	Angle of Repose [°] (10mm)	Angle of Repose [°] (15mm)	Flowability [s/25g] (10mm)	Flowability [s/25g] (15mm)	Flowability [s/25g] (25mm)	CI [%]	HR	Angle of Slide [°] (Line)	Angle of Slide [°] (Layer)	Pycnometer Density [g/cm³]
0	0	39.76	41.00	61.44	22.23	3.64	14.85	1.17	36.6	45.3	1.9239
20	0.4	40.24	40.00	30.21	12.28	3.26	21.07	1.27	31.2	35.8	1.6063
21	0.42	44.52	43.00	-	17.19	4.18	21.02	1.27	32.8	36.5	1.5863
22	0.44	43.64	43.40	-	-	4.00	21.89	1.28	32.4	35.6	1.5773
23	0.46	43.34	44.20	-	-	4.04	22.58	1.29	31.9	35.1	1.5704
24	0.48	43.92	43.20	-	13.11	3.33	23.42	1.31	31.8	35.0	1.553
25	0.5	44.38	44.20	-	-	3.78	20.11	1.25	31.4	36.6	1.5427
26	0.52	43.94	44.10	-	-	3.46	21.45	1.27	31.8	37.2	1.5388
27	0.54	42.54	43.00	-	-	3.73	22.59	1.29	32.6	37.7	1.5264

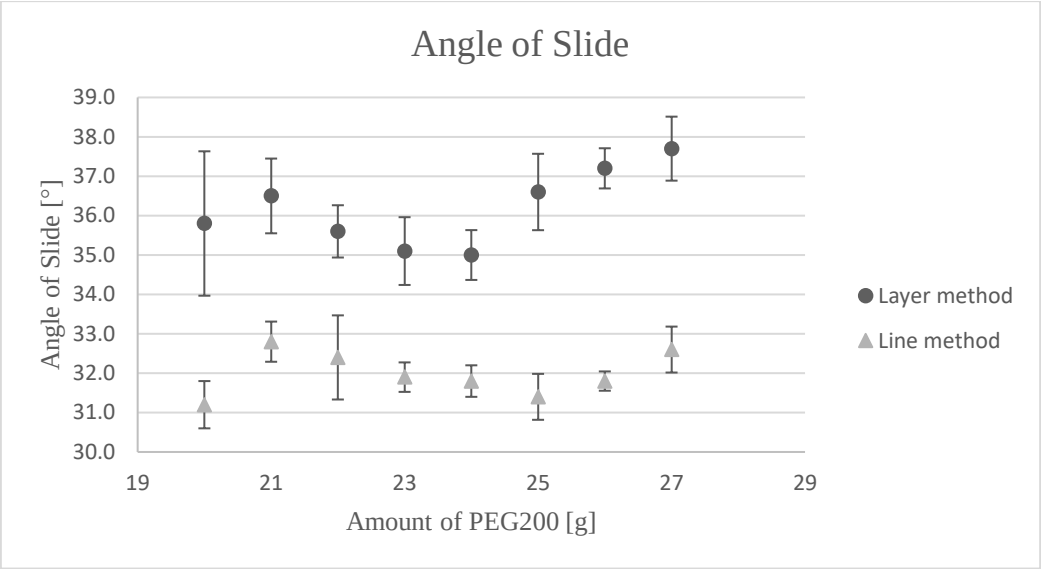

Figure 9 - Evaluation of the Angle of Slide of the mixture with Neusilin® US2 (37.5g), Chitosan (12.5g) and PEG200 using the line method and the layer method.

From the determination of the Angle of Repose with a 10mm orifice was possible to identify a correlation of the amount of PEG 200 added to the blend. The Angle of Repose values increased from 39.76 ± 0.48° to 40.24 ± 0.26° with the addition of 20g of solvent (Table 8). Subsequent addition of 1g of solvent increased the Angle of repose up to 44.52 ± 0.30° that was the highest value registered.

Initially, flowability has a value of 3.64 ± 0.31 s/25g but after a 20g addition of solvent, its value decreases to 3.26 ± 0.26 s/25g (orifice diameter of 25 mm). Further additions of PEG 200 lead to a minimum value of 3.33 ± 0.05 s/25g.

Mixing Neusilin® US2 with Chitosan indicated values of 14.85 ± 0.48% and 1.17 ± 0.01 respectively, corresponding to a good flow character (34). However, adding the initial amount of PEG 200 (20g) to the blend, increased CI up to 21.07 ± 1.33% and HR up to 1.27 ± 0.02. Further additions lead to the highest value of CI and HR (23.42 ± 1.35% and 1.31 ± 0.02) that were measured in the blend containing 24g of solvent.

Evaluation of the pycnometer density (Table 8) implied the same conclusion as in the case of mixtures with different ratios presented before in this thesis.

The determination of the Φ-value depends on the Angle of Slide method used. The formula (Equation 1) and the weight of the carrier are the same for both methods. Φ-value is 0.42 with the line method as the ratio of the amount of liquid vehicle (21g) and weight of carrier (50g). In the layer method, the amount of PEG 200 used to calculate the Φ-value (0.48) was 24g.

4. DISCUSSION

The main objective of this work was to evaluate the flowable liquid retention potential of carrier mixtures for the preparation of liquisolid systems using Polyethylene Glycol 200 (PEG 200) as a solvent. According to recommended scientific literature focused on the flowable liquid retention potential and liquisolid systems' angle of slide is the main parameter for these determinations. Its optimal and desiring value is 33° (31). Nevertheless, other parameters such as Angle of Repose, Density determined by a pycnometer, Flow rate through an orifice, Compressibility Index (CI) and Hausner Ratio (HR) were also measured to enable easier and clearer conclusions from samples with a different Neusilin:Chitosan ratio. During all the experimental work, temperature and humidity were registered to oscillate from 21.6°C to 23.6 °C and 29.8% to 31.8%, respectively.

The evaluation of carriers' properties individually imply that Chitosan is a carrier with a "poor" flow character (34). Therefore, these initial results are a good indicator of why Chitosan needs to be mixed with another carrier possessing enough flow properties. On the other hand, Neusilin® US2 results show that it has a "good" flow character, meaning aid is not necessary in order to demonstrate acceptable flow properties. However, when a non-volatile solvent is added to a carrier or a mixture of carriers, the flow properties differ according to the carriers' proportion in the mixture.

In a liquisolid mixture with only Neusilin® US2 the continuous additions of liquid vehicle lead to a decrease in the Angle of Slide values proving an improvement in the flow character of the mixture. However, this increasing amount of solvent did not improve the Angle of Repose and Flowability of the liquisolid mixture and even changed the character of flow from "Fair" to "Passable" (34). The pycnometer density evaluation indicated that increasing the amount of PEG 200 decreased the value of the pycnometer density of the mixture. This could be explained by a higher amount of liquid vehicle being absorbed by Neusilin® US2 and filling the pores which are not available anymore for helium and hence decreasing the pycnometer density of the liquisolid blend. Moreover, the obtained results implied that 1g of Neusilin® US2 can retain 1.06 of PEG 200 (layer method) and 0.44g of PEG 200 (line method), concerning the flowable liquid retention potential.

The blend containing Neusilin® US2 and Chitosan in an even proportion (50:50) with the addition of solvent improved its flow character according to the Angle of Slide measurements. Other parameters such as Angle of Repose, CI and HR revealed an increase of its values with an increasing amount of PEG 200 corresponding to a "Passable" flow character.

A decrease both on flowability and pycnometer density values is connected and can be explained. An increasing amount of liquid phase in relation to the carrier material fills Neusilin® US2's pores, hence decreasing the pycnometer density. Scientific literature has shown that most of the liquid vehicle is sorbed deep into the macropores o Neusilin® US2 and also into the mesopores (35). The determination of the flowable liquid retention potential (Φ-value) shows that 1 g of Neusilin® US2 and Chitosan can retain 0.48g and 0.50g of PEG 200, using the line and the layer method respectively.

In the evaluation of Neusilin® US2/Chitosan mixtures (57.3:42.7 ratio) under the same continuous solvent additions, CI and HR measurements implied that increasing quantity of liquid has a negative effect on the mixture's flow properties. Nevertheless, according to these results, the liquisolid mixture has a passable flow character (34). Despite an increase in the flow rate through an orifice values with an increasing amount of PEG 200, there was still registered a slight enhancement of the flowability of the admixture. Furthermore, in the pycnometer densities it was possible to observe the same phenomenon as in the cases of mixtures with different ratios. Results also show that 1 g of Neusilin® US2 and Chitosan can retain 0.54g and 0.48g of PEG 200, using the line and the layer method respectively.

From a 75:25 Neusilin® US2/Chitosan ratio, it could be observed that the effect of the addition of PEG 200 implied a decrease in the Angle of Slide values. Flow through an orifice measured in seconds per 25g with an orifice diameter of 25 mm proved that the increasing amount of liquid improved the flow properties of the liquisolid mixture. It was observed that the Compressibility Index (CI) and Hausner Ratio (HR) values increased after the addition of a liquid phase. The results demonstrated the deterioration of the flow properties that was evident with the change from a good flow character to a passable flow character (34). The continuous decrease of pycnometer densities could be explained by the filling of carriers pores with polyethylene glycol 200. The flowable liquid retention potential (Φ-value) calculations implied that 1 g of Neusilin® US2 and Chitosan can retain 0.42g and 0.48g of PEG 200, using the line and the layer method respectively.

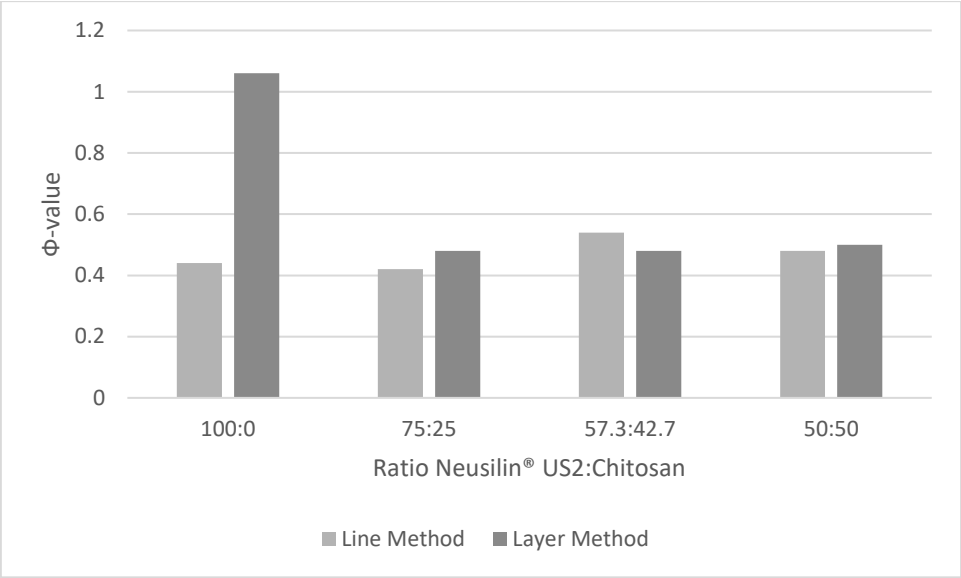

Figure 10 - The flowable liquid retention potential (Φ-value) of Neusilin® US2 and Chitosan.

5. CONCLUSION

The flowable liquid retention potential is defined as the maximum weight of the liquid that can be retained per unit weight of the powder mixture in order to have the desired flow properties. This is preferably determined by measuring the Angle of Slide of the previously prepared liquisolid admixture. The measurement of the Angle of Slide, as well as other pharmacopoeia parameters for powder flow properties, were employed in the experiments. Based on the results obtained, the suitability of the high functionality excipient Neusilin® US2 as a carrier in a liquisolid system is confirmed. From the Angle of Slide measurements, it was possible to obtain close results to the recommended value in the scientific literature. However, for the various mixtures of Neusilin® US2 and Chitosan, the increasing amount of a non-volatile solvent led to a negative effect on the mixture's flow character. So, when mixing Neusilin® US2 and Chitosan, results show that the amount of PEG 200 retained depends on the Angle of Slide method as well as the ratio between carriers. In conclusion, it is possible to state that for the formulation of polysaccharide-based liquisolid systems using Chitosan as a carrier, it would be required a lower ratio of this carrier in the overall blend.

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