Analysis of Possible Ingredient and Manufacture Steps of Oral GLP-1 Receptor Agonists

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Abstract: Glucagon-like peptide 1 receptor agonists (GLP-1RAs) is a efficient medicine treating diabetes 2 and the dosage form are mainly injection. The Rybelsus is the only oral dosage form at current. This paper analyzes the possible ingredient and pharmaceutical techniques for different steps when putting GLP-1RAs into manufacture process like the choose the excipients, granulation and coating. The analysis based on the research on peptide drugs and the assignment regarding the details of Rybelsus. The data involved come from different studies or journal and the assignment published by Novo Nordisk. This paper also analyzes the feature the excipient need to have, the possible advantages and different between the freeze drying, dry granulation and direct compression and sort out the two with greatest possibility to be applied based on the feature of API, the importance of coating for biologics will be stated, the function and feature of the coating will be mentioned and a few common example with good quality will be given.

1 INTRODUCTION

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are a member of peptide drug which is a unique medicine used to treat diabetes 2. At present, the most common dosage form of GLP-1 receptor agonists is the solution for injection as the first oral semaglutide discovered by Novo Nordisk has finished the clinical trial and being qualified to publish in 2020 (European Medicines Agency, 2020). The main difficulties that limit the clinical use of GLP-1 receptor agonists are the extreme short half-life time of injection (1.5-5 min) in plasma as it can be break down by dipeptidyl peptides 4 (DDP-4) rapidly (Hui, 2002).

According to the statistic of a clinical trial that have been done in Japan with the purpose to sort out which dosage form, oral or injection, leads to a better efficacy and acceptance among Japanese diabetes 2 patients. The overall statistic stated that the oral dosage form would result in a better blood sugar control and the risk of hypoglycemia. The oral dosage form has been provide with a better acceptance among about 1000 patient (Davies, 2017). This statistic shows the significance of putting forward the research on oral GLP-1 receptor agonists for diabetes 2 patient.

This paper will analyze the possible ingredients and pharmaceutical techniques that could apply to different manufacture steps of GLP-1RAs tablets based on the current research progress on GLP-1RAs and the details of approved sample Rybelsus (semaglutide).

2 LITERATURE REVIEW

Functionally, glucagon-like peptide 1 receptor agonists imitate the function of GLP-1 that secret in to hepatic portal system by the intestinal L cell located in the colon and distal ileum and this type of hormone can decrease the concentration of glucagon and concentration of available fatty acid, slow down the gastric emptying, increase the insulin sensitivity and the secretion amount (Baguio, 2007, Hinnen, 2017, Prasad-Reddy, 2015). The other effects of GLP-1 receptor agonists including positive impacts on weight, blood pressure and the cholesterol level. Using GLP-1 receptor agonists to treat diabetes 2 has a relatively low risk of suffering hypoglycemia as the effect of GLP-1RAs depend on the blood sugar concentration and the effect is in direct proportion to blood sugar level. However, the most common side effects of taking GLP-1 receptor agonists includes

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nausea, vomit and the discomfort at the site of injection (Prasad-Reddy, 2015).

At present, GLP-1 receptor agonists includes exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide and semaglutide. There are great different between each agent in the pharmacokinetic, pharmacodynamic and clinics (Prasad-Reddy, 2015). The most common dosage form of GLP-1 receptor agonists is the solution for injection as the first oral semaglutide discovered by Novo Nordisk has finished the clinical trial and published in 2020 (European Medicines Agency, 2020). The main difficulties that limit the clinical use of GLP-1 receptor agonists are the extreme short half-life time of injection (1.5-5 min) in plasma as it can be break down by dipeptidyl peptides 4 (DDP-4) rapidly (Hui, 2002).

The techniques can apply to the manufacture of GLP-1 receptor in different steps.

2.1 The Selection of Excipients

The first oral GLP-1 receptor agonist, semaglutide, which has shown in Figure 1, has been published by Novo Nordisk in 2020 (European Medicines Agency, 2020). Before Rybelsus has been published, the GLP-1 receptor agonists can only be used in injection. In order to designed it into oral dosage form, the excipients which contribute to the formulation that Novo Nordisk have chosen are massive. In this section, the author will use the example of Rybelsus to analyze what features the excipients should have so that they can be used to form an oral GLP-1 receptor agonists tablet.

According to the public assignment report that published by Novo Nordisk, the excipient used in Rybelsus are salcaprozate sodium, microcrystalline cellulose, povidone K90 and magnesium stearate (European Medicines Agency, 2020).

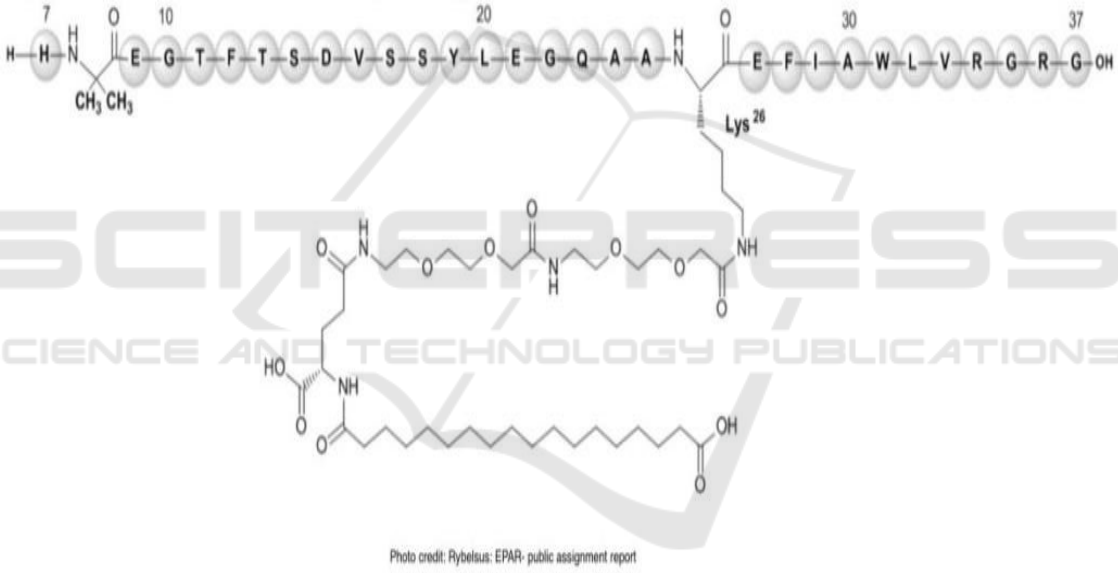

Figure 1: Structural formula of semaglutide.

Microcrystalline cellulose (MCC) is a pure and partially depolymerized cellulose with the chemical formulation (C6H10O5)n. It is widely used in pharmaceutical industry as a disintegrant, filler, binder and absorbent. It also act as a dry binder and filler in direct compression as it could improve the compatibility and compressibility of the mixture. Overall it is a comprehensive excipients (Chaerunisaa, 2019). Povidone K90 stands for the term “polyvinylpyrrolidone K-90”, a soluble PVP product with the outstanding solubility in all conventional solvent and it often act as a binder, bioavailability enhancer and film formation. Additionally, the ability of Povidone K90 to form water-soluble complex with active substance to improve the rate of release and solubility (Folttmann, 2008).

Magnesium stearate, $Mg(C_{18}H_{35}O_2)_2$, is a common chemical compound that participate in formulation as a lubricant to prevent the tablet stick on the die whereas it increase the liberation and disintegrate time by acting as a film formation (Uzunović, 2007).

Salcaprozate sodium ($C_{15}H_{20}NNaO_4$) is an excipients that has been mentioned alone in details in the public assignment report as a new excipient which

has been added into the formulation to improve the bioavailability of semaglutide. Basically, salcaprozate sodium is a sodium salt form of salcaprozate and it is a powder with the color between white and almost white, but it worked as an excipient with polymorphism. As a oral absorption promoter, the function is to promote the absorption of specific macromolecules such as insulin. The solubility of salcaprozate sodium is about 10 mg/ml when the pH value is between 2-4 but the solubility in the environment of pH value around 8 is about 300 mg/ml (European Medicines Agency, 2020; Twarog, 2019). The structure is shown in Fig. 2.

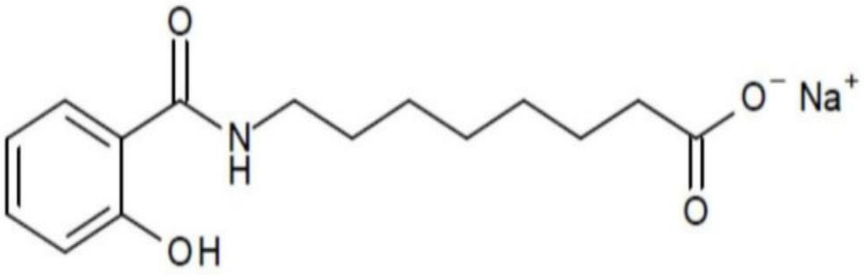

Figure 2: Structure of salcaprozate sodium.

In summary, due to the extreme short half-life of GLP-1 receptor agonists, 3 out of 4 excipients used have the ability of improving bioavailability and film formation. Undoubtedly, the general excipients like filler, disintegrant and binder should be include. Additionally, the formulation of Rybelsus shows that most of the excipient should be provided with the ability to enhance the bioavailability and some general function.

2.2 Freeze Drying, Granulation and Direct Compresssion

Both freeze drying and granulation are common in the manufacture of tablet. However, as a peptide drug that belong to the biologics, it is more common to include freeze drying instead of granulation in the manufacture process due to the similarity between peptide and protein. Basically, peptide is a short chain of amino acid that combined by peptide bond, and the peptide that include over about 50 amino acid is the big molecule that been named as protein (Hamley, 2020). The reason of using freeze drying is that the peptide could denature if it experienced a high temperature condition so the efficacy of peptide drug could be reduced (Hamley, 2020). Freeze drying is a process that dries the peptide drug by place it in extreme low temperature to turn it into solid state which is a more stable state because the peptide could hardly form a chemical reaction such as oxidation and hydrolysis etc (Rey, 2010).

The process of freeze drying generally involve 3 main steps: 1. Freezing 2. Primary drying or sublimation of ice 3. Secondary drying of unfrozen water (Rey, 2010).

In the freezing stage the peptide drug would usually be put into a condition that the temperature is about -40°C or even colder for a period of time to freeze the water completely. The freezing stage is the most vital part in the whole freeze drying process as this step would vastly affects the speed on reconstitution, the duration of freeze drying cycle, the proper crystallization and the stability of the product. In the primary drying, the product of last process will be placed in a vacuum environment and the product will be heat up to sublimate the ice particles. It is crucial that the thermal energy has been provided and the sublimation of ice reach a balance, so the API could remain active. Some residuary water may remain in the product, so the goal of secondary drying is to remove the residuary water but not to dry it excessively (ensure the appropriate moisture of the product) (Rey, 2010). Overall, the proper freeze drying could be a appropriate technique that can apply to the manufacture of oral GLP-1 receptor agonists for a few reasons summarised as keeping the biologics active and ensuring the GLP-1 receptor agonists would not have adverse reactions. The drying chamber that participate in the freeze-drying process has shown in Fig. 3 with its structure (Garcia-Amezquita, 2016).

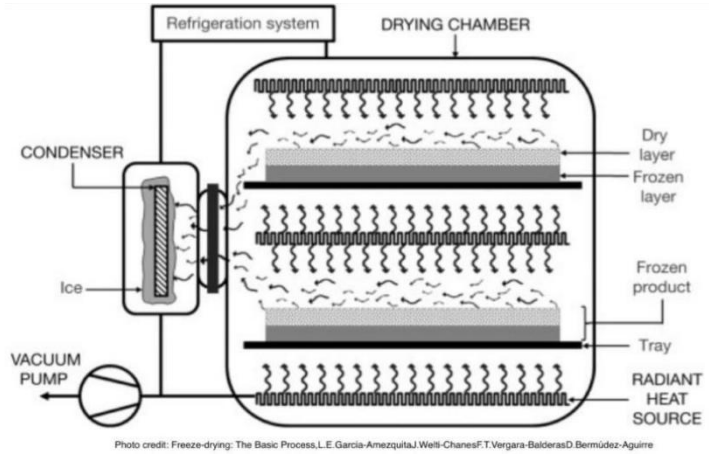

Figure 3: A freeze dryer.

In fact, granulation is a relatively less common pharmaceutical process that apply to biologics and peptide drug. However, according to the Novo Nordisk's public assignment report, the company involved the granulation step in the manufacture process instead of the freeze drying (European Medicines Agency, 2020), which stated that granulation can be applied to GLP-1 receptor agonists as semaglutide falls into the category of DLP-1 receptor agonists. In the second half part of this section, the author will analyze the possibility and appropriateness of different granulation when applying to the actual production of oral GLP-1 receptor agonists.

The granulation can be divided into 2 types: wet granulation and dry granulation. Basically, the main difference is wether the API would be put into a solvent.

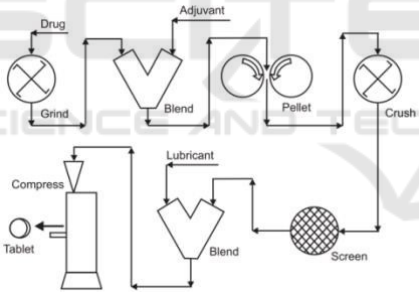

Figure 4: Dry granulation.

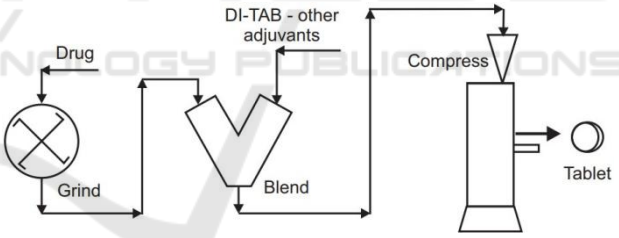

Figure 5: Direct compression.

The two main solvent that been used in wet granulation are aqueous and organic solvent. However, peptide drug has a low solubility in organic solvent, the solubility are different from individual cases. The problem with using aqueous solvent in wet granulation to manufacture GLP-1 receptor agonists is the drying step to evaporate the solvent. Generally, the boiling point of purified water is 100° C, but most of the peptide and protein will denatured under such high-temperature condition, so this may be a risk that the heat cause negative impacts to the API (GLP-1Ras). As a member of peptide drug family, the two problem that peptide drug meet when processing wet granulation would also apply to GLP-1 receptor (Jenssen, 2008).

Dry granulation is simple and low cost method and it brings the powder particles together by putting on a high pressure to the mixture. The general steps of dry granulation shows in order: grind the API and excipients to form powders, mix the powder, compression, screening the product from step 3, lubricant and disintegrant are added and mixed, final compression (Jannat, 2016).

Factually, there is two type of compression (step 3) which are slugging process and roller compaction. The slugging process use tablet press to put on pressure on the powder particles whereas roller compaction press the powder to a strip, but these two steps mainly aimed for the same goal. Even though the slugging process have the requirement on compressibility, compression ratio and density of the

powder (Jannat, 2016), these can be enhanced to achieve the standard by selecting the appropriate excipients and design a reasonable formulation. As a pH and temperature sensitive drug, the whole process of dry granulation has excluded most of the risky issue so this may be an possible and ideal technique that can apply to the manufacture of GLP-1 receptor agonists in future. The order of the process has shown in Fig. 4 (Mistry, 2021).

The last technique the author want to mention is the direct compression (DC), this technique usually used when then drug is moisture and heat sensitive (Iqubal, 2014), the later which is the feature that peptide drugs has been provided with (Garcia-Amezquita, 2016). In the excipients that Novo Nordisk used when producing Rybelsus (semaglutide), microcrystalline cellulose is a material that has been widely used in the direct compression stage (Chaerunisaa, 2019), so although the medicine that can attend direct compression are really limited as the compressibility and compatibility should be critically considered, can this technique be applied in the manufacture of GLP-1 receptor agonists has not been proved yet. This mostly depend on the constitution of formulation, which means that the ingredient powder can form a perfect tablet after mixed and tablet press, there is no any granulation included in direct compression (Jannat, 2016). However, there is still a possibility of involving direct compression in the manufacture of oral GLP-1 receptor agonists production in future. Each steps of direct compression are demonstrate in Fig. 5 (Mistry, 2021).

Overall, the freeze drying and dry granulation are the most appropriate method to manufacture oral GLP-1 receptor agonists tablet as one is the traditional and widely accepted manufacture process for peptide drugs, the latter one is more flexible, simple and having the advantage of relatively lower cost if the cost are considered. For the direct compression, as there is an extreme strict requirement on the constitution of formulation, the requirement can be hardly achieved by GLP-1 receptor agonist as well as other oral medicine.

2.3 Coating

Stomach is a human organ that all oral medicine need to pass through, the medicine could only reach small intestine after that. The acidic environment that between the pH value of 1.5 and 2.5 is mostly contribute by hydrochloric acid and pepsin, such as protease which break down proteins are also in the stomach (Piper,1965). As a member from peptide family, GLP-1 receptor agonists are also pH sensitive drugs and it is certain that the drug can easily denatured and lose the efficacy if the surface does not covered by any edible anti-acid material.

Tablet coating is a common pharmaceutical technique with a variety of advantages such as protect the tablet being broken down by pepsin and provide a physical and chemical protection to the tablet to achieve a successful delay release. A polymer-based film would usually be sprayed on the surface of tablet after tablet compression or over up the surface of granules. Additionally, the author could not found any description on the original taste of the oral GLP-1 receptor agonists tablet, but the coating could also be used to enhance the flavor if the taste is not pleasant (Ankit, 2012).

Take Eudragit as a example, it is a typical sample of enteric coatings which shows frequently in the pharmaceutical industry. Eudragit is a poly acrylate polymers that needs up with different acidic or alkali end groups, different individuals have their own solubility in specific ph value as they dissolve by forming salt with acid/alkali substances. The most ideal option in Eudragit family seems to be Eudragit S100, which dissolve under the condition of pH value greater than 7 and the pH value at the beginning of the small intestine is about 8, so hopefully the tablet would break down in the main organ for absorption and attend a successful delay release (Arruebo, 2020). Additionally, polymer is a chemically inert compound so the interaction between the coating and the ingredient could hardly form, which stated that Eudragit S100 might be a ideal coating material when manufacturing GLP-1 receptor agonists tablet.

3 CONCLUSIONS

Nowadays, Diabetes has become a common disease with large group of patient and the age of patient started to experience a trend of getting younger. In these cases, the mission of inventing a safer and effective medicine with a more convenient administration route become more and more vital and oral GLP-1 receptor agonist would be an ideal medicine to put forward the drug therapy for diabetes 2. Manufacturing the GLP-1 receptor agonists into oral dosage form (tablet) would partially reduce the inconvenient and the problem with self-injecting which requires the professional skill. Based on the approved sample of Rybelsus and the chemical and biological feature of GLP-1 receptor agonists, the theoretical analysis shows the possible ingredient and techniques that may generally apply to most GLP-1

receptor agonists in key steps when they are put into manufacture stage. The critical control of variables in the manufacture process could achieve the best efficacy of the tablet so that it can be more effective for diabetes 2 patients. The greatest problem of putting forward the production of oral tablet is the short half-life in plasma, however, this problem could be solved by taking appropriate amount of DDP-4 inhibitor along with GLP-1 receptor agonists but can not be addressed only by GLP-1RAs.

The analysis may not be specific enough to theoretically apply to specific peptide drug falls in to the family because it is based on the general feature of GLP-1RAs. As Rybelsus is currently the only oral dosage form, so the excipients sample is relatively less but still a valuable sample.

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