UNIVERSITY OF PARDUBICE

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Influence of lubricant on dissolution behaviour of matrix tablets

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Diploma thesis

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Vliv lubrikantu na disoluční chování matricových tablet

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Zásady pro vypracování

1. Vypracujte literární rešerši na téma „Lubrikanty používané v matricových tabletách".
2. Metodou přímého lisování připravte matricové tablety s různým množstvím a typem lubrikantu.
3. Proveďte disoluční zkoušku připravených tablet v kyselém žaludečním médiu.
4. Získané disoluční profily vyhodnoťte pomocí vhodných matematických modelů.
5. Diskutujte vliv použitého lubrikantu na disoluční profil studovaných tablet.

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ANNOTATION:

This thesis assesses the ability of tested lubricants to influence properties of matrix tablets such as release rate and tablet hardness. Both hydrophilic (Kolliphor® P 188, Kolliphor® P 407) and hydrophobic (Kolliwax® S, magnesium stearate) lubricants have been tested. Twenty formulations prepared by direct compression were individually characterised by the dissolution test and hardness test. To assess the mechanism and rate of release of tramadol hydrochloride (as an active pharmaceutical ingredient) from the formulations understudy, mathematical models of the first order, Korsmeyer-Peppas, and Higuchi, were applied. The dependence of the release rate and tablet hardness on the kind of lubricant used was determined.

KEYWORDS:

Tramadol hydrochloride, matrix tablets, direct compression, dissolution kinetics, lubricants, hardness test.

ANOTACE:

Tato práce hodnotí schopnost testovaných lubrikantů ovlivňovat vlastnosti matricových tablet jako je rychlost uvolňování a tvrdost. Byly testovány jak hydrofilní (Kolliphor® P 188, Kolliphor® P 407), tak hydrofobní (Kolliwax® S, stearát hořečnatý) druhy lubrikantů. Dvacet formulací připravených přímým lisováním bylo jednotlivě charakterizováno disoluční zkouškou a testem pevnosti. K vyhodnocení mechanismu a rychlosti uvolňování tramadol hydrochloridu (jako účinné látky) z testovaných formulaci byly použity matematické modely prvního řádu Korsmeyer-Peppas a Higuchi. Byla stanovena závislost rychlosti uvolňování a tvrdosti tablet na druhu použitého lubrikantu.

KLÍČOVÁ SLOVA:

Tramadol hydrochlorid, matricové tablety, přímé lisování, disoluční kinetika, lubrikanty, zkouška pevnosti.

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List of abbreviations and symbols

API	active pharmaceutical ingredient
DF	dosage form
EX	extended release
GIT	gastrointestinal tract
HPMC	hydroxypropyl methylcellulose
MAO	monoamine oxidase inhibitors
MCC	microcrystalline cellulose
PVP	povidone
R^2	coefficient of determination
RH	relative humidity
SEM	scanning electron microscopy
SR	sustained-release
TH	tramadol hydrochloride
UV/VIS	ultraviolet and visible spectroscopy

Introduction

Tablets are a solid dosage form obtained by pressing powders and granules containing one or more pharmaceutical ingredients with or without excipients. This is the most common dosage form. Currently, in the pharmaceutical industry, almost all tablets are made using excipients [1,2].

Excipients are not drugs and usually do not independently exert an effect on the body, but at the same time play an important functional role in the formulations of finished dosage forms. In the manufacture of drugs, only those excipients are used that are approved for medical use by the relevant regulatory documentation [2].

Excipients in the tabletting process have three important functions. Firstly, the excipients are designed to give the tabletted mass the necessary technological properties that ensure dosing accuracy, proper strength, tablet disintegration, and other properties. Secondly, excipients ensure the bioavailability of drugs. And thirdly, they can improve or simplify the process of making tablets. Nowadays, the chemical industry produces a wide range of excipients for the production of tablets. All quality parameters of a medicinal product to one degree or another depending on the excipients used, therefore, more and more attention is paid to their optimal selection. A reasonable choice of excipients makes it possible to obtain tablets with maximum therapeutic activity with a minimum dosage and side effects [1, 3].

1 Theoretical part

1.1 Characterization of tablets

Tablets are a dosage form obtained by pressing active pharmaceutical ingredients (APIs) or a mixture of API and excipients, intended for internal, external, sublingual, implantation, or parenteral use. Tablets as a dosage form are widely used throughout the world. Currently, tablet preparations make up about 80 % of the total volume of finished pharmaceutical products.

The positive qualities of the tablets provide: [4, 5]

- the proper level of mechanization at the main stages and operations, ensuring high productivity, cleanliness and hygiene of the production of these dosage forms;
- dosing accuracy of medicinal substances introduced into tablets;
- portability of tablets, ensuring the convenience of their dispensing, storage and transportation;
- long-term preservation of medicinal substances in a compressed state;
- for substances not stable enough - the possibility of applying protective shells;
- the possibility of masking unpleasant organoleptic properties (taste, smell, coloring power), which is achieved by coating;
- a combination of medicinal properties that are incompatible in physical and chemical properties in other dosage forms;
- localization of the action of the drug in a specific part of the gastrointestinal tract - by applying membranes that are soluble in an acidic or alkaline environment;
- prolongation of the action of medicinal substances (by applying certain coatings, using special technology and the composition of core tablets);
- regulation of the sequential absorption of several medicinal substances from the tablet at certain intervals of time (multilayer tablets);
- prevention of errors when dispensing and taking medications - thanks to the application of appropriate inscriptions on the surface of the tablets.

However, tablets have some disadvantages: [4,5]

- the action of drugs in tablets develops relatively slowly;
- tablets cannot be administered with vomiting and fainting;

- during storage, tablets can be cemented, which increases the disintegration time;
- the tablets may contain excipients that have no therapeutic value, and sometimes cause some side effects (for example, talc irritates the gastric mucosa);
- some APIs form highly concentrated solutions in the dissolution zone, which can cause severe irritation of the mucous membranes [6];
- not all patients, especially children, can freely swallow the tablets.

1.2 Classification of tablets

1.2.1 Based on methods formulation

Tablets are commonly manufactured by [7]:

- Wet granulation
- Dry granulation
- Direct compression

1.2.2 Based on the route of administration

Depending on the purpose and method of administration, the tablets are divided into the following groups [7]:

Oral tablets - these are tablets taken orally. Medicinal substances are absorbed by the mucous membrane of the stomach or intestines. These tablets are taken orally with water. The oral group of tablets is the main one. [8]

Sublingual tablets - these tablets are put below the tongue; medicinal substances are absorbed by the oral mucosa. [9]

Chewable tablets – should be chewed before swallowing. Containing medicinal substances that affect the mucous membrane of the mouth or gastrointestinal tract. Usually contain flavours. [10]

Effervescent tablets - give the rapid release of active substances and excipients due to the reaction between organic carboxylic acids (citric acid, tartaric acid, adipic acid) and baking soda in contact with water. The result of this reaction is the formation of unstable carbonic acid, which immediately decomposes into carbon dioxide and water. The formed bubbles of gas work as a super leavening agent. This dosage form is the best way to avoid the disadvantages of classic tablet forms (slow dissolution and release of API in the stomach) and liquid dosage forms

(microbiological and chemical instability in water). Effervescent tablets rapidly absorb, give a fast-therapeutic effect, improve the taste of APIs, and do not harm the digestive system. [11]

Implants – tablets made aseptically, are used for implantation. Designed for delayed absorption of medicinal substances in order to prolong the therapeutic effect. [12]

1.2.2 Based on structure

By their structure, tablets can be divided into single-layer and multi-layer (at least 2 layers), with or without coating. Single-layer matrix tablets have an insoluble framework, that can be obtained by homogeneously dispersion of an API in an inert material. The matrix's voids are filled with an API, so a tablet resembles a sponge soaked in a medicine substance. When such a pill is taken, its matrix does not disintegrate but diffuses the drug in the gastrointestinal tract. Depending on the properties of the used materials, matrix can be swelling and slowly dissolving hydrophilic or non-swellable hydrophobic that retains its geometric shape. The other important factor affected by the nature of the used materials is a rate of drug release. [13,14]

In multilayer tablets, medicinal substances are arranged in layers. Multilayer tablets allow you to combine substances that are incompatible in physical and chemical properties, prolong the effect of medicinal substances, and regulate the sequence of their absorption at certain intervals. The number of layers in layered tablets is different, but, as a rule, more than 2-3 APIs are rarely combined in one pill. [15-17]

The bilayer tablets are designed so that the first layer provides immediate release and the second sustained release layer maintains the desired drug concentration. Two-layer tablets are also used in cases where delivery of two drugs is required without any dynamic and pharmacological interaction. [16,18]

In triple layer tablets the first layer gives immediate release of drug, the second one is for sustained release, and the third one works as the middle barrier layer in order to separate two drugs which have interactions in them. [15-18]

The production of multilayer tablets, each layer of which contains the desired medicinal substances, requires, first, a precise layer-by-layer dosage separately. If it is necessary to completely exclude the contact of medicinal components, each layer is covered with an inert shell (drained). Such semifinished cores are pressed into a layer of a tablet mixture with different physicochemical properties. [16-18]

Substances are added to the top layer of the tablet and the finish coat to dissolve directly in the mouth, stomach or upper small intestine. The inner membranes and layers dissolve in the underlying sections, often only in the presence of certain enzymes, which ensures exceptional selectivity of the action of medicinal components and prevents the appearance of unwanted side effects. [16, 18]

By the nature of the coating: sugar-coated, film, enteric and pressed dry coating. The shapes of tablets produced by the chemical-pharmaceutical industry are very diverse: cylinders, balls, cubes, triangles, quadrangles, and others. [19-21]

1.2.3 Based on modified release mechanism

Oral modified release formulations combine not only sustained or sustained-release APIs but also more complex release kinetics. When creating a modified release formulation, many factors of the drug are considered, namely: the conditions of absorption in the gastrointestinal tract, - the place, rate, and mechanism of absorption, - solubility in the gastrointestinal environment, especially pharmacokinetics and pharmacodynamics. The gastrointestinal tract presents a wide range of barriers to drugs administered orally: morphological barriers (mucus layer, microvilli, etc.), physiological barriers (pH, enzymes, specific transport, transit time) that limit absorption. For absorption of poorly or slowly dissolving drugs, a longer time is required for dissolution in the stomach than the duration of physiological transit through the stomach. For the absorption of highly lipophilic drugs that are poorly soluble in the aqueous medium of the gastrointestinal tract, special drugs are also needed to ensure their dispersion in the aqueous medium. To increase the absorption of poorly soluble drugs, several technologies are used: solid dispersions of APIs, microparticles to increase the surface area, carrier systems (polymer mycelium, microemulsions, etc.). Modified release formulations allow solving all the main problems: changing the rate and duration of API release, the place of API release, as well as the intensity of the therapeutic effect of the drug. Besides, oral drug delivery systems have additional properties: protection of drugs from degradation in the gastrointestinal tract under the influence of hydrochloric acid and digestive enzymes, increased transit time in the upper gastrointestinal tract, and improved permeability through epithelial barriers. [13, 40]

Modified release tablets can be coated or uncoated, containing special excipients, or obtained using a special technology that allows you to program the rate or place of drug release. Several types of modified-release oral drug products are recognized: [22,26]

Target release – API does not affect the body as a whole, but only those cells and tissues for which the drug was intended. This increases the effectiveness of treatment, avoids unwanted side effects. It also makes it possible to use a number of potentially highly effective drugs that were not used in treatment due to poor biodistribution or specific side effects. The principle of targeted delivery is that the drug itself, and more often its delivery "vehicle", is modified by molecules that recognize receptors on target cells. A classic example is a work of folic acid molecules, which are actively taken up by tumour cells. Antibodies can be universal molecules that recognize the surface of the target cell. It is only necessary to know which surface antigens of the cells need to be designed. [22, 24, 25]

Repeat action dosage form (Figure 1) – can be two types: 1) biphasic release where the first phase of drug release is the rapid release of a portion of the dose that creates a therapeutic concentration of the drug immediately after administration, and the second is extended release phase for providing a portion of the dose required to maintain an effective therapeutic concentration over an extended period; 2) pulsating release that aims at delivering a portion of the released drug at regular intervals. [26]

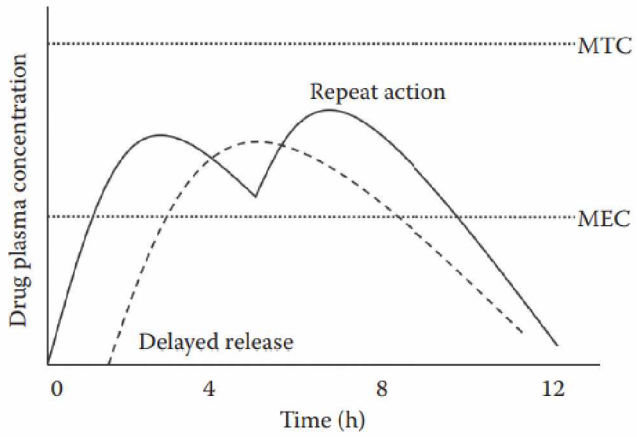


Figure 1: A graphical comparing of a repeat action and a delayed release. [30]

Delayed-release (Figure 1) – the release of the API from such modified-release tablet is delayed for a certain period after administration lasts longer than from a conventional one. A subsequent release is similar to that of an immediate release dosage form. Often tablets with this modification are enteric-coated. [22, 26]

Controlled release, those formulations are characterized by a change in the release time of the API by the required characteristics of the therapeutic effect and must meet several conditions. The release of API should occur according to a given speed program and should be described by a known type of mathematical dependence such as zero-order, t1/2, 1st order, etc. The release process should not depend on the influence of various physiological or pathological factors (food

intake, the action of enzymes, etc.) and be determined only by the parameters of the system itself. So, the controlled release tablets are characterized by predictability and accuracy in terms of the rate, duration, and location of the release of API, which allows predicting the development of the therapeutic effect. If any condition is not met, then such dosage form refers to the time-release category (Figure 2). [16,18,19]

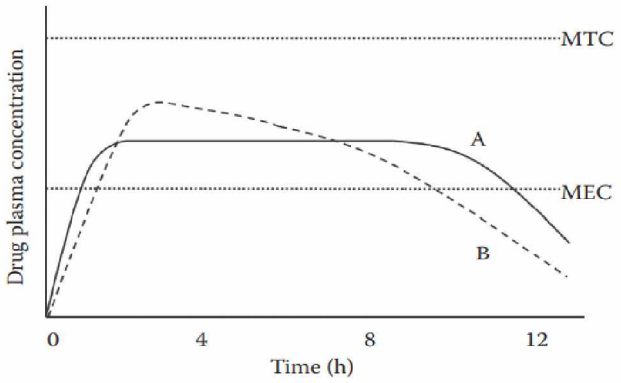


Figure 2: A graphical comparing of controlled (A) and sustained/extended (B) release. [30]

Dosage formulations with extended or sustained release must also meet certain requirements: to provide an optimal concentration of API without strong fluctuations for a long time; the excipients used must be harmless to the body and completely excreted; the technologies used should be simple and accessible. They are characterized by drug release in several portions or slowly and evenly. Allow providing a therapeutically effective concentration of drugs in the body for a long time. [27, 30]

Comparing extended and sustained release can be said that there is not a big difference between those two modified dosage forms. Extended-release products contain a higher drug load. That's why any loss of integrity of the release characteristics of the dosage form may lead to overdosing. They both (EX and SR) are designed to make the drug continuously available at a constant level within a specific frame of time, such as 12 or 24 hours after administration. [27,28, 30]

Time-release can be achieved by the physicochemical properties of the matrix in which the API is located: a slowly disintegrating polymer substance capable of swelling (hydrogels), biodegradation, or pore formation; The API can be complexed with a poorly soluble matrix material (HPC, PVP, HPMC). Hydrogels were first developed for oral sustained release formulations due to their swelling properties. As a result of swelling, cells or pores of a certain size are formed in the hydrogel; if the size of the API molecules is larger than the size of the cells of the hydrogel, its slow release occurs. [28, 30-32]

Usually, drugs for which there is a need to create sustained-release systems have a significant relationship between concentration and the development of pharmacodynamic effects, including side effects. For such drugs, it is very important to eliminate "peak" concentrations so that the concentration level is kept within a certain range to prevent the development of toxic or "peak" concentrations. This is clinically important for drugs with a narrow therapeutic index that has concentration-dependent toxic side effects, as well as for drugs that have concentration-dependent undesirable effects that worsen the tolerability of therapy. The use of DF with controlled or sustained release helps to reduce the frequency of drug intake to 1–2 times a day, which increases patient compliance and clinical efficacy of pharmacotherapy and improves its tolerance. [28, 30]

1.3 Matrix categories

Matrix tablets are tablets with continuous, uniformly extended release and supporting drug action. It is obtained by incorporating the drug into a network structure of insoluble excipients or a matrix of hydrophilic substances but forming a high viscosity gel. Do not disintegrate in the gastrointestinal tract. Depending on the nature of the matrix, they can swell and slowly dissolve or retain their geometric shape during the entire period of stay in the body and be excreted in the form of a porous mass, the pores of which are filled with liquid. The drug is released by leaching. [13,14]

The rate of release of a drug is determined by such factors as the nature of the excipients and the solubility of the drugs, the ratio of drugs to the matrix-forming substances, the porosity of the tablet, and the method of its preparation. Excipients for the formation of matrices are divided into a hydrophilic and hydrophobic polymer or lipid. [13,14]

1.3.1 Hydrophilic matrix

Hydrophilic polymers are most commonly used because they are biodegradable. Also, this class of polymers belongs to the group of gelling polymers-hydrocolloids. Each such polymer has its own degree of swelling, which helps in modelling the release kinetics. Most often, cellulose derivatives are used as hydrophilic matrix-forming polymers, natural polysaccharides - gums (xanthan, guar, arabic, pectins, alginic acid and its sodium salt, etc.), synthetic polymers - carbopols and polyethylene oxide. The ability of matrix-forming polymers to swell or dissolve in an aqueous medium is determined by the chemical structure, flexibility of macromolecules, molecular weight (degree of polymerization), the presence of crosslinks between polymer chains and their frequency. [28, 30,31]

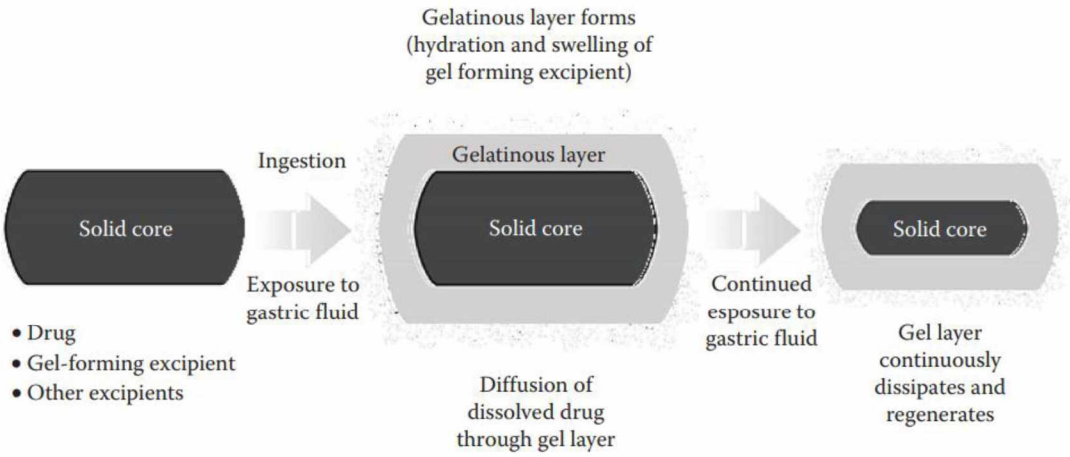


Figure 3: Release of drug from a hydrophilic matrix dosage form. Schematic shows the hydration, swelling, drug diffusion, and continuous erosion of the gel layer. [30]

After administration, tablet with hydrophilic matrices swells in the aqueous medium. Thereafter, a gel is formed that controls the release of API (Figure 3). In the process of swelling, gastric fluid diffuses into the pores of the hydrophilic matrix and divides it conditionally into 3 zones: a swollen matrix (peripheral gel layer), which eventually undergoes erosion; swelling matrix (rubbery region); glassy core, where API's concentration is the highest. The gel layer can adhere to the mucosal surface (mucoadhesion), which can lead to uneven drug release. [28, 30-32]

The release from such matrices is carried out in stages. In the first stage the drug particles dissolve from the tablet surface. As gastric fluid penetrates the matrix, API dissolves and diffuses through the gelatinous layer and micropores formed in it. Easily soluble drugs are released by diffusion, while moderately and poorly soluble ones are released by washout of solid particles (erosion). Water-soluble drugs can act as blowing agents and accelerate release. Hydrophilic matrices are often used to provide sustained release of slightly or moderately water-soluble APIs. [28, 30-32]

1.3.2 Hydrophobic matrixes

1.3.2.1 Polymeric matrix

As an alternative for sustained release tablets, polymeric matrices (also inert) can be used. Inert matrices are obtained from hydrophobic polymeric substances insoluble in water and physiological fluids - polyethylene, polyvinyl chloride, ethyl cellulose, acrylic acid polymers and its copolymers. However, the use of these polymers has a number of limitations, because they are not biodegradable. [35] The main mechanism for the release of hydrophobic polymer matrices is diffusion. API's particles, which are in the polymer matrix, dissolve after exposure biological fluids into it (Figure 4) and leach out either diffusely through the matrix itself or through a network of pores formed during direct pressing of the tablet. Concentration gradient provides the driving force of drug both inside and outside the matrix. At the same time, as a result of the action of gastric fluid, surface erosion of the matrix occurs with a poorly wetting solvent, providing, in addition to the diffuse release mechanism, also the leach out of the drug solution formed due to the penetration of the solvent. The efficiency of transport from the porous eroded matrix is higher. [13, 28, 33-35]

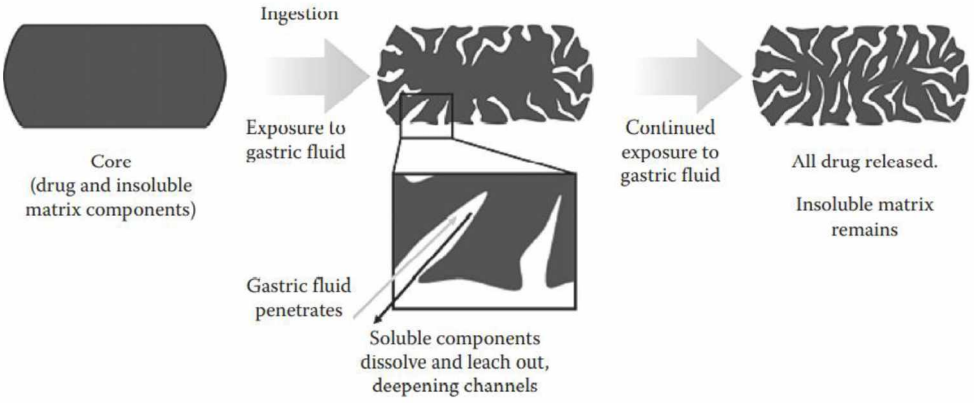


Figure 4: Release of drug from a granular insoluble matrix dosage form. Schematic shows the receding boundary as drug diffuses from the dosage form.[30]

Often, pore-forming agents are included in the tablet to affect the release of the API from the inert matrix. When such substances dissolve, they form channels through which the API can freely diffuse into the dissolution medium. The rate and rate of release of APIs from inert matrix tablets can be controlled by the type and number of pore-forming agents, but also by the type of the polymer itself. [28, 32, 34, 35]

1.3.2.2 Lipid matrix

Lipid matrices are prepared from fatty waxes (carnauba wax), fatty acids and alcohols (stearic acid, behenic acid, and triglycerides), higher fatty alcohols, natural waxes, hydrogenated vegetable oils. Lipid matrices are sensitive to pH and composition digestive juice, biodegradable when it enters the gastrointestinal tract. In an aqueous medium, dissolution and leaching of water-soluble components, including drugs, leads to the appearance of microcracks, microchannels and pores in the matrix due to its erosion. Microchannels are formed inside the matrix and on its surface, thus increasing its porosity. The rate of entry of drugs from the hydrophobic matrix into the environment is determined by the shape of the tablet, its porosity, size, and length of the channels formed in it. An increase in the proportion of matrix-former in tablets leads to an increase in the length of the channels and a slower release. [13, 28, 36-38]

Graphic comparing of matrices with different properties with extended release are shown in Figure 5.[30]

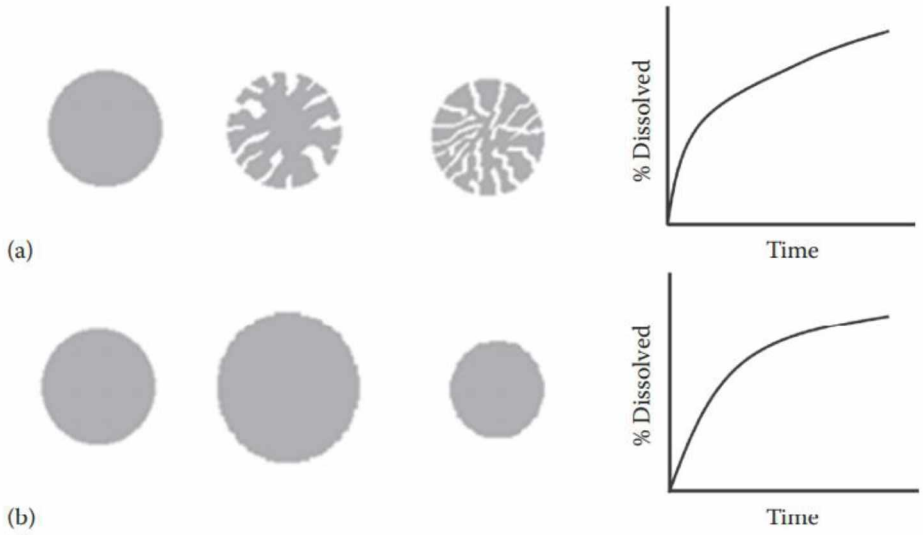


Figure 5: An illustration of cross section of matrix systems, and their corresponding drug release rate by diffusion through channels from an insoluble matrix (a), and swelling and eroding matrix (b).[30]

The addition of disintegrants (disintegrants) and water-soluble pore-forming substances, for example, polyvinylpyrrolidone, lactose, mannitol, helps to increase the number of pores, channel lumen and accelerate the release of drugs. The porosity of the matrix is also influenced by the pressing pressure. High pressing pressure reduces porosity and slows down the release. [49, 55, 56]

1.4 Pharmacological excipients

Currently, any medicinal substance does not enter the body in its pure form. It has a dosage form corresponding to its purpose, which is a kind of composition of an active substance and at least one excipient. Excipients not only help to give the drug the desired dosage form, forming an easily dosed, compressible mass and a set of necessary physicochemical properties for proper distribution throughout the body, but can also potentiate the action of the main active ingredient of the drug or smooth out its side effects. That is why the choice of excipients must be approached especially carefully. [51] In other words, the excipient should not be used in general, but specifically with the individual preparation. Unjustified use of excipients can lead to a decrease, distortion or complete loss of the therapeutic effect of the medicinal substance. This is mainly due to the interaction of medicinal and excipients, during the manufacture of drugs in the dosage form itself or, more often, after its appointment to the patient. [41, 42, 44, 46, 50]

1. The following requirements must be met for excipients [41-44, 46, 50]:
2. Excipients should not influence the bioavailability of the drug.
3. Should not have an allergenic and toxic effect.
4. Excipients should give the dosage form the required properties. Structural and mechanical, physicochemical ensure bioavailability.
5. Must be chemically indifferent.
6. Be affordable and relatively cheap.

All excipients are classified (Figure 6, 7): by origin, chemical structure and depending on the effect on the physicochemical characteristics and pharmacokinetics of dosage forms. [45,50]

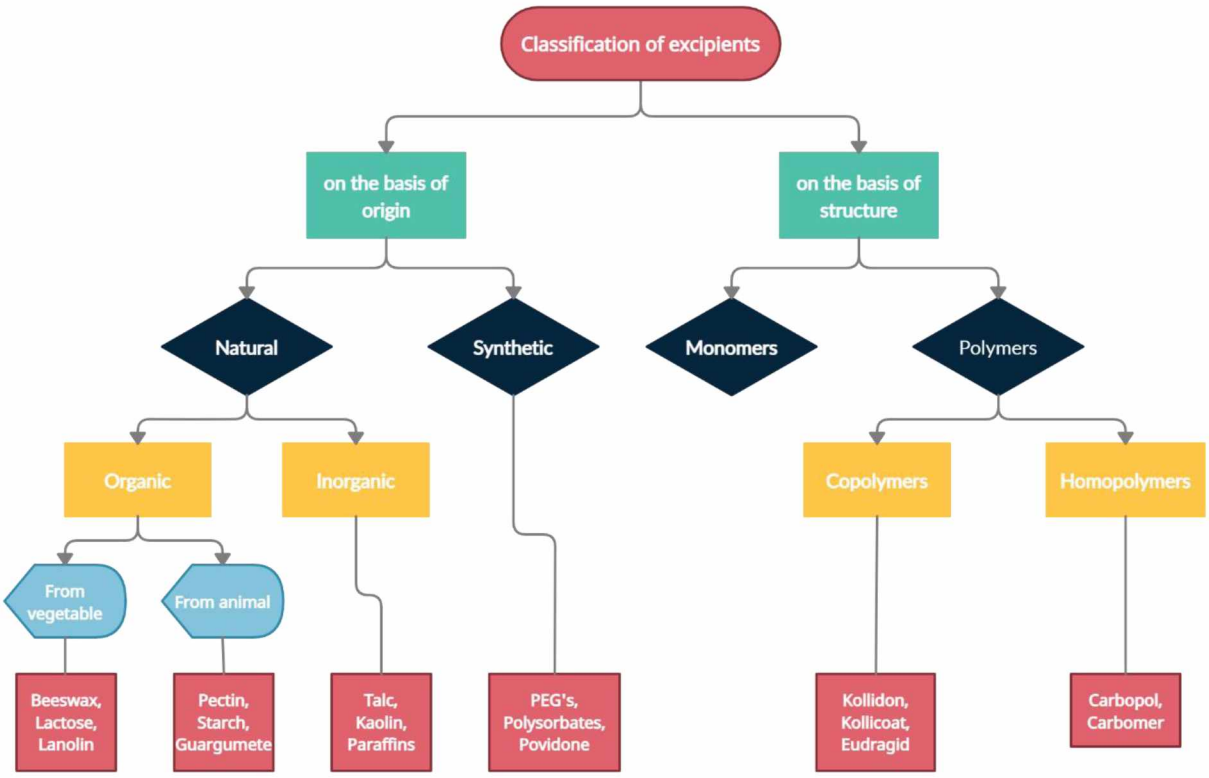


Figure 6: Ecxipient's classification. [45, 50]

Depending on the effect on the physicochemical characteristics and pharmacokinetics of the dosage forms, the excipient can be divided into the following groups (Figure 7)[47,48]:

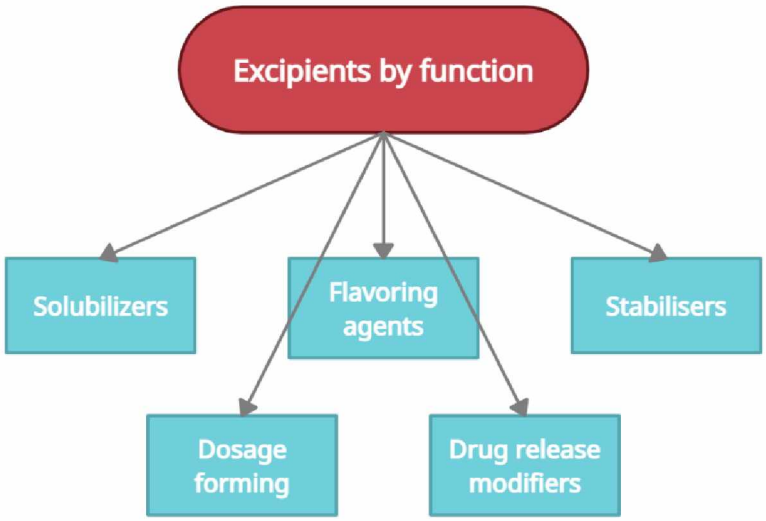


Figure 7: The main excipient's functions. [47]

This group of excipients is used as fillers for solid dosage forms (powders, pills, tablets, etc.). Dosage forming excipients make it possible to create the required mass or volume, to give

a certain geometric shape. The function of the filler can be performed by carrier, binders and retardants. There are specific excipients for each dosage form. [51, 54]

Stability is the property of drugs to retain their physicochemical and microbiological properties for a certain time from the moment of release. Chemical stabilizers are used in the manufacture and long-term storage of pharmaceuticals. This type of stabilization is of great importance for medicinal forms undergoing various types of sterilization, especially thermal. [48, 53]

Solubilization is the process of spontaneous transition of a water-insoluble substance into an aqueous solution. The use of solubilizers makes it possible to prepare dosage forms with insoluble or difficult to dissolve medicinal substances and to increase their bioavailability. The function of solubilizators can do disintegrants, pH adjusting excipients, amorphous solid dispersions, surfactants, self-emulsifying drug delivery systems, soluble and insoluble filler materials and sugars. [48, 49]

Flavouring agents include excipients that make it possible to correct the taste, colour, odour of various medicinal substances. Most often used in children's practice. Natural and synthetic substances in the form of solutions, syrups, extracts, essences are used as corrective substances. [48, 54]

Excipients that influence delivery of a drug with a delay after its administration or for a prolonged period of time are called drug release modifiers. They can also ensure that the optimal level of the drug in the body is maintained, without sharp fluctuations in its concentration. There are various technological methods for prolonging the release time: increasing the viscosity of the dispersion medium (enclosing a drug substance in a gel); use coating; suspension of soluble drugs; use of multi-layer delivery systems. [47, 48, 54]

Figure 8: Common excipients used in tablets. [52]

For example, in tablet manufacturing, excipients with special properties are used. They provide dosing accuracy, mechanical strength, disintegration, tablet stability as well as optimize their production and subsequent storage. As a result, for the technology of tablet production, a corresponding special classification of excipients was developed, dividing them into groups depending on the purpose (Figure 8). [50-52]

1.4.1 Binders

The particles of most drugs have a small adhesive force with each other. Therefore, their tabletting requires the use of high pressure, which is partly the reason for the untimely wear of the tablet press tool and the production of low-quality tablets. To achieve the required adhesive force at relatively low pressures, binders are added to the tabletting substances. Their function is that by filling the interparticle space, they increase the contact surface of the particles and the cohesiveness. [46, 55-57]

Binders (Figure 9) are particularly important when pressing complex powders. During the operation of the tablet machine, powders can delaminate, which leads to the production of tablets with different contents of the incoming ingredients. The use of a certain type of binders and their amount depend on the physicochemical properties of the compressed substances. [46, 55, 57]

The functions of binders can be performed by various substances as well as some binders can perform functions other excipients and serve as fillers, retardants or disintegrant. It is very common practice to use a combination of binders without changing the drug release mechanism and efficacy. [46, 51, 55, 57]

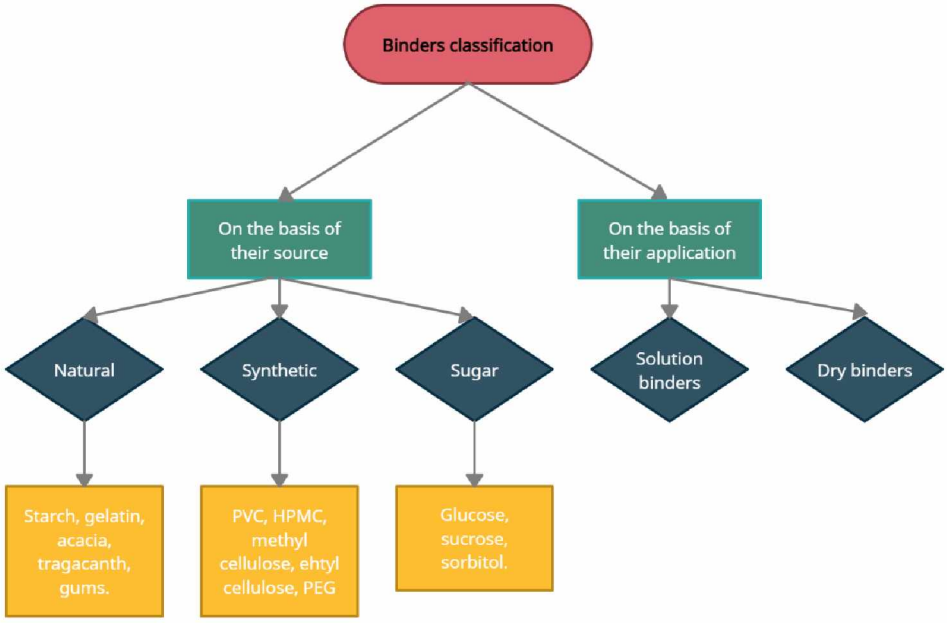


Figure 9: A brief binder's classification. [57]

As for all excipients there are some requirements for binders as well. Binders should:

- have good fluidity;
- be neutral, tasteless, colourless;
- be relatively inexpensive;
- do not reduce fluidity and compressibility.

1.4.1.1 Prosolv® SMCC 90

To increase the lubricity and flowability of MCC, JRS Pharma (Germany) has developed a silicon-microcrystalline cellulose under the PROSOLV® trademark. PROSOLV® is a proprietary combination of 98 % MCC and 2 % colloidal silicon oxide. There are several commercial types of PROSOLV®, differing in particle size and bulk density. [51,58]

The average particle size of Prosolv® SMCC 90 is 125 µm and its bulk density is 0.25 - 0.37 g/ml. It is a multifunctional excipient that has excellent binding properties, provides both optimal compression and flow properties. Due to homogeneous and fine spraying of CSD, an increase in the specific surface area and an increase in compaction by 30–50 % are achieved in comparison with microcrystalline cellulose. Exceptional compressibility, excellent flowability, and the ability to significantly reduce the amount of required excipients make this co-processed dry binder widely used as a mixed filler and binder in tablet and capsule formulations in both wet granulation and direct compression. [51, 58]

1.4.1.2 HPMC

One of the polymers widely used as a hydrophilic matrix-forming agent is hydroxypropyl methylcellulose (HPMC), a non-ionic cellulose ether (Figure 10). It is a water-soluble and polar organic solvent powder polymer from white to light yellow colour, odourless and tasteless, belonging to synthetic binders. HPMC hydration occurs rapidly, resulting in the formation of a gel layer. Since the viscosity of HPMC practically does not change in a wide pH range, and in strongly acidic or alkaline media it slowly decreases, the integrity of the matrix structure is preserved for a long time. The release of PS from matrices based on HPMC can proceed by the type of diffusion or erosion, as well as a combination of these mechanisms, which is largely determined by the solubility of the PS. [13, 51, 59]

This polymer exists in a wide range of molecular weights due to the content of methyl and hydroxypropyl radicals. The use of HPMCs of different molecular weights makes it possible to obtain gels with a given viscosity and, therefore, with different swelling properties. [13, 51, 59]

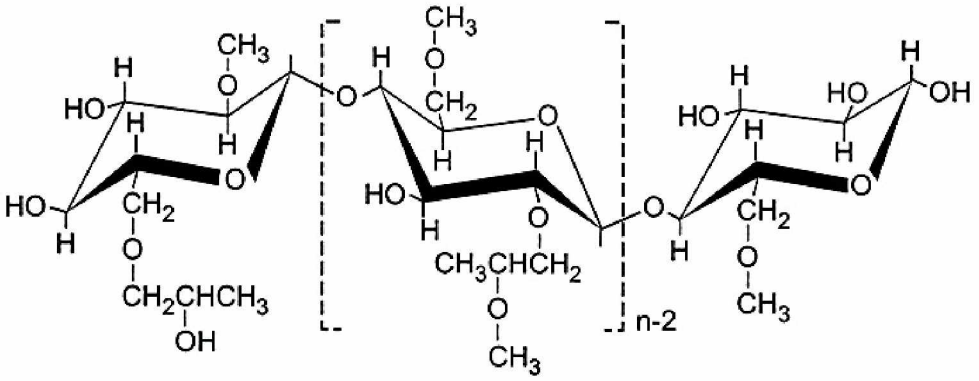


Figure 10: Structure of hydroxypropyl methylcellulose [60]

There are various HPMC brands approved for pharmaceutical use. These include the Methocel™ range of HPMCs in various viscosities. Within the line for the production of tablets, the following brands are suitable: Methocel™ K4M, Methocel™ K100 LV, Methocel™ Premium, Methocel™ Premium CR. The content of methoxyl groups varies from 19.0 to 30.0 %, and hydroxypropyl - from 4.0 to 12.0 %. For example, to obtain tablets with prolonged release, polymers of this line with medium or low viscosities can be used. [59, 60]

The letter (K, E or F) in the name determines the type HPMC and percentage of the Methoxy and Hydroxypropoxy groups, respectively. Number (K4, K100) identifies viscosity mPa·s 2 % solution in H_2O 20°C, and CR identifies a physical form - controlled-release grade. [59, 60]

1.4.1.3 Kollidon® 17, 25, SR

Polyvinylpyrrolidone (PVP) (Figure 11) is widely used in tablet production. The advantages of using povidones / polyvidones are their easy solubility in water and alcohol, as well as their ability to improve the dissolution and bioavailability of drugs (antibiotics, analgesics, chemotherapeutic agents) due to the formation of water-soluble complexes. PVP is produced under various brand names. BASF produces Kollidons® (both water-soluble and water-insoluble) with various physicochemical and technological characteristics, which makes it possible to select a specific brand for a specific process and with specified properties. Various grades of Kollidon® are obtained from the polymerization of N-vinylpyrrolidone. Due to the mechanism of the reaction at the final stage, PVP of practically any molecular weight can be obtained. Soluble grades of Kollidon® (Povidones) are today considered one of the most versatile and widely used excipients in the pharmaceutical industry. Insoluble species (Crospovidones) are widely used in pharmacy. Characteristics such as the ability to improve the disintegration of tablets, hydrophilize insoluble drugs, as well as adsorb and form complexes, allow them to be used as disintegrants, binders, as well as fillers. All Kollidon® brands are pharmaceutically pure. They are free-flowing white or yellowish-white powder with particles of various sizes. [51, 61-63]

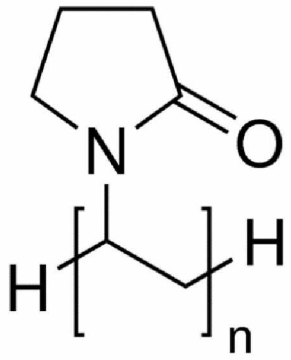


Figure 11: The chemical structure of PVP (Kollidon®). [62]

Kollidon® 17 PF and Kollidon® 25 are representatives of Kollidon® brand instant pharmaceutical products. The abbreviation "PF" stands for "Pyrogen Free", which means that the product does not contain bacterial endotoxins. The numerical value indicates the average molecular weight, which is always part of the trade name. One of the main characteristics of Kollidon®'s soluble grades is their universal solubility in a wide range of solvents, from highly hydrophilic such as water to hydrophobic liquids such as butanol. [61, 63]

The structure of Kollidon® is such that its various brands form complex compounds with a number of substances, including pharmacologically active substances. Almost all such complexes dissolve in water faster and more easily than a pure drug substance. [61, 63]

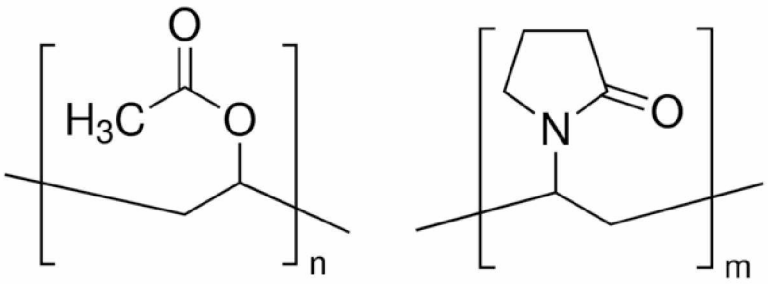


Figure 12: The chemical structure of Polyvinyl acetate-Polyvinylpyrrolidone mixture (Kollidon® SR). [64]

Hydrophobic polymer matrices are obtained from polyvinyl acetate, namely Kollidon® SR, which is a physical mixture of 19 % polyvinylpyrrolidone, 80 % polyvinyl acetate, 0.2 % aerosil and 0.8 % sodium lauryl sulphate (Figure 12), obtained by spray drying. Due to the presence of hydrophobic vinyl acetate groups, Kollidon® SR is insoluble in water. This makes it suitable for use in modified release matrix forms using direct compression, wet granulation or extrusion technology. Kollidon® SR is a slightly yellow free flowing powder, non-ionic compound and inert to the drug. The ionic composition, the pH of the medium, the pressing force and the strength of the matrix practically do not affect the ability of the matrix to sustained release. The release of PS from tablets based on Kollidon® SR is determined by their solubility and the dependence of this parameter on pH. [51, 61, 64]

1.4.2 Fillers

Fillers are used to provide the required mass of tablets at low doses of API or when tableting potent, poisonous and other substances, they can be used to regulate some technological parameters (strength, disintegration, etc.). [46, 49, 51, 56]

The use of fillers is optional if there is sufficient drug substance for each tablet. Typically, the tablet weighs 500 mg and low drug tablets require diluent to bring the total tablet weight to 500 mg. [46, 49, 51, 56]

Fillers determine the technological properties of the mass for tableting and the physico-mechanical properties of the finished tablets. For example, fillers that have good flowability and compressibility are used for direct compression. They are not inert form-formers, but largely determine the rate of release, the rate and completeness of absorption of the drug, as well as its

stability, therefore, their choice in each case must be scientifically substantiated. In the case of direct compression of the mixture, they can also exhibit binding and slip properties (PVP, MCC). [46, 49, 51, 56]

1.4.3 Retardants

In the development of drugs to provide modified release resorting to physical and physicochemical, chemical, technological methods. To achieve prolonged release, the most widely used physical and physicochemical methods are based on the processes of swelling of the matrix former and diffusion of the solvent into it. The swelling also provides the ability to impart gastro-retentive, mucoadhesive properties to the tablets, helping to slow down their transition from the stomach to the intestine. Such tablets are often prepared on the basis of hydrophilic matrices which, in the presence of an aqueous medium, form a strong gel that provides a sustained release of the drug. [46, 49, 51, 56]

This effect is provided by retardants which, in addition to the formation of a gel or an insoluble matrix, can also provide an increase in the duration of action of the drug, depositing the drug in organs and tissues or preventing the inactivation of the active substance by enzymes and the rate of its excretion from the body. Prolongers include MC, CMC, HPMC, polyacrylamide, polyvinylpyrrolidone, polyvinyl alcohol, glyceryl dibehenate, etc. [46, 49, 51, 56]

1.5 Lubricants

There is may be confusion in the definition of a lubricant because this word can be used to describe three interrelated groups of excipients: glidants, anti-adherent, lubricants, and "lubricants" as a part of this group. This happens because material usually possessing more than one property. It may be defined as a material, a small amount of which (usually 0.25–5.0 %, w/w) reduces friction arising at the interface. [65, 66]

Lubricants are necessary to prevent the tablet mass from sticking to the surface of the dies of the press machines. They also provide a smooth ejection of the finished tablet from the die. Lubricants not only reduce friction at the contact areas but significantly facilitate the deformation of particles due to the adsorptive decrease in their strength due to penetration into micro-crevices. [65, 66]

During tableting, a resistance known as friction must be overcome. The walls of matrix nests and hoppers are not perfectly smooth and have different irregularities which may be large compared to particles of tableting mixture. When surfaces of matrix nest's wall and tableting

mixture are brought together contact occurs at points on highest asperities. With the further application of the load, frictional resistance occurs, which leads to the shearing of the softer material by the movement of the harder material along with it. Lubricants reduce the shear strength of junction and prevent the asperity contact by forming a continuous film to the walls of matrix nests and hoppers or by boundary films, which do not cover the sliding surfaces. [65, 66]

There are four lubrication mechanisms: hydrodynamic lubrication, elastohydrodynamic lubrication, mixed lubrication, and boundary lubrication. The listed three mechanisms are related to the usage of fluid lubricants. Fluid lubrication is not a surface phenomenon, its use makes surfaces fully separated by a continuous film of the lubricant itself. On the other side boundary lubrication is a surface phenomenon. It separates the sliding surfaces or interfaces in order to reduce friction. [66]

The effectiveness of the lubrication is characterized by how well the film is formed and how thick the film is in order to cover the surface in several layers, thereby masking the force field of the underlying surface. This effect is usually observed in substances with a layered structure, whose molecules have a long chain and end with active groups. These groups allow molecules to easily adsorb on surfaces both at the powder-tool interfaces and at the particle-particle interfaces. [66]

1.5.1 Type of lubricants

Typical end groups include [66]:

- –OH (long-chain alcohol);
- –COOH (long chain fatty acids);
- –NH2 (long chain amine);
- metal ions such as Mg2 +.

Typical frontier lubricants used in pharmaceutical processes are, of course, metal salts of fatty acids such as magnesium stearate and stearic acid, but fatty acid esters, inorganic materials, and polymers are also used. [66]

1.5.1.1 Metallic salts of fatty acids

The best and most commonly used lubricants are metal stearates, especially magnesium stearate. Also popular are calcium, zinc, sodium and aluminium stearates, as well as metal oleates, elaidates, laurates, and myristates if magnesium stearate cannot be used in the formulation due to chemical stability problems. Working concentration - 0.25–1.0 %. [101, 102]

In the case of metal stearate, lower melting points generally contribute to lower expulsion forces, and polyvalent (especially divalent) salts are superior to monovalent salts. These

compounds are hydrophobic and usually have a detrimental effect on the disintegration, hardness and dissolution of the tablets. The nature of the cation affects the thermal stability of the salt. There are no general rules of incompatibility, each of which requires individual evaluation, but they all hydrolyse aspirin due to their alkaline nature. [101, 102]

In practice, particle size rather than surface area is much more commonly used as a measure of lubricant performance. This is mainly due to the fact that the measurement of the particle size of the powder material is faster. The same amount of lubricant, but with different particle sizes, gives tablets that differ in hardness, disintegration and dissolution. Therefore, it is believed that the specific surface area rather than the amount should be used to describe magnesium stearate. [101, 102]

1.5.1.2 Fatty acids

Fatty acid loses its lubricity above its melting point. As in other examples, the longer the carbon chain length, the better the lubricity. These compounds are more effective than alcohols or hydrocarbons, but negatively affect the hardness and disintegration of the tablets. The most popular fatty acids are C10 to C24. Examples of this group are lauric, myristic, palmitic and stearic acids, the latter being the most used. It provides better lubrication than shorter carbon chain compounds such as decanoic (C10) and dodecanoic (C12) acids, or longer carbon chain relatives such as eicosanoic (C20), docosanoic (C22) and tetracosanoic acids (C24). [101, 102]

There are three polymorphs of stearic acid, Forms A, B and C, which have been prepared using different organic solvents under different crystallization conditions. Form C is the most stable. Form B has an irreversible endothermic phase transition to form C at 54 ° C, and form A converts to form C at 64 ° C. DSC and TGA thermograms show that stearic acid from different suppliers shows very little variability from batch to batch or from manufacturer to the manufacturer. [101, 102]

1.5.1.3 Hydrocarbons

They are rarely used because they give a weak lubricating effect, worse than fatty acids or alcohols. But they have less effect on the hardness and disintegration of the tablets. Typically, as the length of the carbon chain increased, the effectiveness of the lubricant increased, but up to a certain point. It is also believed that the lower melting point of materials in this category is the reason for their lower lubricity efficiency compared to metal stearates. [101, 102]

1.5.1.4 Fatty alcohols

Because of their low polarity, saturated straight chain aliphatic alcohols exhibit liquid lubricant properties. Their lubricity decreases with decreasing carbon chain length, which corresponds to a decrease in viscosity, but again to a certain point. Octadecanol (C18) provides a more effective lubricating effect than alcohols with longer or shorter carbon chains. These compounds are less effective than fatty acids, but more effective than hydrocarbons. May slightly reduce tablet hardness. Examples are lauryl, myristic and stearyl alcohols. [101, 102]

1.5.1.5 Fatty acid esters

Various fatty acid esters also perform well as a lubricant. For example: sodium stearyl fumarate (Pru), 1–3 % (w / w), sodium lauryl sulfate, 1 % (w / w), magnesium lauryl sulfate, glyceryl behenate (Compritol 888), 1.5–3 % (w / w), dodecane triglyceride, 1 % (w / w), glyceryl palmitostearate (Precirol ATO), 0.5 % (w / w), sucrose monopalmitate, sucrose monolaurate, 0.12 % (w / w), samarium stearate. [100, 101]

The most common of this group are sodium stearyl fumarate (Pruv) and glyceryl behenate (Compritol 888). Both of these lubricants do not have a strong effect on tablet strength and do not affect dissolution of the tablets. [101, 102]

Glyceryl Behenate or Compritol 888 does not adversely affect tablet hardness or disintegration time even at high concentrations, but its lubricity is inferior to sodium stearyl fumarate. [101, 102]

Some oils such as hydrogenated vegetable oil (Lubritab), hydrogenated castor oil (Cutina HR), hydrogenated cottonseed oil (Sterotex K) are also used as lubricants. Unlike magnesium stearate, mixing time does not degrade the physical properties of the tablets. Therefore, formulations with Lubritab have much higher strength and faster dissolution.Combining palmitic and stearic esters of glycerols gives the same effect as magnesium stearate, but in a higher concentration. It has little effect on the properties of the tablets, including the stability of aspirin, in the absence of alkaline impurities. [101, 102]

1.5.1.6 Alkyl sulphate

Examples are the magnesium and sodium lauryl sulphate salts, which are mainly used as surfactants. The lubricating properties of magnesium lauryl sulphate are better than sodium lauryl sulphate and can be equated to the lubricating performance of magnesium stearate. But it does not have its waterproofness, since it is a water-soluble lubricant. Has a strong retarding effect. [101, 102]

1.5.1.7 Inorganic materials

These compounds are generally anti-adhesives rather than lubricants, and although they appear slippery, they cannot exert their beneficial effects with the forces used in tableting. [101]

Boric acid is used but not for oral tablets due to its toxicity. Talc is commonly used. It is a natural hydrous magnesium silicate, insoluble in water, and due to the change in impurities, there will be fluctuations from batch to batch. The physical properties of talc from several batches or suppliers can also be different, namely different sizes, characterized as layered flakes (2–5 μm) and aggregates of flakes (50–150 μm). It is a weaker lubricant than magnesium stearate, but it glides well and resists sticking. It has a retarding effect on the dissolution and disintegration of tablets. The concentration used is 1 to 5 % by weight. [101, 102]

1.5.1.8 Polymers

When it is not possible to use magnesium stearate because of its compaction problems, lubrication, chemical instability, or other biopharmaceutical reasons, some polymers can be used as a preferred lubricant for tablets. The main representatives are polyethylene glycols (PEG 4000, PEG 6000 (Carbowax 6000)) of various molecular weights. Obtained by the polycondensation reaction of ethylene oxide and water. PEGs are soluble in water, its the working concentration is 14 %. They have reduced particle size, which can improve lubrication. Generally not as effective as stearic acid salts. They are reported to have a retarding effect on disintegration, tablet hardness and stability of aspirin. [101, 102]

Polyoxyethylene glycol or polyoxyethylene monostearate, is a producte of the direct reaction of alkylene oxide and stearic acid. Polyoxyethylene glycols are water-soluble, slightly less effective than PEGs, sucrose esters and magnesium stearate. Like PEG, it affects the disintegration of tablets and their hardness, but to a lesser extent. Its working concentration is 3%. [101, 102]

Another example from this group is polytetrafluoroethylene, which has been used successfully in various solid dosages. It has similar lubricating properties to the magnesium stearate in tablets with acetylsalicylic acid, but it does not remove the electrostatic charges of the API, as it does magnesium stearate. [101, 102]

1.5.2. Used lubricants and their properties

1.5.2.1 Internal lubrication

Internal lubrication is the procedure for incorporating lubricant into the tabletting mixture before pressing it. Lubricant, like other components, is mixed in granular or powder form in a blender. [101, 102]

The first thing that affects the choice of lubricant is the type of mixing equipment, which in turn affects the lubrication process itself and ultimately the properties of the tablets. So, for example, the strength or dissolution time of the tablets depends on the mixing time of the tabletting mass and the lubricant and the compression force. In addition, with an increase in the mixing time or mixing intensity, the adhesion of the tablets to the lower surface of the punch decreases and, accordingly, the ejection force of the tablet decreases. This effect is especially pronounced with magnesium stearate and other lubricants such as hydrogenated vegetable oil, glycerides, talc and PTFE. [101, 102]

1.5.2.2 External lubrication

When the tabletting mix is very sensitive to lubricants, an external lubricant is used. This only lubricates the lower punch and die, not the final mixed material. The working concentration is only 0.08 % of the amount required for internal lubrication. This results in tablets having 40 % higher crush strength, lower total pore volume, without increasing disintegration time, and in some cases higher API activity. In addition, the tablets produced require lower compression energy but higher ejection energy. [101, 102]

The external lubricant option is well suited when internal lubrication has a big impact on the tensile or dissolution strength of the tablet. And since the larger scale often exacerbates the adverse effects of the lubricant on tablet properties, the use of an external lubricant should help avoid such problems. [101, 102]

1.5.3. Lubricants and their properties

1.5.3.1 Magnesium stearate

Magnesium stearate is the chemical combination of magnesium salt and stearic acid (Figure 13). It is a crystalline powdery substance with white or colourless crystals, a finely dispersed powder slightly soapy to the touch. Not soluble in water, but readily soluble in oils and warm ethyl alcohol. [66, 67]

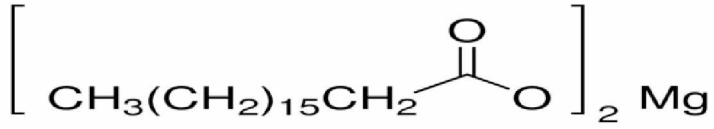


Figure 13: The chemical structure of magnesium stearate. [67]

Magnesium stearate is prepared using aqueous solutions of magnesium chloride with sodium stearate or by reacting magnesium oxide, hydroxide, or magnesium carbonate with stearic acid at elevated temperatures. Or it can be obtained from plants and animal sources. [66]

Relative to fatty acids stearic acid has the highest melting point (of about 69 °C), the metallic salts of fatty acids have much higher melting temperatures: zinc stearate (120 °C), magnesium stearate (140 °C), and calcium stearate (160 °C). The optimal chain length lets it to achieve the desired friction coefficient reduction. There are magnesium stearate's four hydration states: anhydrite, monohydrate, dihydrate, and trihydrate that can form upon exposure to humidity. Those states are not stable and its amount and ration interchange, depending on temperature and relative humidity. Each of the hydrates has its own physical and chemical properties, its effectiveness as a lubricant. Dihydrate is believed to have the best lubricating ability. So, when you buy a commercial product what you get is a mixture of various hydrates in unknown ratios that further can change by moisture content or the RH of storage conditions. Another factor that depends on the degree of hydration is the external characteristics of the particles. The size, surface area and particle shape of materials from different manufacturers or different batches have different properties. With an increase in surface area or a decrease in particle size, lubricating efficiency is improved. [66]

Magnesium stearate is a very popular excipient in pharmaceutical industry, it is a part almost of 90 % of tablets. The working concentration 0,5–5 %. At high concentrations, the area of the hydrophobic coating increases, which in turn weakens the bond between the particles of the tableting mass and because of these weak tablets are formed. In addition, the hydrophobic film covering the API slows down its dissolution. Other undesirable effects of stearate are associated with the presence of impurities such as magnesium oxide and palmitic acid. Under the influence of temperature, humidity and pressure during tablet compression or storage, these contaminants can react with the API (ketoprofen, ibuprofen, acetylsalicylic acid ect. [66]

1.5.3.2 Kolliwax® S

Kolliwax® S (Figure 16) is a binary mixture of stearic acid (Figure 14) and palmitic acid (Figure 15). Kolliwax® S is supplied as white, slightly yellow coarse or fine powder (Table 1)

that is solid at room temperature. The product's origin is based on vegetable and synthetic raw materials. [68, 69]

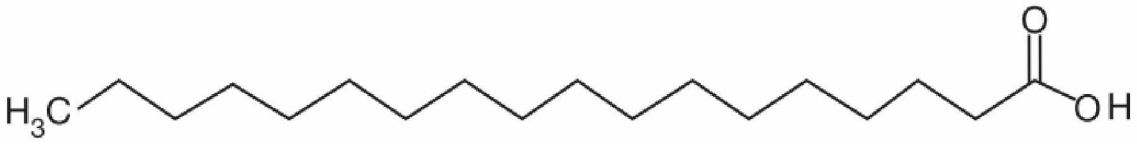


Figure 14: The chemical structure of stearic acid. [68]

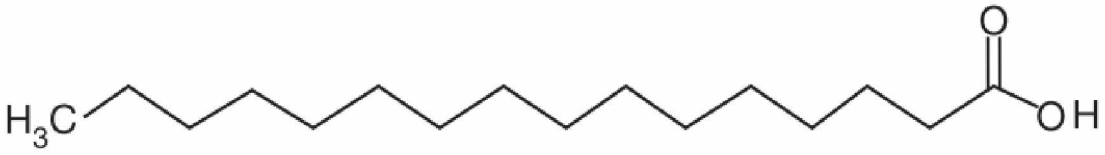


Figure 15: The chemical structure of palmitic acid. [68]

Table 1: Physical characteristics of Kolliwax® S.

Tap density	Bulk density	BET-surface area [m^2/g]	Particle size
0.55 g/ml	0.51 g/ml	0.51	<100µm max 10 % <200µm max 25 % <400µm max 50 %

Kolliwax® S is a versatile product that can be used for oral solid and semi-solid dosage forms. It can function as a lubricant or matrix-forming agent in oral dosage forms, an emulsifying and solubilizing agent in topical formulations, and a curing agent in glycerol suppositories. As lubricant it is an effective alternative to magnesium stearate. In this case the optimal working concentration starts at 2 %. Another way of it use is as a film coating, together with hydroxypropoylmethylcellulose (HPMC) and microcrystalline cellulose (MCC) it protects against moisture. In emulsions, Kolliwax® S can work as a structure-building consistency factor (with working concentration 10–15 %) and co-emulsifier (with working concentration 3–5 %) in topical pharmaceutical applications. [68, 69]

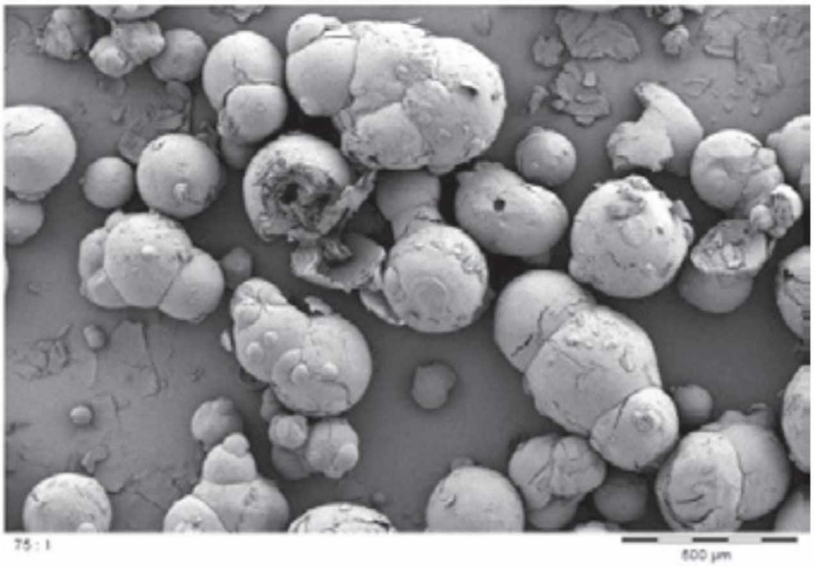


Figure 16: The SEM photo of Kolliwax® S. [69]

1.5.3.3 Kolliphor® P 188, Kolliphor® P 407

Another product line from the BASF company is Kolliphor® P (Figure 17). Those are synthetic copolymers of ethylene oxide and propylene oxide, also are called poloxamers. Poloxamers have ABA structure wherein *a* is PEO or polyethylene oxide and *b* is PPO, polypropylene oxide blocks have the following values, for P 188 *a* = 80, *b* = 27, and for P 407 *a* = 101, *b* = 56. Both Kolliphor® P grades are produced as a white to almost white, coarse-grained powders with waxy consistency and contain an appropriate quantity of antioxidant BHT. In the name of each Kolliphor® is placed an information about a product (Table 2). So, in the name "Kolliphor® P 188" the last number characterizes the amount of PEO in it (8 = 80 % m/m PEO). The first two numbers describe molecular weight of PPO blocks (18 = 1800 [g/mol]). All Kolliphor® P grades are prepared by "prilling" process that allows to form spherical granules with excellent flowability and particle size of about 600 – 800 μm (Figures 18, 19). [70, 71,74]

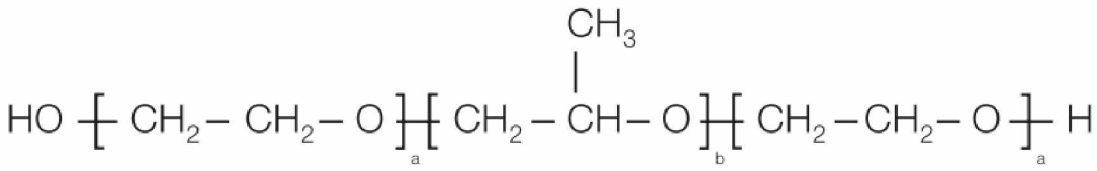


Figure 17: The chemical structure of Koliphor P. [71]

Because of the structure and the presents of hydrophilic blocks – PEO and hydrophobic blocks PPO, Kolliphor® P can form micelles in aqueous solution. Due to the ability to form micelles, Kolliphor® P is a good solubilizer. However, P 407's ability is better. [70, 71,74]

Table 2: Physical characteristics of poloxamers. [70, 71, 74]

Grade	Tap density	Bulk density	M/w (g/mol)	PEO (% m/m)
188	0.55 g/ml	0.51 g/ml	7.680 - 9.510	79,9 – 83,7
407	0.60 g/ml	0.50 g/ml	9.840 – 14.600	71,5 – 74,9

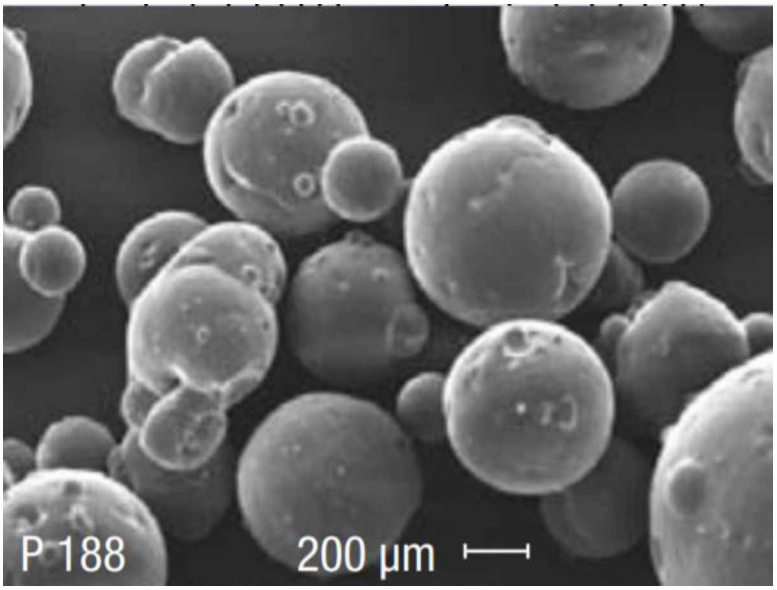


Figure 18: The SEM photo of Koliphore P 188 from. [70]

In addition to lubricants, they can perform many other functions. They both can improve the solubility of the drug, and with it its bioavailability, both are suitable for extrusion, and can also serve as a plasticizer, solubilizer, emulsifier and co-emulsifier, stabilizer for suspensions for topical application. [70-74]

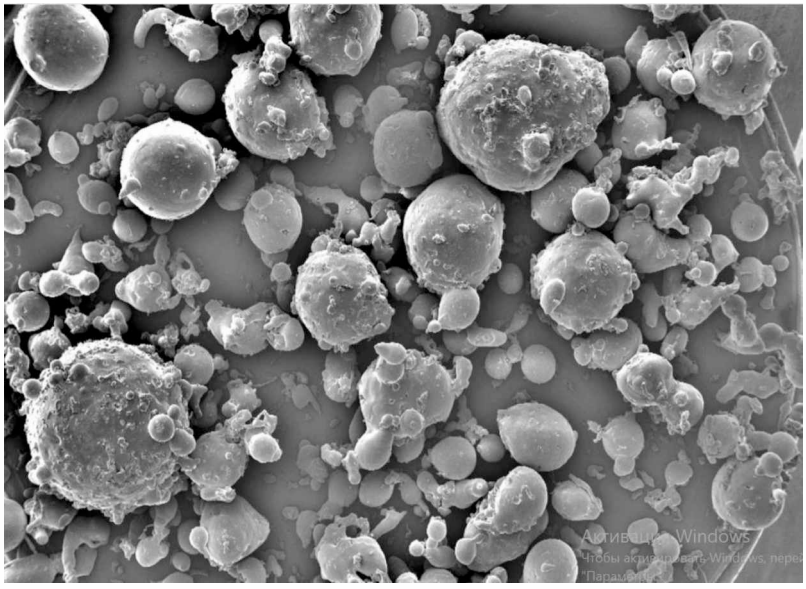
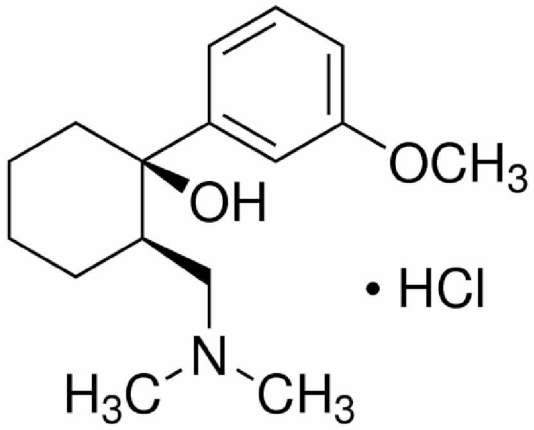


Figure 19: The SEM photo of Koliphor P 407. [74]

1.6 Tramadol hydrochloride



Chemical name: 2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol

Molecular formula: $C_{16}H_{25}NO_2$

Molecular mass: 263.381 g/mol

Figure 20: Structural formula of Tramadol hydrochloride. [75]

Tramadol hydrochloride (Figure 20) is an opioid synthetic analgesic, a derivative of cyclohexanol, which has a central action and action on the spinal cord (promotes the opening of K + and Ca2 + channels, causes membrane hyperpolarization and inhibits pain impulses). It is a white crystalline powder, odourless, bitter taste, readily soluble in water and ethanol. [76 - 78]

1.6.1 Indications and usage

Pain syndrome of moderate and severe intensity (including with malignant neoplasms, injuries, in the postoperative period). Pain relief during painful diagnostic or therapeutic interventions. [76, 78]

1.6.2 Contraindications

Hypersensitivity to tramadol. Acute alcohol intoxication; acute poisoning with hypnotics, analgesic, opioid or psychotropic drugs; severe hepatic / renal impairment (creatinine clearance <10 ml / min); simultaneous use of MAO inhibitors (and 2 weeks after their cancellation); epilepsy uncontrolled by treatment; drug withdrawal syndrome. [76, 78]

1.6.3 Side effects

Central nervous system: dizziness, weakness, drowsiness, confusion; in some cases - seizures of cerebral genesis (with intravenous administration in high doses or with the simultaneous administration of antipsychotics). [76, 78]

Cardiovascular system: tachycardia, orthostatic hypotension, collapse. [76, 78]

Digestive system: dry mouth, nausea, vomiting. [76, 78]

Metabolism: increased sweating. [76, 78]

Musculoskeletal system: muscle weakness. [76, 78]

1.6.4 Pharmacodynamics properties

Tramadol is a centrally active opioid analgesic that has a mixed mechanism of action. It is a nonselective pure agonist of opioid μ, d and κ receptors with maximum affinity for μ receptors. Other mechanisms involved in providing the analgesic effect of tramadol are inhibition of the reuptake of norepinephrine in neurons and an increase in the serotonergic response. Tramadol also has an antitussive effect. Unlike morphine, analgesic doses of tramadol do not suppress respiration over a wide range. The motility of the digestive tract is also weaker inhibited. The effect on the cardiovascular system is usually weak. The activity of tramadol is estimated in the range from 1/10 to 1/6 that of morphine. [76, 78]

1.6.5 Pharmacokinetics

After oral administration, it is rapidly and almost completely absorbed from the gastrointestinal tract (about 90 %). C_{max} in plasma is achieved 2 hours after oral administration. Bioavailability with a single dose is 68 % and increases with repeated use. [76, 78]

Plasma protein binding – 20 %. Tramadol is widely distributed in tissues. Vd after oral administration and intravenous administration is 306 l and 203 l, respectively. Penetrates through the placental barrier at a concentration equal to the concentration of the active substance in the plasma. 0.1 % is excreted in breast milk. It is metabolized by demethylation and conjugation of up to 11 metabolites, of which only 1 is active. It is excreted by the kidneys – 90 % and through the intestines – 10 %. [76, 78]

1.7 Mathematical models describing drug release from solid dosage forms

In the development of a modified release dosage form, special attention is paid to the release of the drug substance on which the achievement of the pharmacological effect depends. First of all, it is necessary to determine the required release kinetics. Modelling the kinetics of drug release from DF allows obtaining information on the required relaxation time of the polymer, in the case of using swelling polymers, or on the chemical structure, if the use of polymers soluble in alkaline and weakly acidic media is preferred in technology. [79, 82, 83]

Mathematical modelling of kinetics is based on various mathematical functions describing the release profile and can be applied to [79, 82, 83]:

- optimize or determine the drug release kinetics;
- determine the effects of pressing pressure, geometric parameters, composition and optimize them;

- predict the rates of drug release and diffusion from the matrix in order to reduce the number of experiments.

To predict the kinetics of drug release from oral sustained-release formulations, the most suitable models are [79]:

1. Zero order kinetic model
2. First order kinetic model
3. Higuchi model
4. Hixson-Crowell cube root law
5. Korsmeyer - Peppas Model
6. Baker-Lonsdale mode
7. Weibull model
8. Hopfenberg model
9. Gompertz model
10. Gallagher Corrigan model
11. Cooney model
12. Sequential layer model

In general, all models are based on Fick's first and second laws of diffusion. However, both laws have a number of limitations in their application for sustained-release DFs associated with the influence on the release kinetics of various factors, such as drug solubility or polymer relaxation time. [80]

The kinetics is also influenced by the method of release, both the type of DF and the type of drug, namely its solubility. In the case of using a highly soluble drug, the release mechanism will be diffusion. If a sparingly soluble drug is used, then the main mechanism will be erosion and the API can be released from the biodegradable matrix, and can also be cleaved from the polymer molecule due to the hydrolysis of the bond with a change in temperature or pH. [79, 82, 83]

1.7.1 First order kinetic model

The model was developed by Gibaldi and Feldman (1967) and then Wagner (1969). Used to describe drug release. Assumes that the release depends only on the concentration of the drug. This model can be used to quantitatively describe the dissolution of various dosage forms (for example, matrix tablets) or so to determine important pharmacokinetic parameters (absorption and elimination rate constants) when monitoring kinetics in vivo. [79, 81-83]

The amount of drug released in a tablet, as a function of time, is expressed by a differentiation equation (1) [79, 81-83]:

$$\frac{dA}{dt} = -A_t k \quad (1)$$

After integrating and modifying equation (1), we obtain a linear dependence (2):

$$\ln A_t = \ln A_\infty - kt \quad (2)$$

A_t [mol/l] – the amount of released drug at time t

A_∞ [mol/l] – the initial concentration of drug in the tablet

t [s] – time

k [s^{-1}] – first order rate constant

In order to express the amount of active substance released in the dissolution medium, we have to convert equation (2) to equation (3), which is expressed in exponential form [79, 81-83]:

$$A_t = A_\infty \cdot (1 - e^{-kt}) \quad (3)$$

The half-life $t_{1/2}$ [s] expresses the time taken to release half of the maximum releasable amount of the drug. For the first order, the half-life is calculated using equations (4) [79, 81-83]:

$$t_{1/2} = \frac{\ln 2}{k} \quad (4)$$

1.7.2 Weibull model

The Weibull distribution function was first introduced into pharmaceutical practice by Langenbucher (1972). This model is applicable to all types of dissolution curves, it can be used to explain dissolution and release of a drug from matrix systems, as well as to compare several dissolution profiles with each other. It agrees well with experimental data, and is a general empirical equation adapted to the dissolution and release process (4, 5). [79, 82, 83]

$$A_t = A_\infty \left[1 - e^{-\frac{(t-T)^b}{a}}\right] \quad (4)$$

$$A_t = A_\infty - A_\infty \cdot e^{-kt^b} \quad (5)$$

A_t [mol/l] – the amount of released drug as a function of time t

A_∞ [mol/l] – total amount of drug being released

T [s] – the lag time, the time interval resulting from the delay at the beginning of the dissolution process

a [s] – a scale parameter that describes the time dependence

b – describes the shape of the dissolution curve progression

So according to the parameter b three situations are possible:

For b = 1, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant $k = 1/a$

If $b > 1$, the curve has a steeper slope in the initial section than corresponds to the exponential.

If $b < 1$, the shape of the curve is sigmoidal.

1.7.3 Korsmeyer - Peppas Model

Korsmeyer et al. (1983) proposed a relationship describing the release of drugs from polymer systems. The equation is used to describe drug release from modified release formulations. To apply the description of drug dissolution according to the Korsmeyer - Peppas model, the first 60 % of the experimental data on the release must correspond to this model (6). [79, 81 - 83]

$$\frac{A_t}{A_\infty} = at^n \tag{6}$$

$\frac{A_t}{A_\infty}$ – fraction of drug released at time t

a [s^n] – the rate constant incorporating structural and geometric characteristics of the delivery system

n – the release exponent indicative of the mechanism of transport of drug through the polymer

The value of n is used to describe the differences in release from matrix tablets of a flat-cylindrical shape (Table 3). [79, 81 - 83]

Table 3: Interpretation of the mechanisms of diffusional release from the polymer layer in the Korsmeyer - Peppas model. [79]

Release Exponent (n)	**Drug transport Mechanism**	**Rate as a function of time**	**Drug release mechanism**
n<0.5	Quasi-Fickian	t^n	non swellable matrix-diffusion
0.5	Fickian diffusion	$t^{0.5}$	
0.5<n<0.1	Anomalous (Non - fickian transport)	t^{n-1}	for both diffusion and relaxation (erosion)
0.1	Case II transport	(time -indepentant)	Zero order release
Higher than 1.0	Super case II transport	t^{n-1}	(relaxation / erosion)

1.7.4 Higuchi model

The mathematical model proposed by Higuchi (1961) is the first to describe drug release from matrix systems as a diffusion process based on Fick's law and depending on the square root of time. It was first developed for planar systems but was later expanded to include geometric and porous systems. Today, the Huguchi equation is considered one of the most common and most widely used equations for controlled release drugs such as transdermal drugs and dissolving drug matrix tablets. [79, 81-83]

The release from homogeneous matrix tablets can be represented by the equation (7) [79, 81-83]:

$$A_t = A \cdot \sqrt{D \cdot (2 \cdot A_\infty - A_S) \cdot A_s \cdot t} \quad (7)$$

A_t [mol/l] – the amount of released drug in time t per unit area A

A_∞ [mol/l] – the drug initial concentration in the tablet

A_s [mol/l] – the drug solubility in the media and D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix

D [m^2/s] – the diffusivity of the drug molecules (diffusion coefficient) in the matrix

In general, the Higuchi model (7) can be represented in a simplified form (8) [79, 81-83]:

$$Q = K_H \cdot \sqrt{t} \quad (8)$$

K_H [$(mol/m^3)\ s^{-1/2}$] – the constant reflecting the design variables of the system

1.8 Dissolution tests

Dissolution test is one of the main analytical tests for all dosage solid dosage forms for internal use (tablets, dragees, capsules, granules). It is designed to determine the amount of API that must be released into the dissolution medium from a solid dosage form over a certain period. The test can be used both in the development of a drug for the selection of the optimal composition of the drug, assessing the quality of the finished drug and the stability of the drug, as well as during the production of drugs and when circulating on the pharmaceutical market to ensure consistency of quality. It occupies a special place in the preliminary assessment of the bioavailability of generic drugs when confirming bioequivalence and its use makes it possible to establish the rate and degree of release of an active substance into the dissolution medium from a

solid dosage form under normalized conditions, which to some extent simulates the behaviour of a dosage form under human conditions in the gastrointestinal path. [84, 86]

Therefore, the choice of dissolution medium is critical when performing the test. The medium most often used is water, artificial gastric juice or solutions of hydrochloric acid of different concentrations, buffer solutions of pH range from 4.1 to 8.0 (in isolated cases - 8.5 and higher). Even though the compositions of the buffer solutions given in different pharmacopoeias differ, the authors did not establish their influence on the dissolution results, explaining this by the identity of pH, buffer capacity, ionic strength, and osmolarity. The temperature of the dissolution medium is usually 37 ± 0.5 ° C; in some cases, testing is carried out at different temperatures. The composition of the dissolution medium is selected for each specific drug, considering the nature of the API, its minimal ionization and the section of the gastrointestinal tract (Table 4) in which the API should be dissolved and absorbed. [40, 84 – 87]

Table 4: Representation of pH changes in the GIT, transit time of non-disintegrating tablets (d = 9 mm). [87, 88]

	Transit time (h) tablets	**pH fasted**	**pH fed**
Stomach	9,6	1-2,5	1,2-5
Small intestine	2	4,4-6,5	6-7
Colon	15,2	6,8-8,0	5,5-8
Total	26,3		

In the case of studying the danger of premature release of API from medicinal products while taking alcohol by patients taking prolonged medicinal products, it is permissible to use a medium with 40 % ethanol content. [84, 86]

In case of non-compliance with the specifications of the drug in the form of hard or soft gelatine capsules or coated tablets, which include gelatine, the addition of pepsin or pancreatin to the medium is permissible. [84, 89]

The volume of the dissolution medium, as a rule, must be 20 times larger than that to obtain a saturated solution of the substance contained in the drug. In most cases, the volume ranges from 500 to 1000 ml. The conditions for mixing the medium should ensure a uniform concentration of API and reproducibility of results in each place of the volume. To improve the mixing process and hydrodynamics, several design solutions are proposed that are suitable for various dosage forms. [84, 86]

Used: apparatus 1 - "Rotating basket", apparatus 2 - "Paddle stirrer", apparatus 3 - "Oscillating drum", apparatus 4 - "Flow cell". For preliminary studies, as well as small size and / or low dosage APIs, mini-mixers are available. [84, 86, 90]

1.8.1 Rotating basket

The apparatus for the rotating basket method (Figure 21) consists of a dissolution vessel with a hemispherical bottom made of borosilicate glass or other suitable transparent inert material. The volume of the dissolving vessel is 1 litre; motor with speed controller; a stirring element (connected to a motor) which consists of a vertical shaft, to the bottom of which is attached a cylindrical basket (also made of inert material). The whole design provides smooth, without significant fluctuations in rotation throughout the experiment. [90-92]

To avoid evaporation of the dissolution medium, the structure is closed with a lid in which there are holes for a thermometer, sampling and an axis for fastening the basket. [90-92]

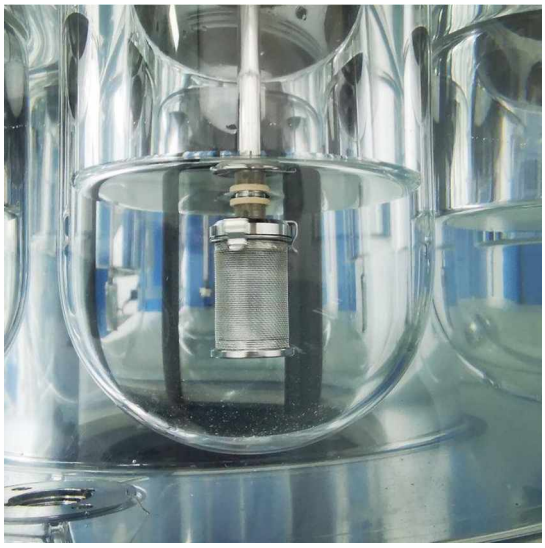


Figure 21: Rotating basket method**.** [92]

This method is suitable for dissolving immediate / delayed and delayed release pop-up forms (tablets, capsules, and granules). It is not suitable for testing tablets that break into pieces that can clog the cells of the basket, as a result of which the uniformity of mixing is disturbed, and the reliability of the test results is reduced. [90-92]

1.8.2 Paddle

The paddle apparatus consists of the same parts as the rotating basket apparatus. The difference between the apparatus lies in the use of a paddle mixer (Figure 22) instead of a rotating basket as a mixing element. The metal stirrer and metal rod are one piece, the bottom edge of which should be 25 mm from the bottom of the dissolution vessel. [90-92]

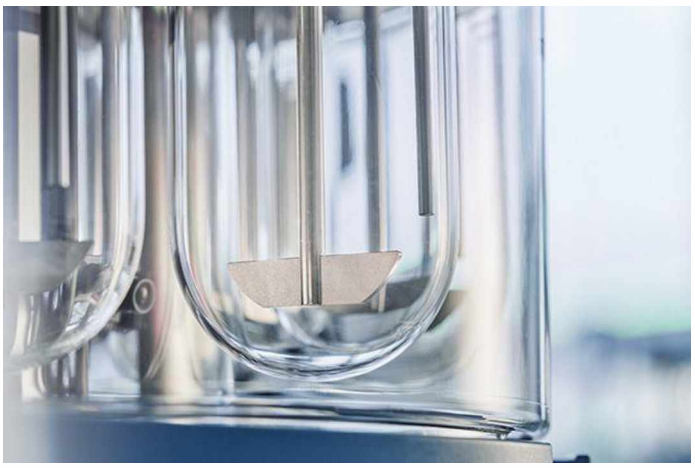


Figure 22: Paddle dissolution method. [92]

With this method, the tablet is loosely placed in a dissolution vessel filled with dissolution medium. This method is suitable for solid dosage forms that do not stick to the bottom or float on the surface. [90-92]

1.8.3 Reciprocating Cylinder

The apparatus reciprocating cylinder consists of a reservoir for the dissolution medium immersed in a water bath with the dissolution medium maintained at a temperature in the range of values (37 ± 0.5); a sinusoidal pump pumping the dissolution medium through the flow cell; the flow rate of the dissolution medium should not exceed ± 5 %; a flow cell with transparent inert material installed vertically above the filter system to prevent undissolved particles from moving towards the top of the cell. This method is suitable for drugs with low solubility (tablets, capsules, implants). [90, 91]

1.8.4 Flow through cell

Dissolution testing of prolonged and hardly soluble drugs is carried out in flow though cells (Figure 23). The sample is placed in a flow through cell, which is made of transparent material and is positioned vertically above the filter system, which prevents undissolved particles from moving towards the top of the cell. The standard cell's diameters are 12.0 and 22.6 mm. A dissolution medium flows through the cell, which is pumped by a pump with a sinusoidal profile of a speed of 120 ± 10 pulses / min. The flow speed of the dissolution medium should not exceed ± 5 %. [90, 91, 93]

Figure 23: Flow though cell method. [93]

1.9 Mechanical strength and direct compression

The strength (hardness) of the tablets depends on the natural and technological properties of the excipients, as well as on the applied pressure. [55, 56]

For the formation of tablets, a prerequisite is the interconnection of the particles. At the beginning of the pressing process, the tableted mass is compacted, crystals randomly oriented to each other are partially destroyed, particles come closer together and conditions are created for the manifestation of forces of intermolecular and electrostatic interaction. At the first stage of pressing the material, the particles of the material are brought together and compacted due to the displacement of the particles relative to each other, filling the voids. [55, 56]

In the second stage, with an increase in the pressing pressure, various types of deformation occur, which provide a more compact packing of particles and intensive compaction of the material by filling the voids. Due to deformation, the particles are mutually wedged, thereby increasing the contact surface. As a result, in the second stage of pressing, a compact porous body with sufficient mechanical strength is formed from the bulk material. [55, 56]

And, at the third, final, stage of pressing, volumetric compression of the formed compact body takes place. [55, 56]

Of all the parameters of the tableting process, the compression force influences the tablet strength the most. The higher it is, the more durable the tablets are. But only up to a certain limit. An increase in pressure leads to a sharp decrease in pores, which significantly worsens the disintegration and dissolution of the tablets. When pressure increases above the critical, the strength of the tablet decreases, since the granulate grains are destroyed, which leads to the

delamination of the tablet. The magnitude of the critical pressure for each material has a specific value; it depends on the bulk density of the material and its moisture content. [55, 56, 97]

At the same time, the strength provides the ability of tablets for further technological operations, therefore tablets of different sizes must have different strength values both for packing and for coating them with shells. Compression of most drugs requires a high pressure, but for each tablet mass, the compression pressure must be optimal, that is, with sufficient mechanical strength, it is necessary to ensure good disintegration of the tablet. The strength of the tablets is also very important for maintaining their integrity during packing, transportation and storage. [55, 56, 98]

In addition to the force of pressure during tableting, the nature of the pressure is also very important. Pressure is called "hard" if it comes on suddenly. This pressure is typical for single-punch tablet machines. The surface of the tablet under the impact of the punches heats up strongly (mechanical energy turns into heat), as a result of which the substances fuse and form a cemented layer. Pressure is called "progressive" if it builds up gradually. This pressure is typical of rotary tablet machines. Pressure is called "step pressure" if several rigid sequential compressions are applied: weaker, stronger, and maximum. The use of progressive pressure gives better results since the duration of the effect of pressure on the tableting mass in this case is longer. This provides more complete removal of air from the mass, which, after the release of pressure, can lead to the destruction of the tablet as a result of the expansion. [55, 56, 98]

Pressure can also be one-sided or two-sided. If only the upper punch is pressing, then the applied pressure is one-sided. Typically, this pressure is severe and typical of a single-punch tablet press. The area of application is limited only to easy-pressing mixtures. Applying big pressure to difficult-to-compress masses results in non-uniformity and delamination of the tablets. Under two-sided pressure, both punches are pressed simultaneously, which is typical for the rotary press. [55, 56, 98]

The strength of the tablets is directly influenced by the moisture content of the tableting mass. Wetter materials have greater ductility, and drier materials have greater elastic deformations. When pressing an excessively wet powder or granules, adhesion to the punches occurs, and dry leads to delamination of the tablets. [55, 56, 99]

Another factor affecting tablet strength is shape. So, pills of a bulky shape or flat with a chamfer are much denser than flat pills, in which, due to the sharpness of the edge, deformation is observed more often. [55, 56, 100]

2 Experimental part

2.1 Laboratory equipment and instruments

- Ordinary laboratory glassware
- Analytical balance Kern ALT 310-4AM (KERN & Sohn GmbH, Germany)
- Grinding chamber
- Homogenizer RETSCH MM200 - Retsch, Haan, Germany
- Hand press H-62- TRYSTOM spol. s.r.o., Olomouc, Czech Republic
- Dissolution Equipment - SOTAX AT 7 Smart - SOTAX Pharmaceutical Testing s.r.o, Allschvil, Switzerland
- UV-VIS spectrophotometer - Agilent 8453- Agilent Technologies Deutschland, Waldbronn, Germany
- Semi-automatic pipette - Ependorf, Germany
- 5 mm cuvettes (Fisher, Munich, Germany)
- MT50-FT manual tablet hardness tester (SOTAX Pharmaceutical Testing s.r.o.)

2.2 Chemicals

- Tramadol hydrochloride (Sigma Aldrich)
- Prosolv® SMCC90 (JRS Pharma GmbH & Co. KG, Rosenberg, Germany)
- Kollidon® SR (BASF, Ludwigshafen, Germany)
- Kollidon® 17 PF (BASF, Ludwigshafen, Germany)
- Kollidon® 25 (BASF, Ludwigshafen, Germany)
- Hypromellose MethocelTMK4MPremium CR (Colorcon GmbH, Germany)
- Hypromellose SheffCel 75HD100CR (Kerry, Hochheim am Main, Germany)
- Magnesium Stearate (Acro Organics, New Jersey, USA)
- Kolliwax® S (BASF, Ludwigshafen, Germany)
- Kolliphor® P 188 (BASF, Ludwigshafen, Germany)
- Kolliphor® P 407 (BASF, Ludwigshafen, Germany)
- Distilled water
- Redistilled water (repeatedly distilled water)
- HCl - hydrochloric acid (p. A. Purity, Penta s.r.o., Prague, Czech Republic)
- NaCl - sodium chloride (p. A. Purity, Lach-Ner s.r.o., Neratovice, Czech Republic)

2.3 PC programs

- MS Excel 2010
- OriginPro 9
- SW Application Creately

2.4 Composition and preparation of tablets

For this thesis, a total of 20 different formulations were studied, the composition of which is shown in Table 4. All tablets were prepared by direct compression, 4 tablets were made for each formulation: 3 tablets with active ingredient TH and 1 tablet without active ingredient that is called a blank sample. In the blank tablet, the API was replaced with the same amount of binder Prosolv® SMCC90.

All components mentioned in Table 5 were weighed on an analytical balance and mixed using a homogenizer at 10, 13 and 15 rpm for one minute. Then the homogeneous mixture was transferred to the mold and was upon direct compression for 5 minutes and with a constant pressing force of 8 kN. As a result, a cylindrical tablet weighing 500 ± 5 mg was obtained. Each finished batch of tablets was stored for 48 hours before being used in a dissolution test.

Table 5: Composition of formulations F1 – F20 (in mg)

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
Kolliwax® S	5	5	5	5	5															
Kolliphor® P 188						5	5	5	5	5										
Kolliphor® P 407											5	5	5	5	5					
Mg-Stearate																5	5	5	5	5
PROSOLV® SMCC90	145	145	145	145	145	145	145	145	145	145	145	145	145	145	145	145	145	145	145	145
Tramadol hydrochlorid	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Kollidon® SR	250					250					250					250				
Kollidon® 25		250					250					250					250			
Kollidon® 17			250					250					250					250		
Methocel™K4M				250					250					250					250	
SheffCel75HD100CR					250					250					250					250

2.5 Dissolution test of tablets with Tramadol hydrochloride

2.5.1 Preparation of the dissolution medium

For the dissolution test, an acidic medium of pH of 1.2 was used. To prepare 2000 ml of such medium, it was required to mix 500 ml of hydrochloric acid stock solution of concentration 0.2 mol/l and 850 ml of sodium chloride stock solution of concentration 0.2 mol/l and then supplemented with redistilled water to 2000 ml. [103]

In turn, to make 2 liters of hydrochloric acid stock solution was made as follows: 35.3 ml of 35 % HCl was mixed, and then supplemented with redistilled water to 2000 ml. [103]

For 2 liters of the NaCl stock solution, it was required to dissolve 23.38 g of sodium chloride, and then it was also supplemented with redistilled water to 2000 ml. [103]

2.5.2 Dissolution testing of tablets with TH

The dissolution test was carried out on a Sotax AT 7 dissolution apparatus (Figure 24) with 7 cylindrical glass vessels and a paddle method. With a graduated cylinder, 900 ml of dissolution medium of an acidic pH equal to 1.2 was poured into each vessel. The rotation speed of the paddles was 100 rpm. The temperature of the dissolution medium was constant throughout the experiment and was equal to 37 ± 0.5 ° C. After heating the water bath and the medium to the desired temperature, a batch of tablets was thrown with blank, inclusive, and stirring was started. During the test, the pump automatically took 3 ml samples. During the first hour 6 samples were taken at 10-minute intervals, then 16 samples were taken after 15 minutes and the last 7 samples were taken after 60 minutes. The total dissolution test time was 12 hours (720 minutes).

Figure 24: Dissolution apparatus Sotax AT 7 Smart. [94]

2.6 Determination of tramadol hydrochloride by UV/VIS spectrometry

After the dissolution test, all obtained samples were analysed using UV/VIS spectrometry (Figure 25). The absorbance was scanned by the method of a fixed wavelength (271 nm) with a three-point background correction in the range of 244–300 nm, always relative to a blank sample taken simultaneously in a 5 mm thick cuvette.

Next, the amount of tramadol hydrochloride released into the dissolution medium was calculated by converting the obtained absorbance values into a concentration according to the calibration line.

Figure 25: UV/VIS spectrophotometer - Agilent 8453. [95]

2.6.1 Calibration line

To determine the calibration dependence, 10 mg of tramadol hydrochloride was dissolved in a dissolution medium of a pH = 1.2, and then supplemented to 100 ml. Further, single samples of the calibration series were prepared from this solution by two-fold dilution. Each sample was then measured with a UV/VIS spectrometer at 271 nm against pure dissolution medium. Based on the obtained absorbance values, a graph of absorbance versus concentration (mg/l) was plotted (Figure 26). The calibration line equation was obtained from the graph, which was then used to calculate the amount of tramadol hydrochloride released from the prepared matrix tablets.

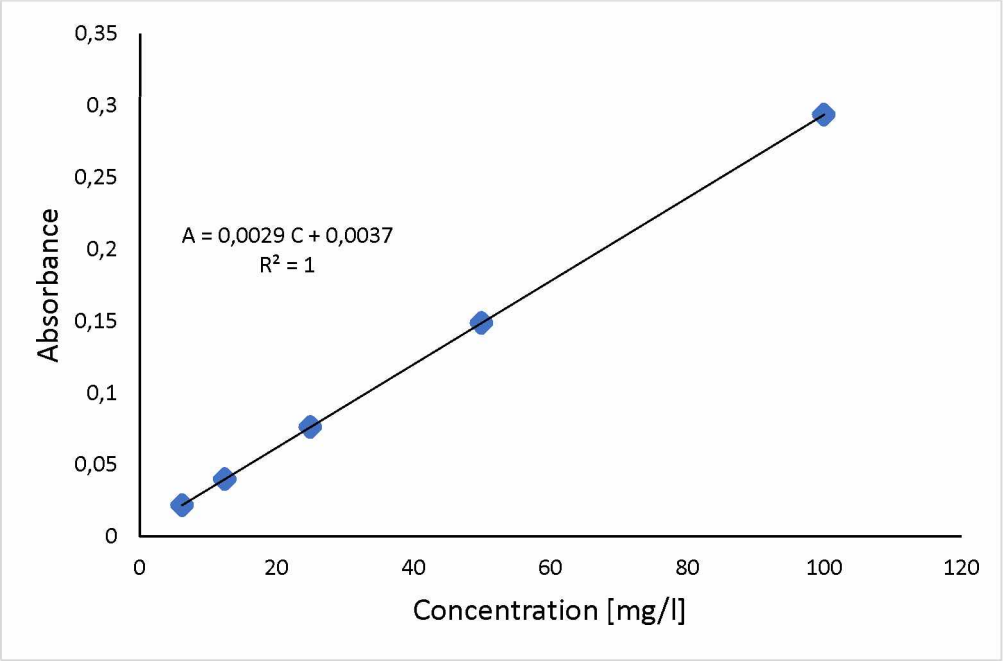


Figure 26: Calibration dependence of TH in dissolution medium pH 1.2

2.7 Determination of hardness of matrix tablets with tramadol hydrochloride

Like the rest, this device (Figure 27) works on the principle of a spring dynamometer. First, measurements were made of the size of the tablet, its height and diameter. The tablet was placed flat on the measuring table and the retractable piston pressed the tablet against the side plate and applied pressure on it until the tablet cracked. In this way, the device measured the forces required to break the structural integrity of the tablet.

Figure 27: MT50-FT manual tablet hardness tester. [96]

3 Results and discussion

For better presentation, all formulations were divided into 5 groups: formulations with Kollidon® SR, formulations with Kollidon® 25, formulations with Kollidon® 17 and formulations with Methocel K4M and with SheffCel 75HD100CR. Abbreviations have been used in the graphs below: Ks – Kolliwax® S, 188 – Kolliphor® P 188, 407 – Kolliphor® P 407 and MgS – magnesium stearate.

For evaluation and comparation of obtained dissolution curves were used several mathematical kinetics models. The obtained results were summarized graphically and in tables.

3.1 Formulations F1, F6, F11 and F16

The tablets of formulations F1, F6, F11 and F16 consisted of a mixture of excipients composed of 29 % PROSOLV ® SMCC 90 as a binder, 50 % Kollidon® SR as a retarding agent, 20 % TH as the active pharmaceutical ingredient and 1 % of lubricant.

Formulation F1 (Figure 28) with tested lubricant Kolliwax® S, released TH completely within 540 minutes. The dissolution profile of formulation 1 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F6 (Figure 29) with tested lubricant Kolliphor® 188, released TH completely within 540 minutes. The dissolution profile of formulation 6 was evaluated by the first order kinetic model and a Weibull mathematical model.

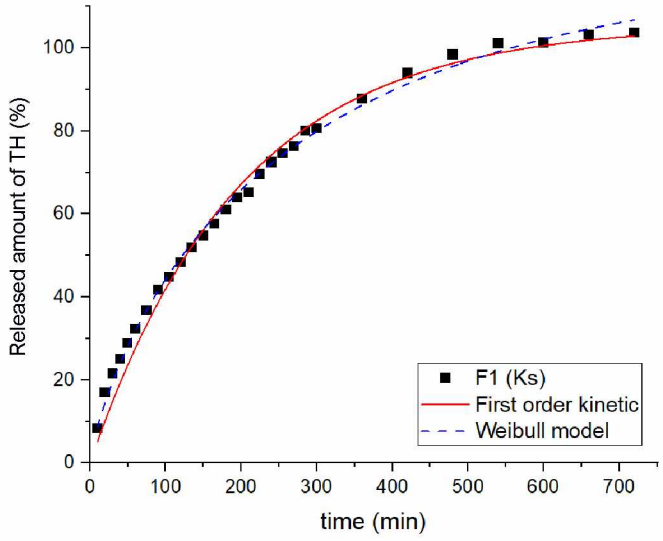


Figure 28: Dissolution profile of formulation F1 fitted to first order model and Weibull model.

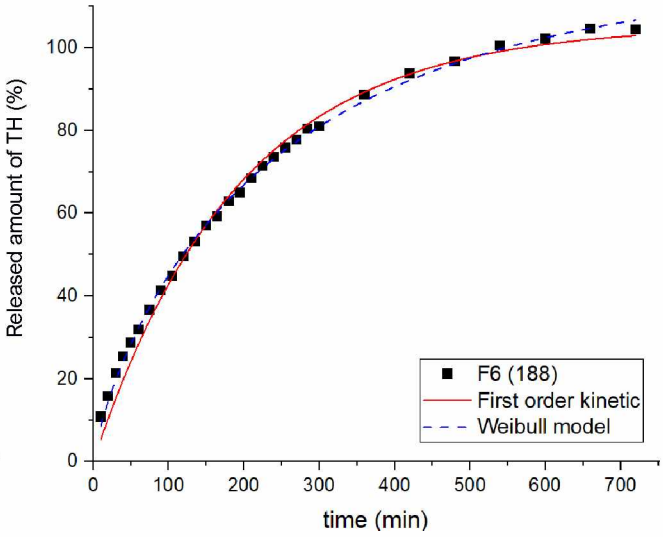


Figure 29: Dissolution profile of formulation F6 fitted to first order model and Weibull model.

Formulation F11 (Figure 30) with tested lubricant Kolliphor® 407, released TH completely within 480 minutes. The dissolution profile of formulation 11 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F16 (Figure 31) with tested lubricant magnesium stearate, released TH completely within 540 minutes. The dissolution profile of formulation 16 was evaluated by the first order kinetic model and a Weibull mathematical model.

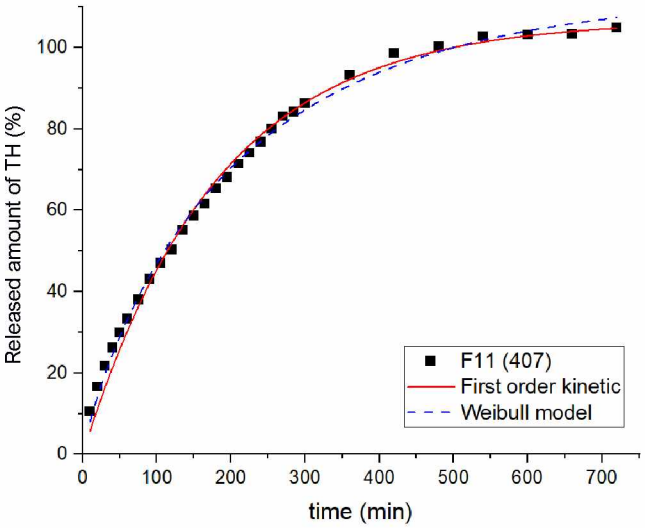


Figure 30: Dissolution profile of formulation F11 fitted to first order model and Weibull model.

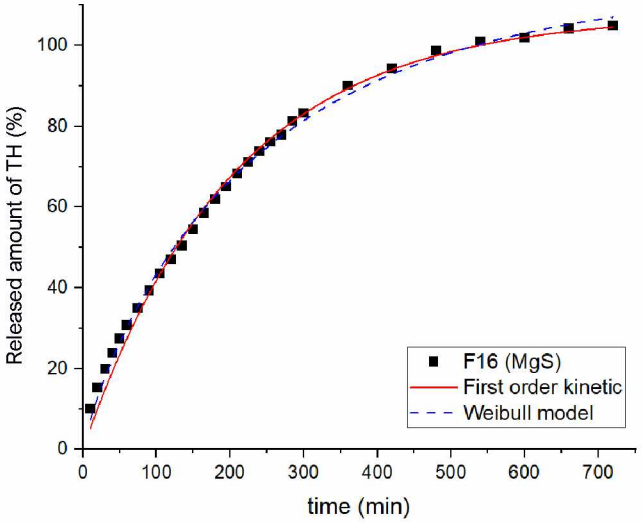


Figure 31: Dissolution profile of formulation F16 fitted to first order model and Weibull model.

For a visual and mathematical comparison of all 4 profiles together, first-order and Weibull models (Figure 32, 33) were also used, as well as Korsmeyer-Peppas model (Figure 34). The graphs show that the release profiles of the F1, F 6 and F16 formulations are practically the same, and only the F11 profile has a faster release of TH. These observations are also confirmed by the values of the release constants presented in tables 7 and 8. The table also shows the R^2 value, which averages 0,991, which in turn means that the first order model is well suitable for describing the release kinetics of TH from these formulations.

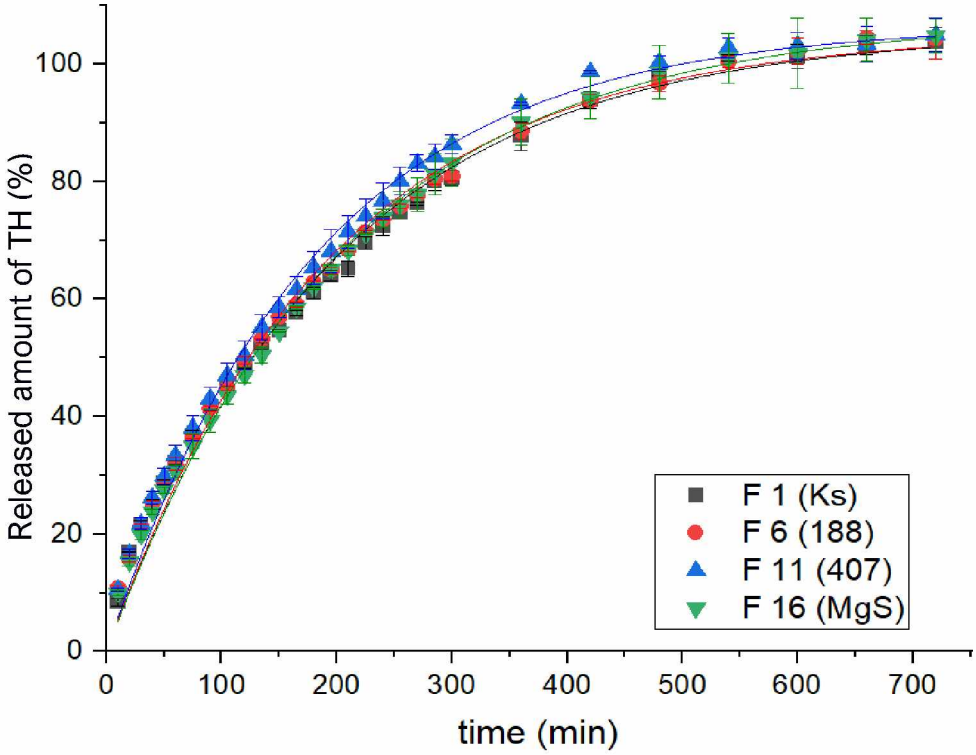


Figure 32: Dissolution profile of Kollidon® SR group formulations fitted to first order model

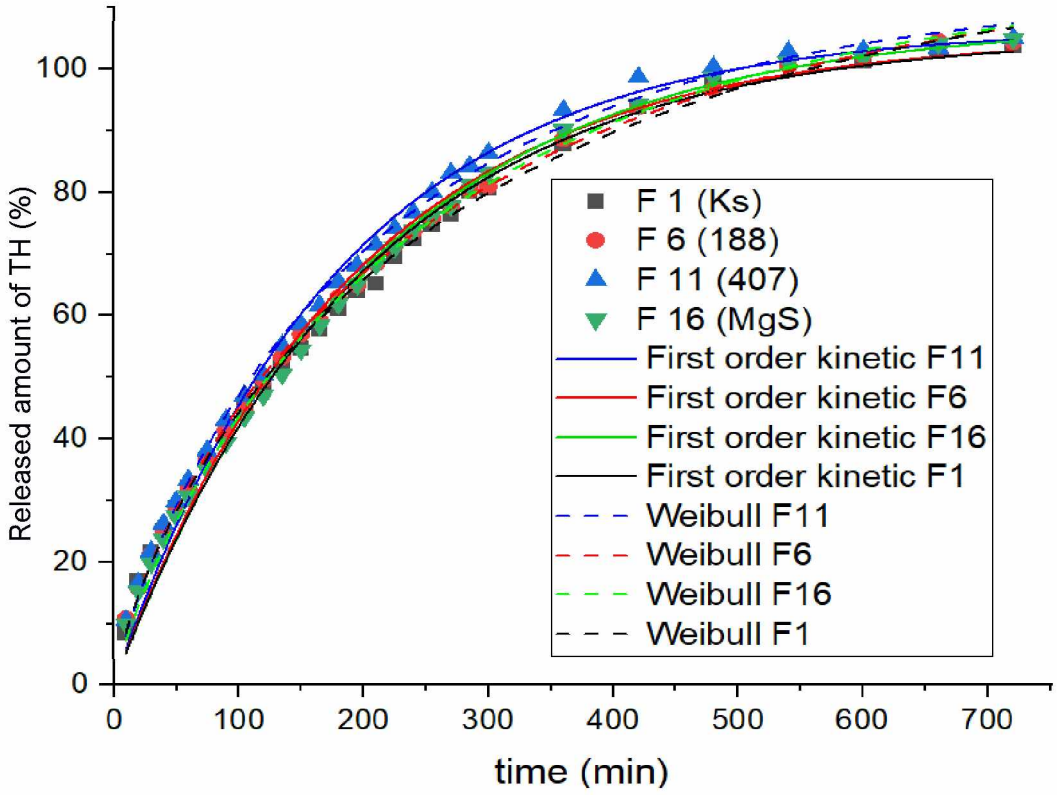


Figure 33: Dissolution profile of Kollidon® SR group formulations fitted to first order model and Weibull model.

Table 6: Evaluation of dissolution profiles of Kollidon® SR group formulations with first order model.

Formulation	First order kinetic $A_t = A_\infty \cdot (1 - e^{-kt})$		
	k ± SD	A_∞ ± SD (%)	R^2
F1	0,0052 ± 0,0002	105,38 ± 1,64	0,9904
F6	0,0051 ± 0,0002	105,62 ± 1,91	0,9877
F11	0,0055 ± 0,0002	106,73 ± 1,42	0,9923
F16	0,0050 ± 0,0002	107,59 ± 1,45	0,9937

Table 7: Evaluation of dissolution profiles of Kollidon® SR group formulations with a mathematical Weibull model.

Formulation	Weibull model $A_t = A_\infty - A_\infty \cdot e^{-kt^b}$			
	k ± SD	A_∞ ± SD (%)	b ± SD	R^2
F1	0,009 ± 0,0009	105,73 ± 2,29	0,86 ± 0,02	0,9972
F6	0,01 ± 0,001	110,52 ±3,32	0,79 ± 0,02	0,997
F11	0,012 ± 0,001	103,53 ± 2,08	0,86 ± 0,02	0,9964
F16	0,01 ± 0,0007	108,15 ± 1,92	0,80 ± 0,01	0,9986

In the case of Kollidon® SR group formulations, the dissolution profiles of all formulations can be fitted to Korsmeyer-Peppas model, which estimated only up to 60 % of the released amount of active pharmaceutical ingredient. The fitting of experimental data using this model is shown in Figure 34. The values of the obtained parameters of the Korsmeyer-Peppas model are summarized in Table 7. The values of parameter n are more than 0,5 and less than 1, so it can be said that the release mechanism of formulations is both diffusion and erosion (as it is described in chapter 1.6.3).

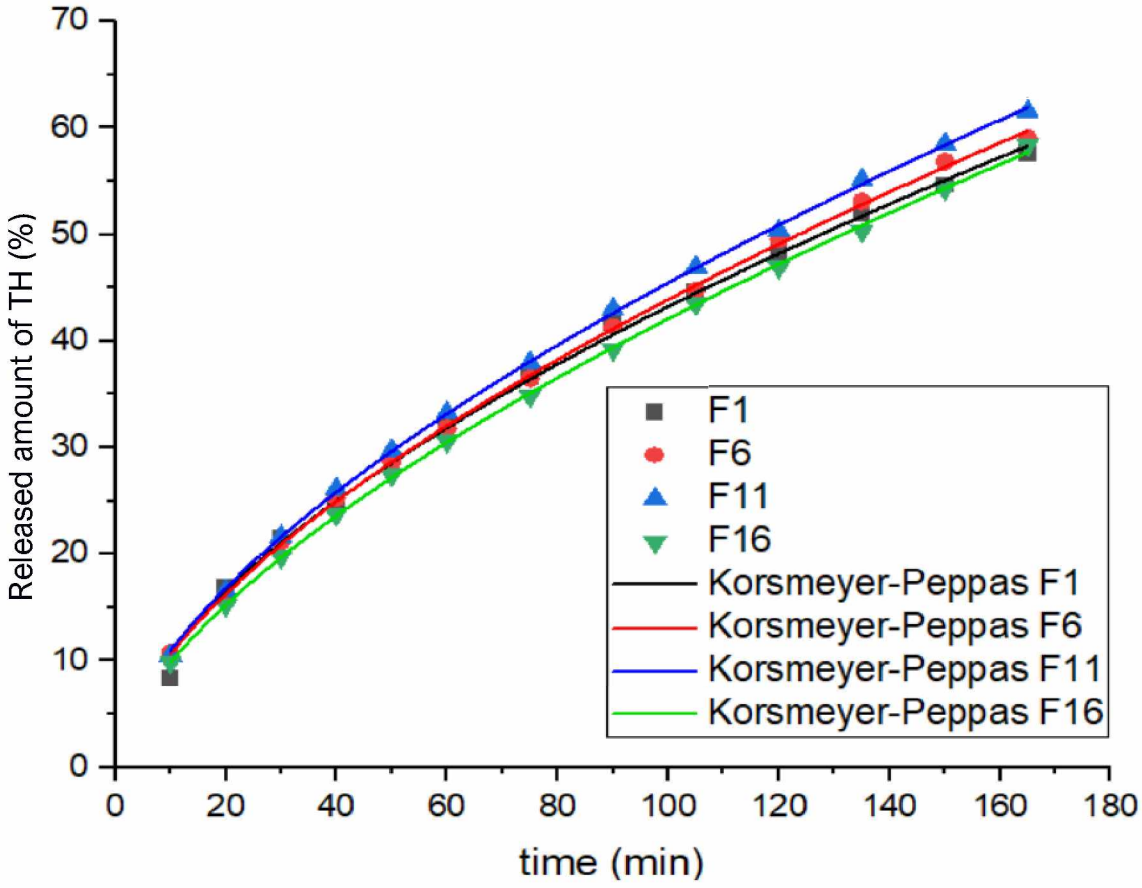


Figure 34: Dissolution profile (first 60 %) of Kollidon® SR group formulations fitted to Korsmeyer-Peppas model.

Table 8: Evaluation of dissolution profiles (first 60 %) of Kollidon® SR group formulations with Korsmeyer-Peppas model.

Formulation	Korsmeyer-Peppas model $\frac{A_t}{A_\infty} = at^n$		
	a ± SD	n ± SD	R^2
F1	2,79 ± 0,17	0,6 ± 0,013	0,9965
F6	2,60 ± 0,07	0,61 ± 0,006	0,9993
F11	2,68 ± 0,06	0,62 ± 0,004	0,9996
F16	2,33 ± 0,05	0,63 ± 0,004	0,9996

3.2 Formulations F2, F7, F12 and F17

The tablets of formulations F2, F7, F12 and F17 consisted of a mixture of excipients composed of 29 % PROSOLV ® SMCC 90 as a binder, 50 % Kollidon® 25, 20 % TH as the active pharmaceutical ingredient and 1 % of lubricant.

Formulation F2 (Figure 35) with tested lubricant Kolliwax® S, released TH completely within 40 minutes. The dissolution profile of formulation 2 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F7 (Figure 36) with tested lubricant Kolliphor® 188, released TH completely within 40 minutes. The dissolution profile of formulation 7 was evaluated by the first order kinetic model and a Weibull mathematical model.

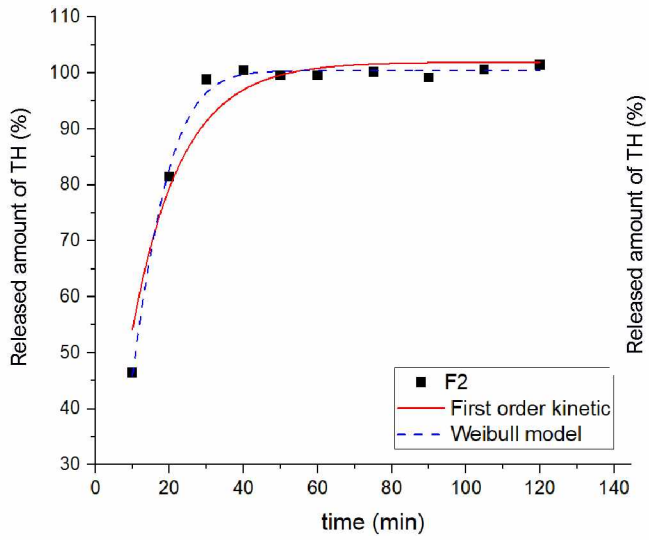


Figure 35: Dissolution profile of formulation F2 fitted to first order model and Weibull model.

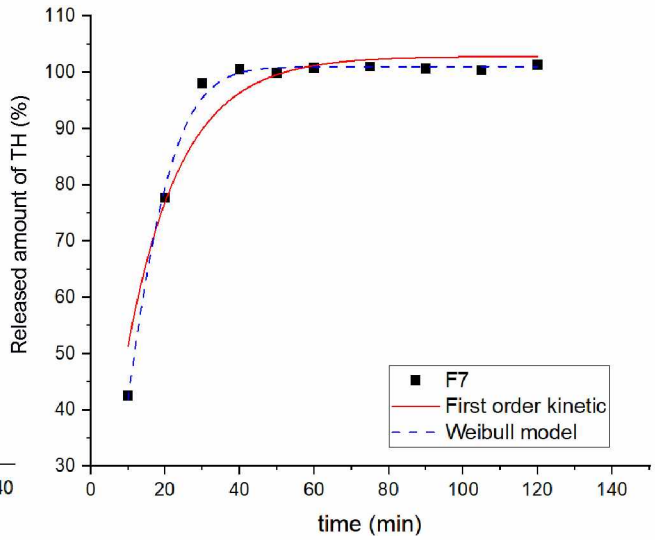


Figure 36: Dissolution profile of formulation F7 fitted to first order model and Weibull model.

Formulation F12 (Figure 37) with tested lubricant Kolliphor® 407, released TH completely within 50 minutes. The dissolution profile of formulation 12 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F17 (Figure 38) with tested lubricant magnesium stearate, released TH completely within 40 minutes. The dissolution profile of formulation 17 was evaluated by the first order kinetic model and a Weibull mathematical model.

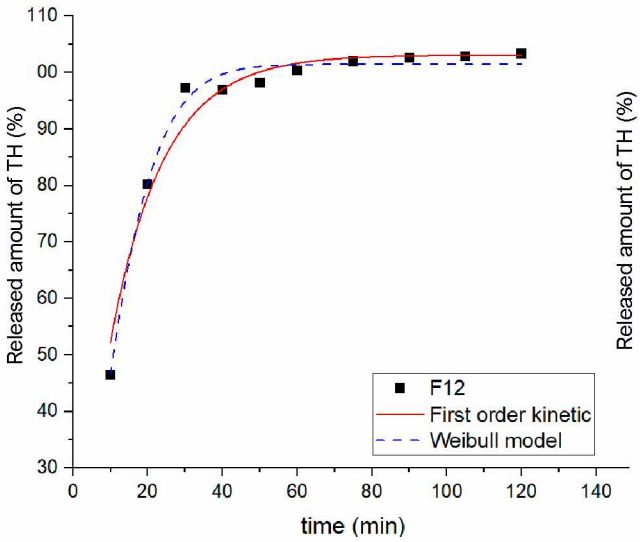


Figure 37: Dissolution profile of formulation F12 fitted to first order model and Weibull model.

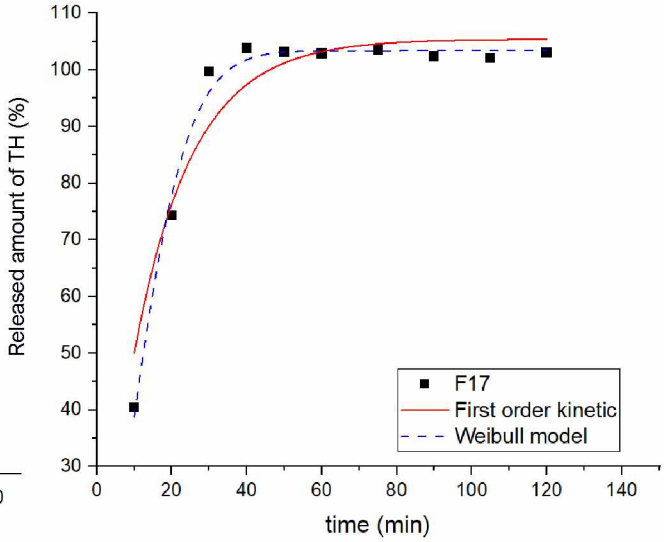


Figure 38: Dissolution profile of formulation F17 fitted to first order model and Weibull model

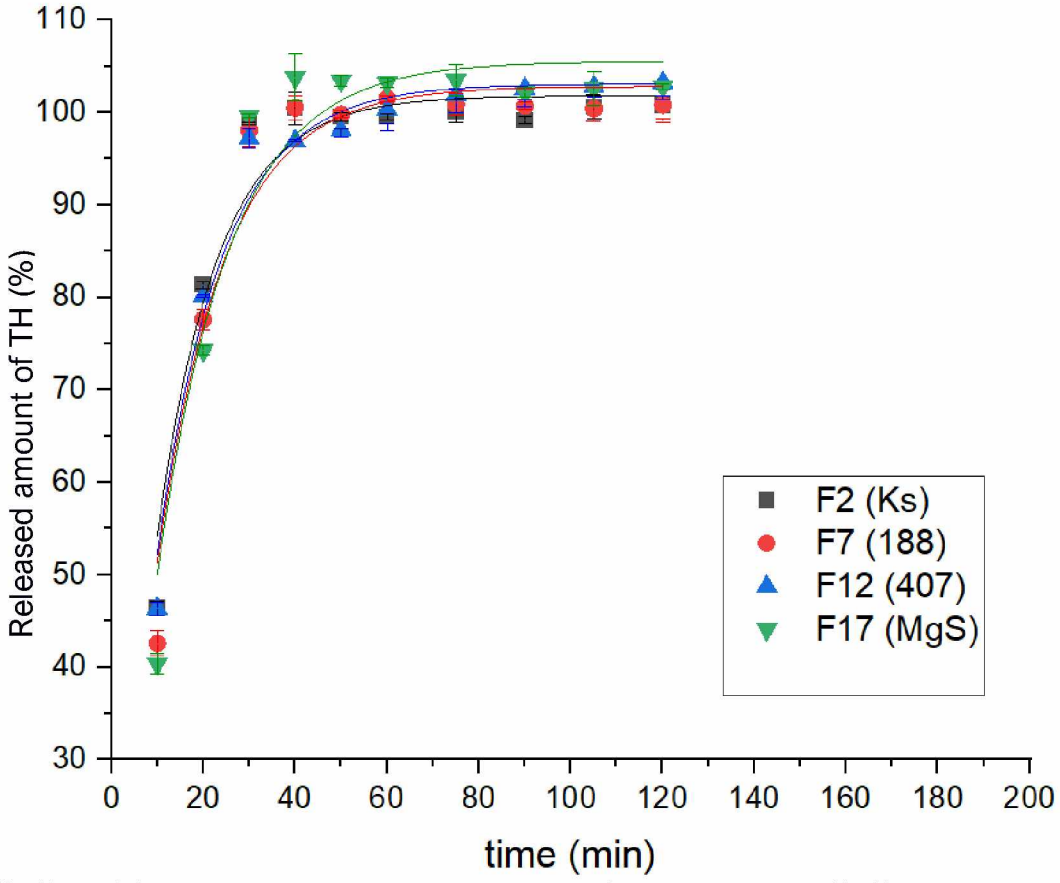


Figure 39: Dissolution profile of Kollidon® 25 group formulations fitted to first order model

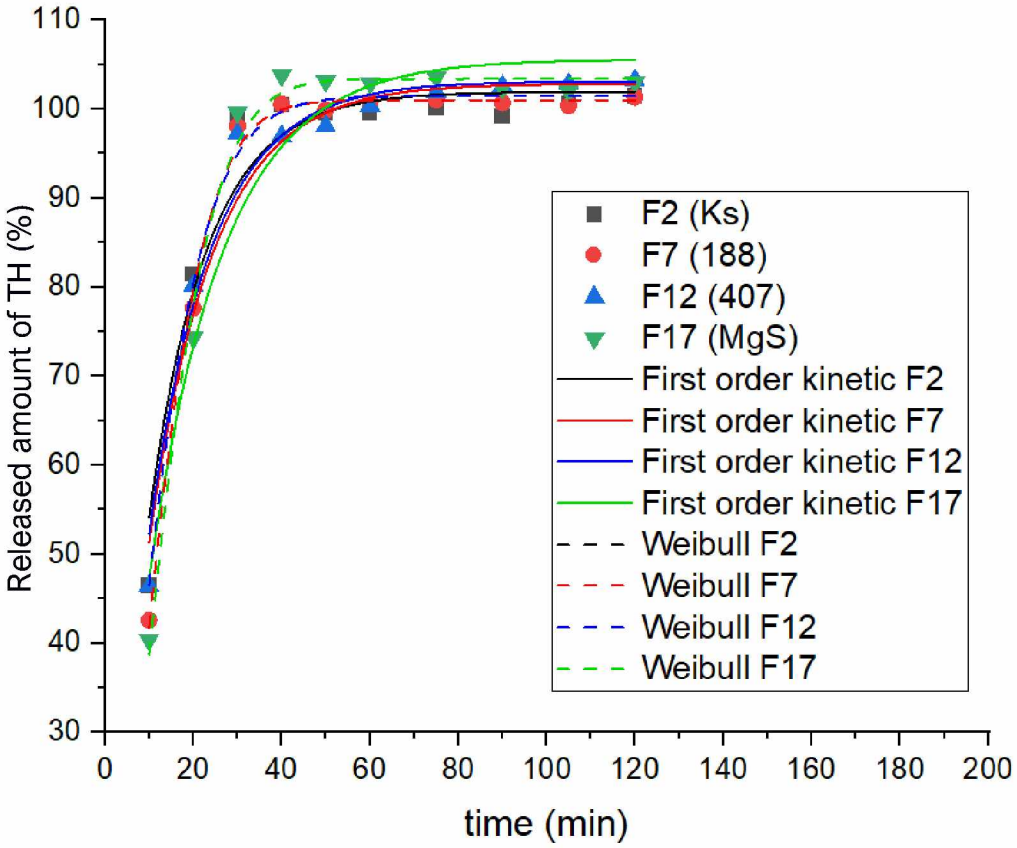


Figure 40: Dissolution profile of Kollidon® 25 group formulations fitted to first order model and Weibull model.

For a visual and mathematical comparison of all 4 profiles together, first order and Weibull models (Figures 39, 40) were also used. The graph shows that the release of all 4 profiles is very similar. A slight slowdown observed in the release of formulation containing magnesium stearate (F17). In tablets containing Kollidon® 25, the amount of the active ingredient tramadol hydrochloride is released relatively quickly. Due to the fast release of the API in these formulations, we have a much smaller number of experimental points, which affects the worst value of the coefficient of determination R^2 (Table 9, 10). The fast release of the API also makes it impossible to use Korsmeyer-Peppas model.

Table 9: Evaluation of dissolution profiles of Kollidon® 25 group formulations with first order model.

Formulation	**First order kinetic $A_t = A_\infty \cdot (1 - e^{-kt})$**		
	k ± SD	A_∞ ± SD (%)	R^2
F2	0,08 ± 0,007	101,93 ± 1,77	0,9474
F7	0,07 ± 0,007	102,83 ± 2,03	0,9458
F12	0,071 ± 0,005	103,09 ± 1,42	0,9694
F17	0,06 ± 0,007	105,58 ± 2,79	0,9255

Table 10: Evaluation of dissolution profiles of Kollidon® 25 group formulations with a mathematical Weibull model.

Formulation	Weibull model $A_t = A_\infty - A_\infty \cdot e^{-kt^b}$			
	k ± SD	A_∞ ± SD (%)	b ± SD	R^2
F2	0,0173 ± 0,003	99,38 ± 0,21	1,55 ± 0,07	0,9893
F7	0,0153 ± 0,0032	100,99 ± 0,54	1,54 ± 0,08	0,9958
F12	0,023 ± 0,008	101,45 ± 0,83	1,36 ± 0,1	0,9896
F17	0,012 ± 0,004	103,38 ± 0,89	1,58 ± 0,12	0,9908

3.3 Formulations F3, F8, F13 and F18

The tablets of formulations F3, F8, F13 and F18 consisted of a mixture of excipients composed of 29 % PROSOLV ® SMCC 90 as a binder, 50 % Kollidon® 17, 20 % TH as the active pharmaceutical ingredient and 1 % of lubricant.

Formulation F3 (Figure 41) with tested lubricant Kolliwax® S, released TH completely within 40 minutes. The dissolution profile of formulation 3 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F8 (Figure 42) with tested lubricant Kolliphor® 188, released TH completely within 50 minutes. The dissolution profile of formulation 8 was evaluated by the first order kinetic model and a Weibull mathematical model.

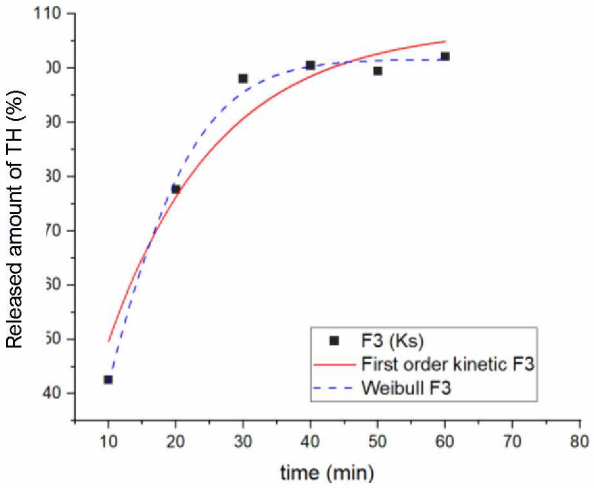


Figure 41: Dissolution profile of formulation F3 fitted to first order model and Weibull model.

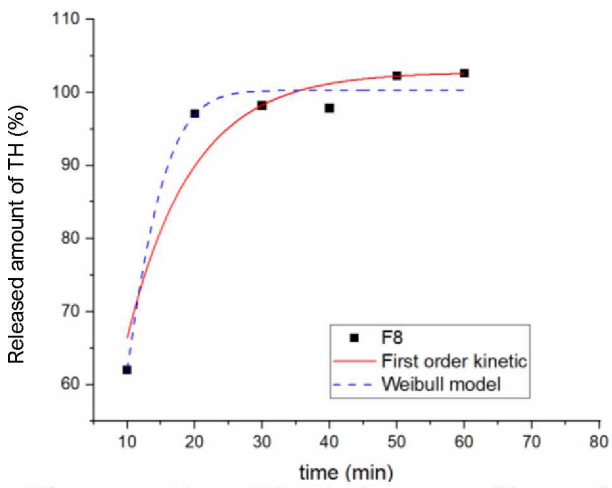


Figure 42: Dissolution profile of formulation F8 fitted to first order model and Weibull model.

Formulation F13 (Figure 43) with tested lubricant Kolliphor® 407, released TH completely within 50 minutes. The dissolution profile of formulation 13 was evaluated the first order kinetic model and a Weibull mathematical model.

Formulation F18 (Figure 44) with tested lubricant magnesium stearate, released TH completely within 30 minutes. The dissolution profile of formulation 18 was evaluated by the first order kinetic model and a Weibull mathematical model.

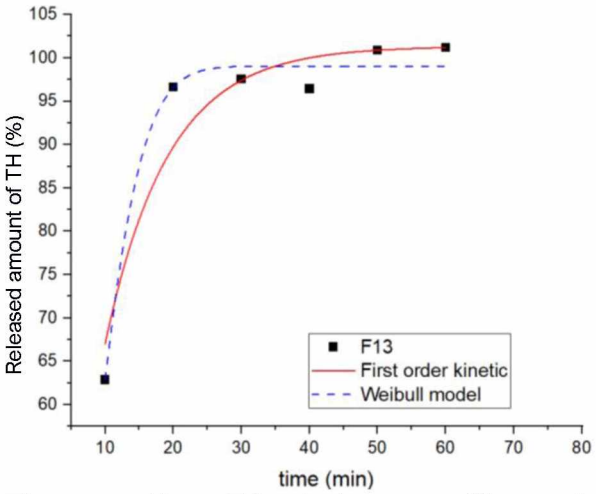


Figure 43: Dissolution profile of formulation F13 fitted to first order model and Weibull model.

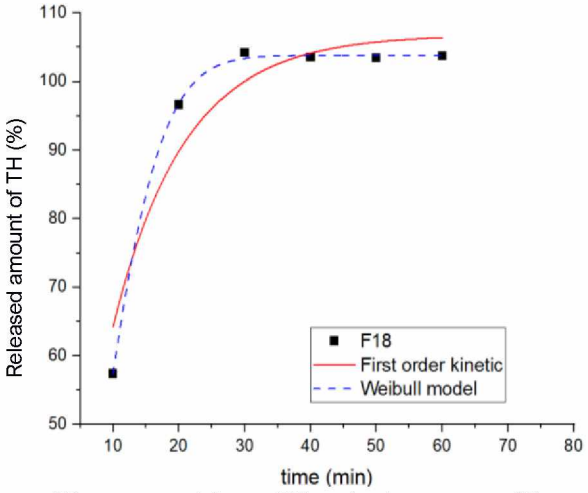


Figure 44: Dissolution profile of formulation F18 fitted to first order model and Weibull model.

Figures 45, 46 represents comparison of all 4 dissolution profiles together, fitted to first order and Weibull models. The fast release of the API from these formulations containing Kollidon® 17 caused a smaller number of experimental points. As the result the worst values of the coefficient of determination R^2 of first order kinetic were obtained (Table 11). Dissolution curves of F8 and F13 have a very similar shape. Formulation F3 containing Kolliwax® S has the slowest release of TH. The fast release of the API also makes it impossible to use Korsmeyer-Peppas model.

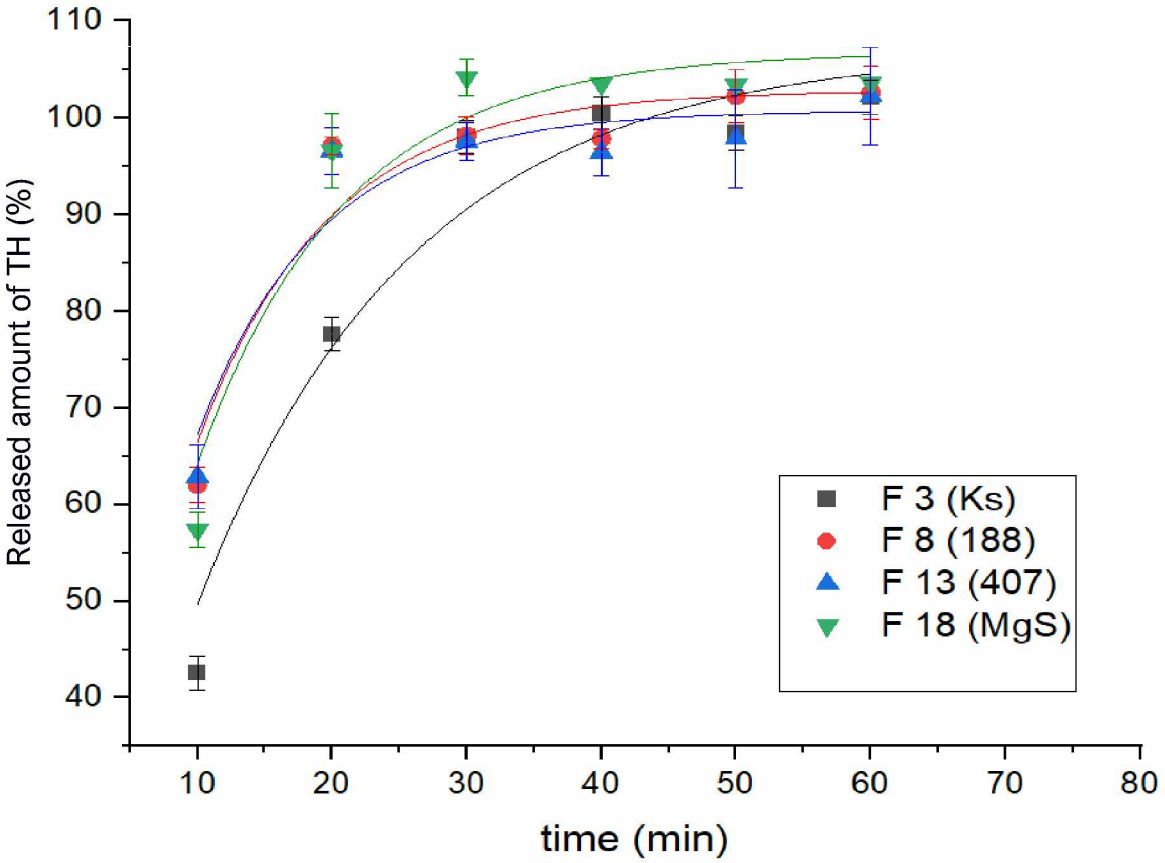


Figure 45: Dissolution profile of Kollidon® 17 group formulations fitted to first order model.

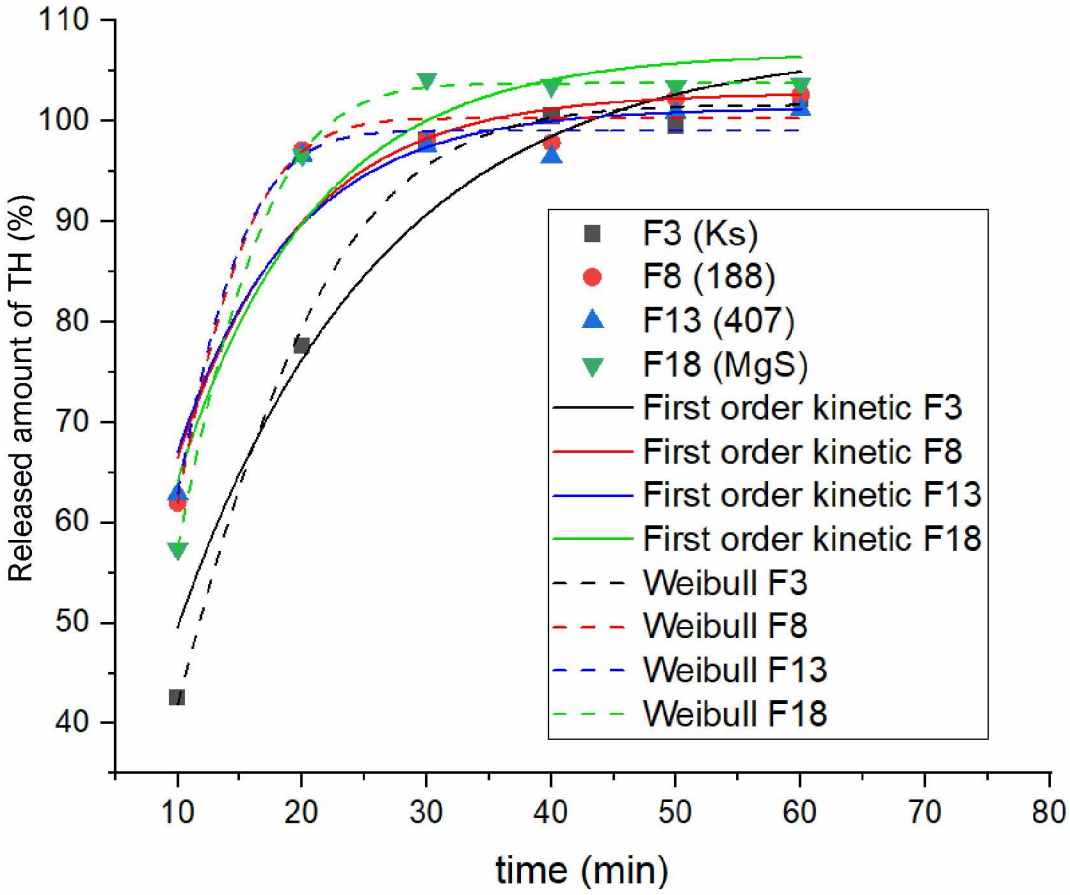


Figure 46: Dissolution profile of Kollidon® 17 group formulations fitted to first order model and Weibull model.

Table 11: Evaluation of dissolution profiles of Kollidon® 17 group formulations with first order kinetic model.

Formulation	First order kinetic $A_t = A_\infty \cdot (1 - e^{-t})$		
	k ± SD	A_∞ ± SD (%)	R^2
F3	0,062 ± 0,009	107,57 ± 5,03	0,9539
F8	0,104 ± 0,013	102,83 ± 2,67	0,9319
F13	0,108 ± 0,013	101,33 ± 2,53	0,9285
F18	0,092 ± 0,013	106,82 ± 3,53	0,9281

Table 12: Evaluation of dissolution profiles of Kollidon® 17 group formulations with a mathematical Weibull model.

Formulation	Weibull model $A_t = A_\infty - A_\infty \cdot e^{-kt^b}$			
	k ± SD	A_∞ ± SD (%)	b ± SD	R^2
F3	0,0161 ± 0,01	101,62 ± 1,38	1,52 ± 0,02	0,9972
F8	0,0145 ± 0,01	100,23 ±1,29	1,82 ± 0,41	0,9971
F13	0,0137 ± 0,01	99,04 ± 1,19	1,87 ± 0,48	0,9964
F18	0,0144 ± 0,002	103,79± 0,03	1,75 ± 0,06	0,9986

3.4 Formulations F4, F9, F14 and F19

The tablets of formulations F4, F9, F14 and F19 consisted of a mixture of excipients composed of 29 % PROSOLV ® SMCC 90 as a binder, 50 % Methocel^{TM} K4M, 20 % TH as the active pharmaceutical ingredient and 1 % of lubricant.

Formulation F4 (Figure 47) with tested lubricant Kolliwax® S, did not release all 100 % TH during the dissolution test but only 90,9 %. The dissolution profile of formulation 4 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F9 (Figure 48) with tested lubricant Kolliphor® 188, did not release all 100% TH during the dissolution test but only 88,4 %. The dissolution profile of formulation 9 was evaluated by the first order kinetic model and a Weibull mathematical model.

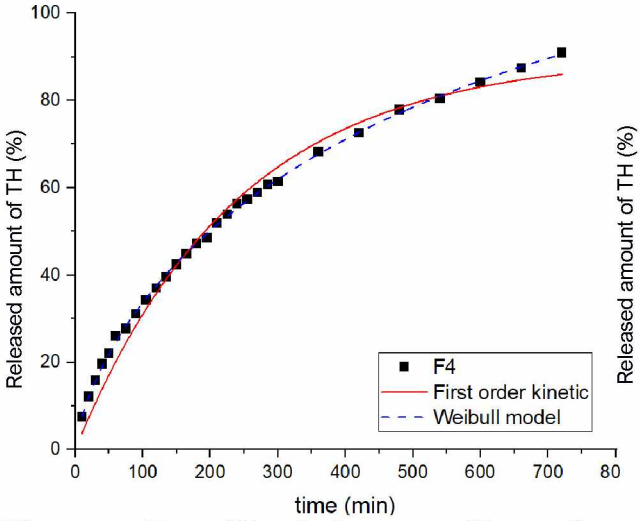


Figure 47: Dissolution profile of formulation F4 fitted to first order model and Weibull model.

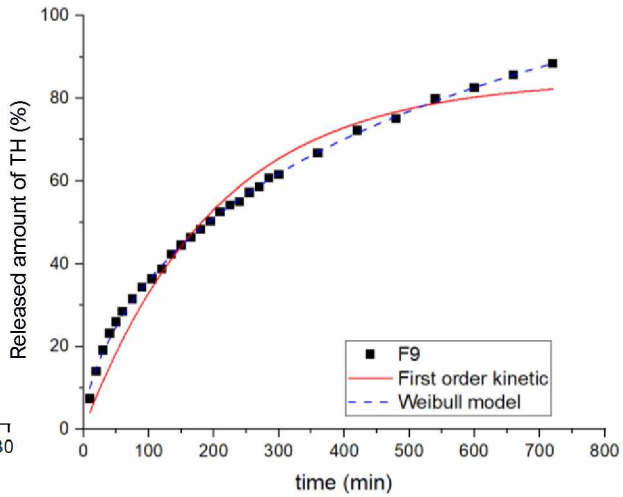


Figure 48: Dissolution profile of formulation F9 fitted to first order model and Weibull model.

Formulation F14 (Figure 48) with tested lubricant Kolliphor® 407, did not release all 100% TH during the dissolution test but only 94,0%. The dissolution profile of formulation 14 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F19 (Figure 49) with tested lubricant magnesium stearate, did not release all 100% TH during the dissolution test but only 81,7%. The dissolution profile of formulation 19 was evaluated by the first order kinetic model and a Weibull mathematical model.

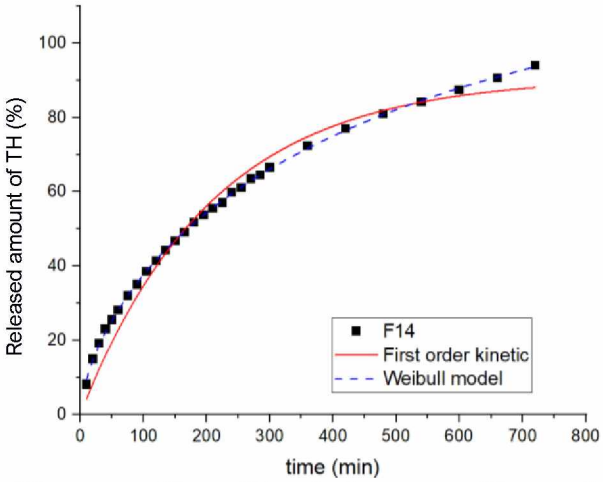


Figure 49: Dissolution profile of formulation F14 fitted to first order model and Weibull model.

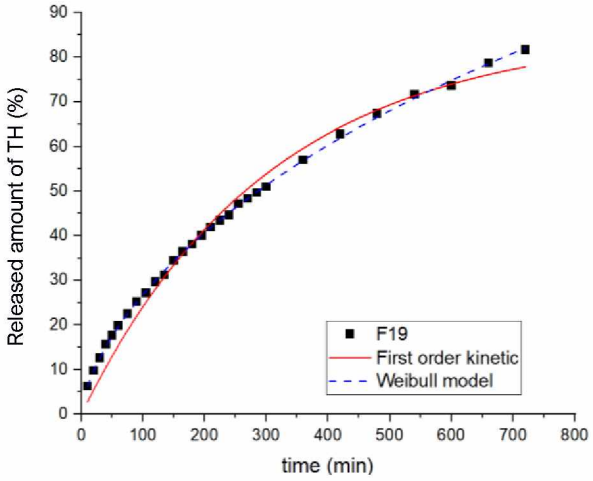


Figure 50: Dissolution profile of formulation F19 fitted to first order model and Weibull model.

None of the formulations in the Methocel K4M group released TH completely during the dissolution test. Formulations F4 and F9 have a similar release process. Formulation with magnesium stearate (F19) has it the slowest. And F 14 dissolved the fastest. This is seen in figures 51, 52 and from comparing the constants from tables 13 and 14. The coefficient of determination R^2 of first order kinetic is not very high so perhaps this model does not describe profiles precisely.

Table 13: Evaluation of dissolution profiles of Methocel K4M group formulations with first order model.

Formulation	First order kinetic $A_t = A_\infty \cdot (1 - e^{-kt})$		
	k ± SD	A_∞ ± SD (%)	R^2
F4	0,0032 ± 0,0002	90,35 ± 2,3	0,9832
F9	0,0049 ± 0,0003	84,59 ± 2,6	0,9635
F14	0,0048 ± 0,0003	90,87 ± 2,4	0,9755
F19	0,0039 ± 0,0002	85,84 ± 2,8	0,9827

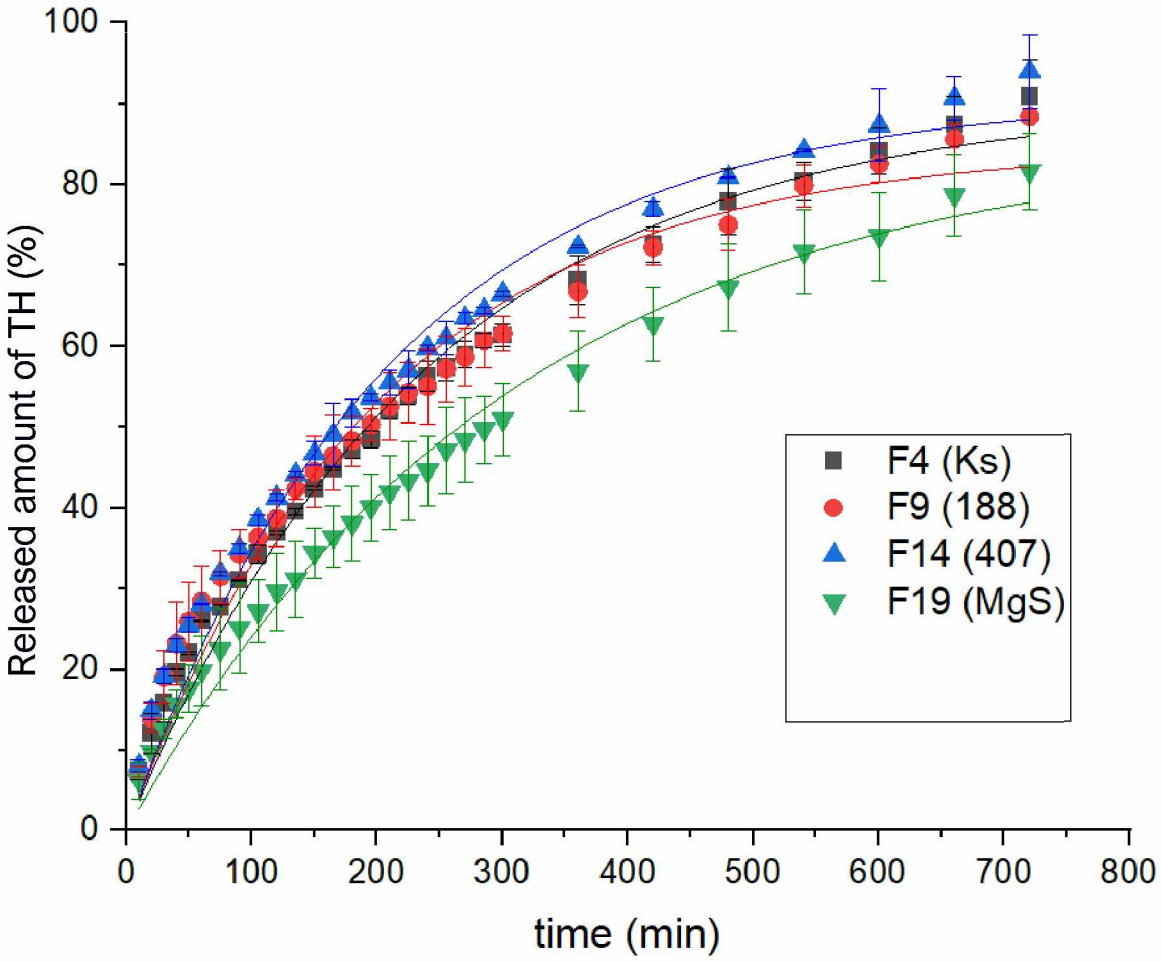


Figure 51: Dissolution profile of Methocel K4M group formulations fitted to first order model.

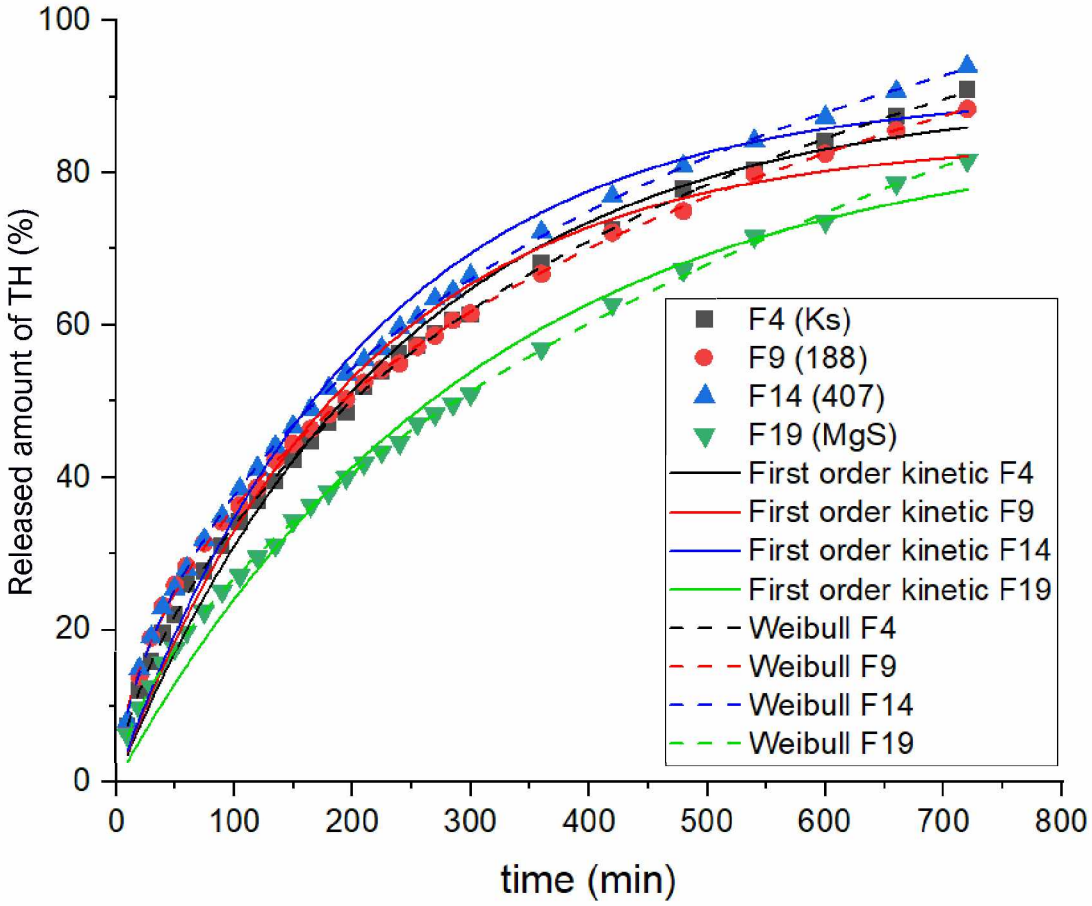


Figure 52: Dissolution profile of Methocel K4M group formulations fitted to first order model and Weibull model.

Table 14: Evaluation of dissolution profiles of Methocel K4M group formulations with a mathematical Weibull model.

Formulation	**Weibull model** $A_t = A_\infty - A_\infty \cdot e^{-kt^b}$			
	k ± SD	A_∞ ± SD (%)	b ± SD	R^2
F4	0,012 ± 0,0003	105,71 ± 2,14	0,7 ± 0,01	0,9994
F9	0,018 ± 5,2	103,58 ± 1,84	0,61 ± 0,01	0,9989
F14	0,016 ± 3,1	101,36 ± 1,07	0,66 ± 0,01	0,9996
F19	0,01 ± 0.0004	103,7 ± 2,67	0,66 ± 0,01	0,9995

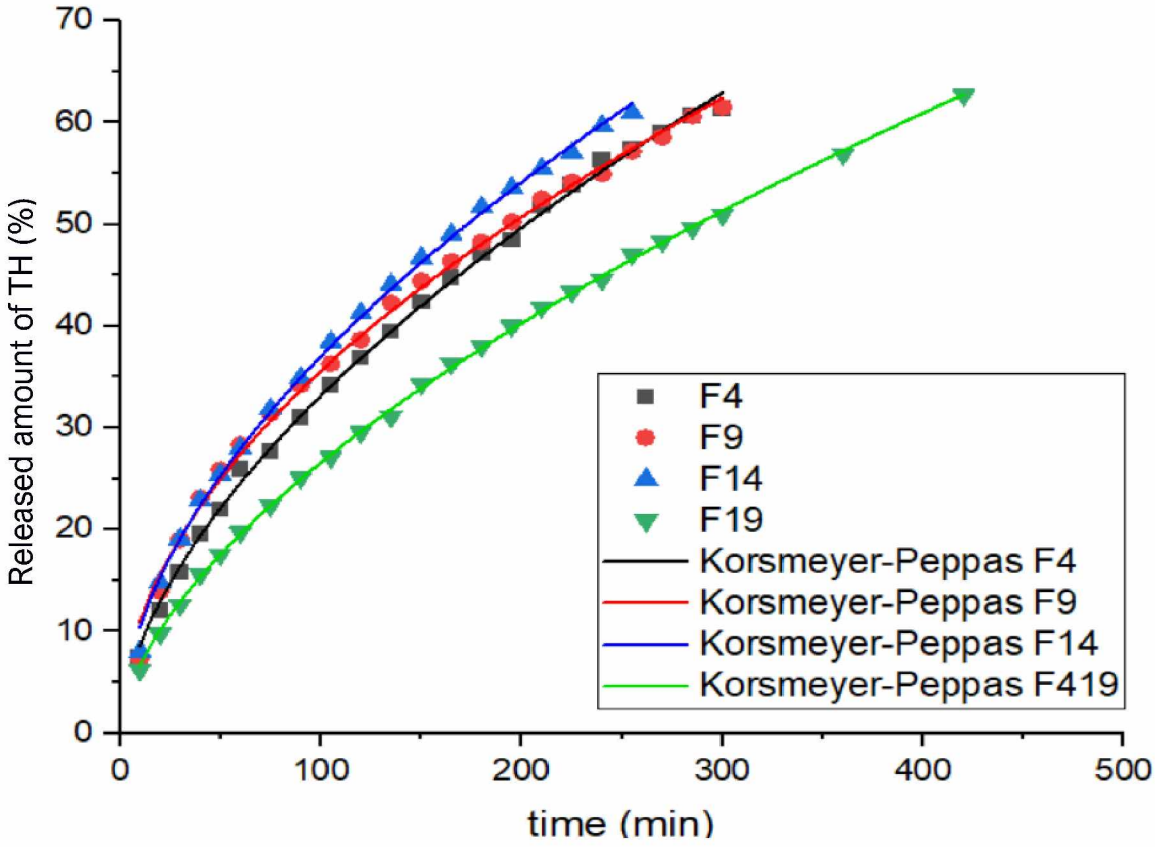


Figure 53: Dissolution profile (first 60 %) of Methocel K4M group formulations fitted to Korsmeyer-Peppas model.

All the dissolution profiles of Methocel K4M group can be fitted to Korsmeyer-Peppas model, which estimated only up to 60 % of the released amount of active pharmaceutical ingredient. The fitting of experimental data using this model is shown in Figure 53. The values of the obtained parameters of the Korsmeyer-Peppas model are summarized in Table 15. The values of parameter n for F4 and F19 are more than 0,5 and less than 1, so it can be said that the release mechanism of formulations is both diffusion and erosion. In case of F9 and F14 the release mechanism can be diffusion only and Higuchi model can be applied (Figure 54).

Table 15: Evaluation of dissolution profiles (first 60 %) of Methocel K4M group formulations with Korsmeyer-Peppas model.

Formulation	**Korsmeyer-Peppas model** $\frac{A_t}{A_\infty} = at^n$		
	a ± SD	n ± SD	R^2
F4	2,77 ± 0,09	0,58 ± 0,007	0,9982
F9	3,41 ± 0,17	0,51 ± 0,010	0,9955
F14	2,98 ± 0,11	0,55 ± 0,008	0,998
F19	1,71 ± 0,03	0,60 ± 0,004	0,9995

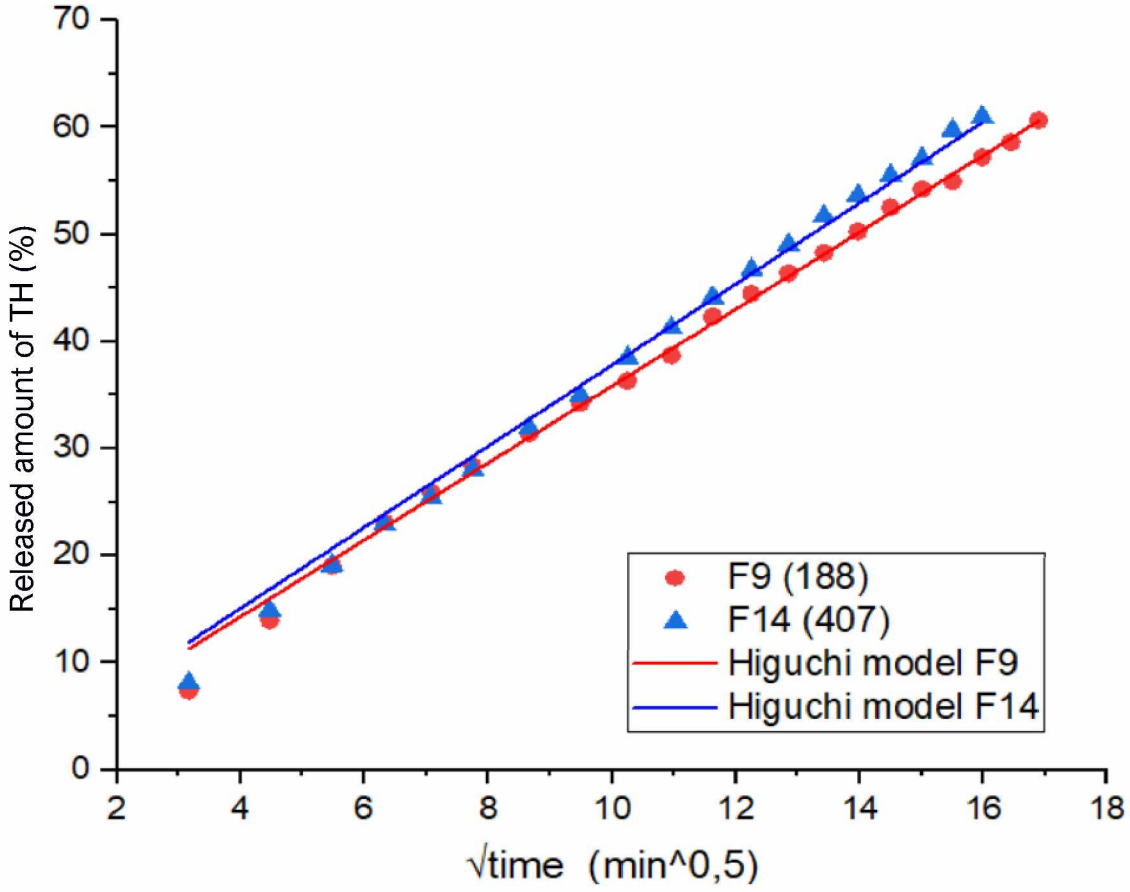


Figure 54: Dissolution profile (first 60%) of F9 and F14 formulations fitted to Higuchi model.

The diffusion mechanism was verified by fitting the experimental data with a mathematical Higuchi model. According to the values of the coefficient of determination (Table 16), the diffusion mechanism of the release of the active substance was confirmed for both formulations.

Table 16: Evaluation of dissolution profiles (first 60 %) of F9 and F14 formulations fitted to Higuchi model

Formulation	Higuchi model $Q = K_H \cdot \sqrt{t}$	
	$K_H \pm SD$	R^2
F9	3,59 ± 0,02	0,995
F14	3,79 ± 0,03	0,993

3.5 Formulations F5, F10, F15 and F20

The tablets of formulations F4, F9, F14 and F19 consisted of a mixture of excipients composed of 29 % PROSOLV ® SMCC 90 as a binder, 50 % SheffCel 75HD100CR, 20 % TH as the active pharmaceutical ingredient and 1 % of lubricant.

Formulation F5 (Figure 55) with tested lubricant Kolliwax® S, release all 100 % TH withing 480. The dissolution profile of formulation 5 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F10 (Figure 56) with tested lubricant Kolliphor® 188, release all 100 % TH withing 480. The dissolution profile of formulation 10 was evaluated by the first order kinetic model and a Weibull mathematical model.

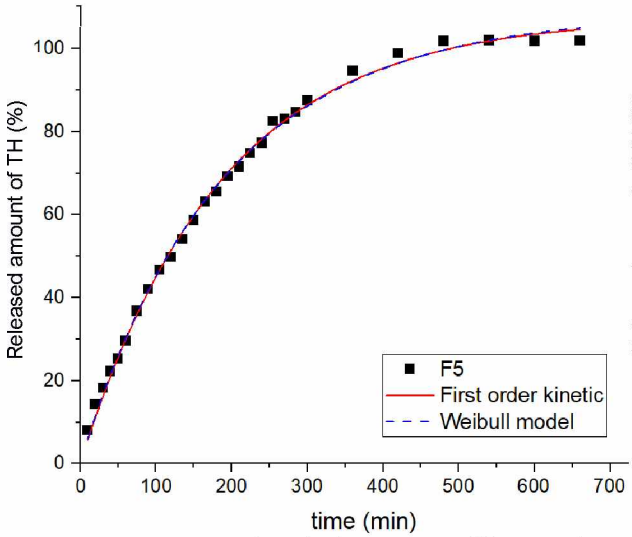


Figure 55: Dissolution profile of formulation F14 fitted to first order model and Weibull model.

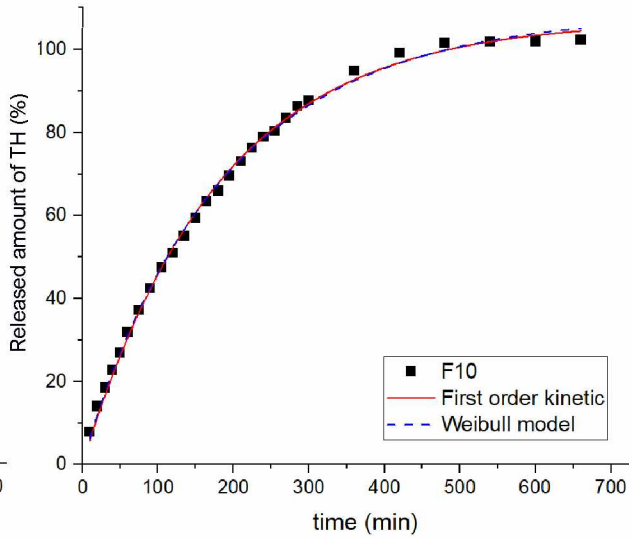


Figure 56: Dissolution profile of formulation F19 fitted to first order model and Weibull model.

Formulation F15 (Figure 57) with tested lubricant Kolliphor® 407, release all 100 % TH withing 420. The dissolution profile of formulation 15 was evaluated by the first order kinetic model and a Weibull mathematical model.

Formulation F20 (Figure 58) with tested lubricant magnesium stearate release all 100 % TH withing 600. The dissolution profile of formulation 20 was evaluated by the first order kinetic model and a Weibull mathematical model.

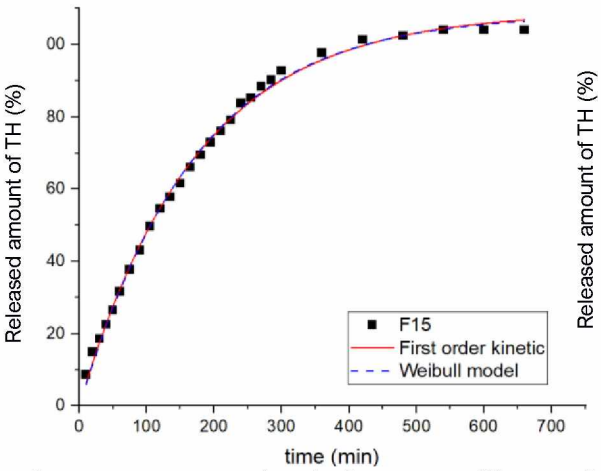


Figure 57: Dissolution profile of formulation F15 fitted to first order model and Weibull model.

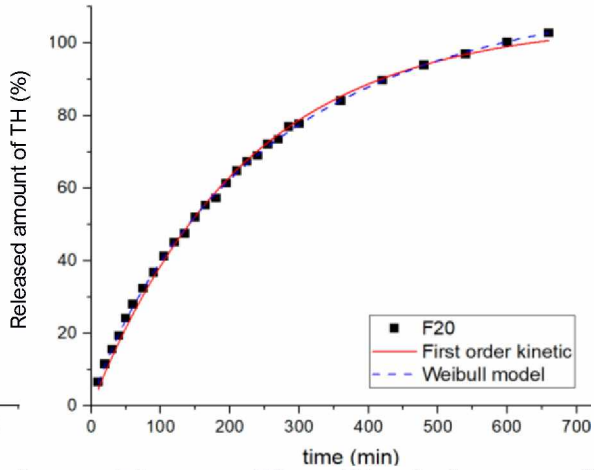


Figure 58: Dissolution profile of formulation F20 fitted to first order model and Weibull model.

For a visual and mathematical comparison of all 4 profiles together, first order and Weibull models (Figure 59, 60) were also used, as well as Korsmeyer-Peppas model (Figure 61). The graphs show that the release profiles of the formulations F5 and F10 have a similar release process. Formulation with magnesium stearate (F20) has it the slowest. And F15 dissolved TH the fastest. These observations are also confirmed by the values of the release constants presented in tables 17 and 18. The table also shows the R^2 value, which averages 0,9974, which in turn means that the first order model is excellent for describing the release kinetics of TH from these formulations.

Table 17: Evaluation of dissolution profiles of SheffCel 75HD100CR group formulations with first order model.

Formulation	**First order kinetic $A_t = A_\infty \cdot (1 - e^{-kt})$**		
	k ± SD	A_∞ ± SD (%)	R^2
F5	0,0054 ± 0,0001	107,65 ± 1,03	0,9971
F10	0,0056 ± 0,0001	107,22 ± 0,91	0,9976
F15	0,0058 ± 0,0001	109,18 ± 0,95	0,9973
F20	0,0045 ± 0,0001	106,04 ± 1,14	0,9974

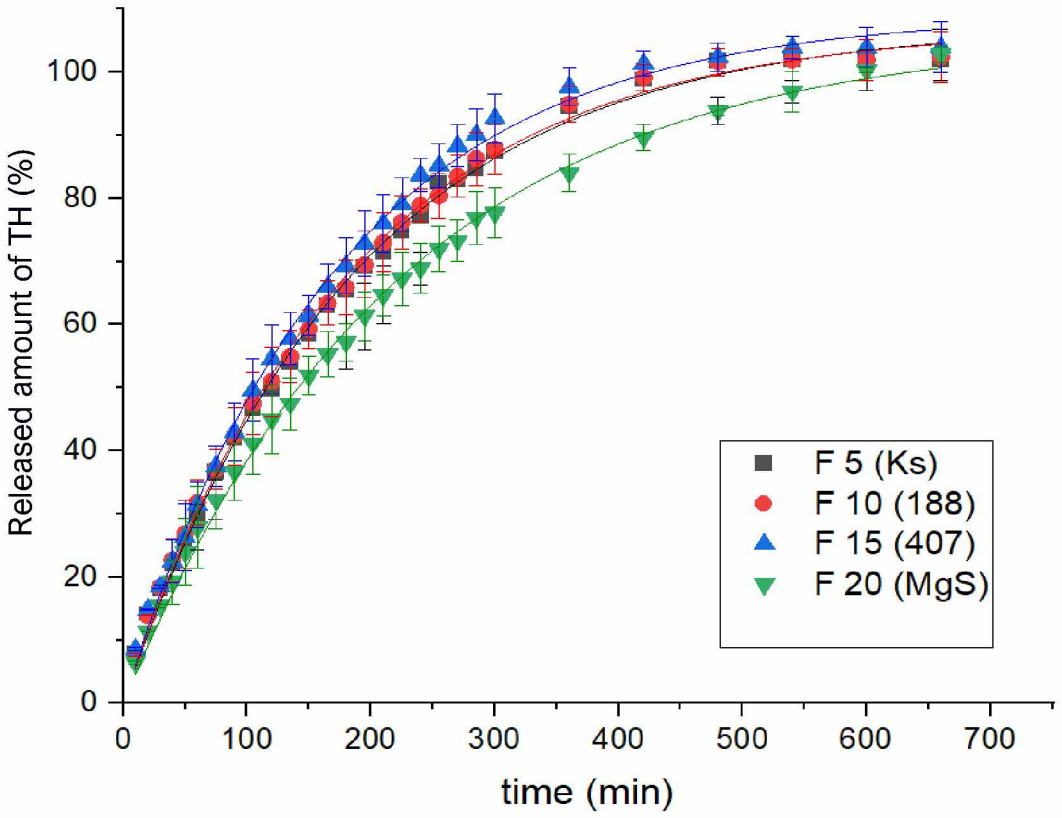


Figure 59: Dissolution profile of SheffCel 75HD100CR group formulations fitted to first order model

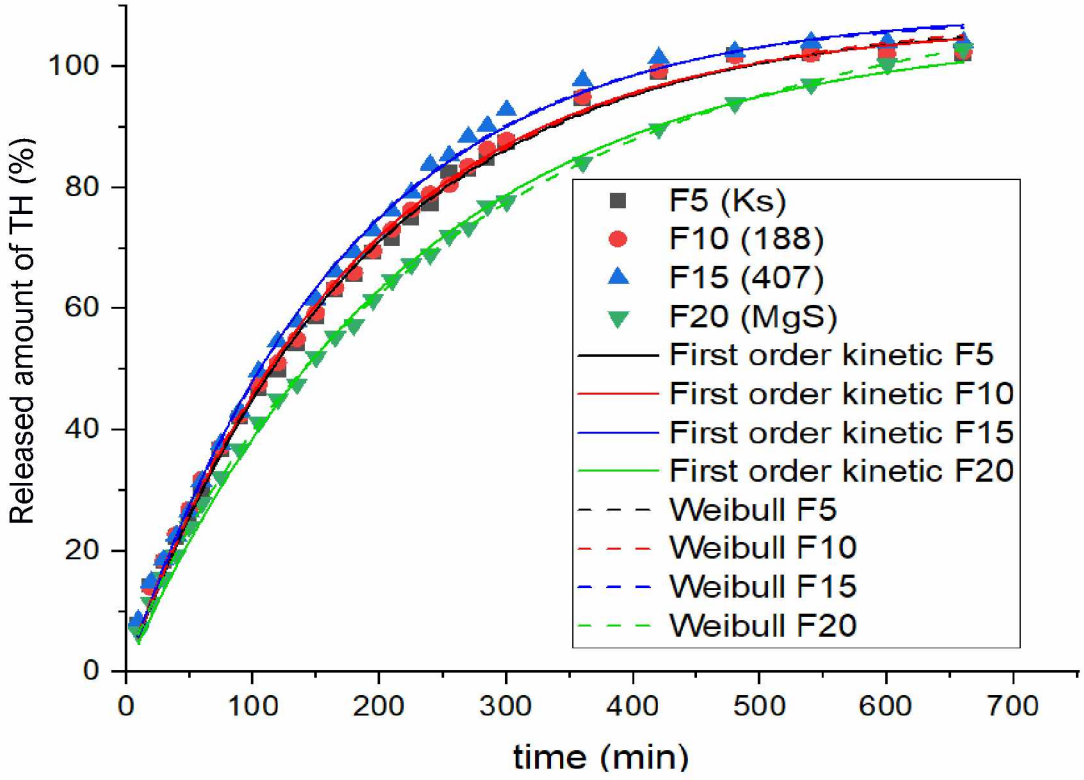


Figure 60: Dissolution profile of SheffCel 75HD100CR group formulations fitted to first order model and Weibull model.

Table 18: Evaluation of dissolution profiles of SheffCel 75HD100CR group formulations with a mathematical Weibull model.

Formulation	Weibull model $A_t = A_\infty - A_\infty \cdot e^{-kt^b}$			
	k ± SD	A_∞ ± SD (%)	b ± SD	R^2
F5	0,006 ± 0,0007	108,6 ± 1,53	0,98 ± 0,025	0,9972
F10	0,007 ± 0,0006	108,77 ± 1,34	0,96 ± 0,021	0,9978
F15	0,005 ± 0,0006	108,37 ± 1,2	1,02 ± 0,024	0,9974
F20	0,0071 ± 0,0003	104,78 ± 1,09	0,88 ± 0,001	0,9996

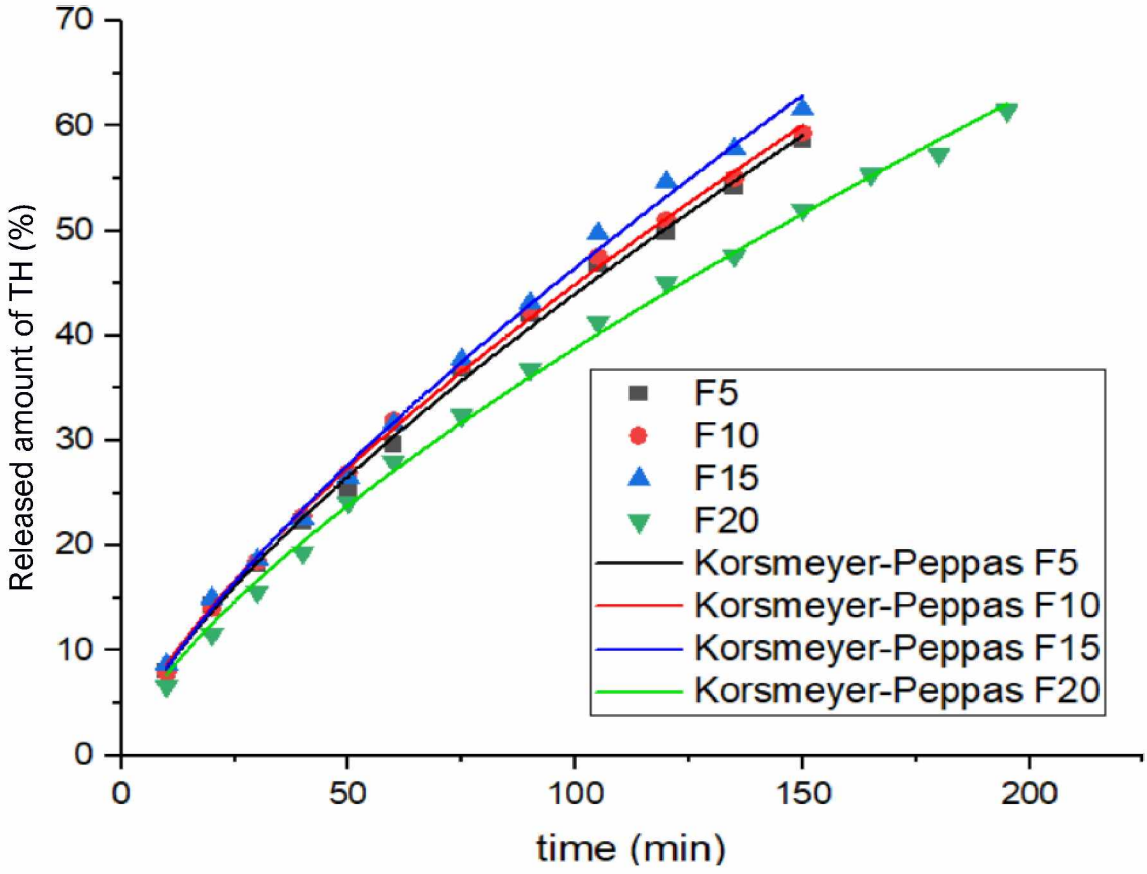


Figure 61: Dissolution profile (first 60%) of SheffCel 75HD100CR group formulations fitted to Korsmeyer-Peppas model.

All the dissolution profiles of SheffCel 75HD100CR group can be fitted to Korsmeyer-Peppas model, which estimated only up to 60 % of the released amount of active pharmaceutical ingredient. The fitting of experimental data using this model is shown in Figure 61. The values of the obtained parameters of the Korsmeyer-Peppas model are summarized in Table 19. The values of parameter n for all four formulations are more than 0,5 and less than 1, so it can be said that the release mechanism of formulations is both diffusion and erosion.

Table 19: Evaluation of dissolution profiles (first 60 %) of SheffCel 75HD100CR group formulations with Korsmeyer-Peppas model.

Formulation	Korsmeyer-Peppas model $\frac{A_t}{A_\infty} = at^n$		
	a ± SD	n ± SD	R^2
F5	1,56 ± 0,11	0,72 ± 0,015	0,9982
F10	1,67 ± 0,10	0,71 ± 0,012	0,9955
F15	1,57 ± 0,11	0,75 ± 0,016	0,9980
F20	1,50 ± 0,10	0,70 ± 0,013	0,9995

3.6 Tablets hardness

Tables 20 and 21 summarize the result of tablet size and strength values. Parameter H represents value of hardness in N, D is diameter in mm of a tablet and WD is tablet thickness (or height) expressed in mm. The table shows the average values obtained from the measurement of 3 three tablets for each formulation.

Table 20: Size and hardness of tablets with Kollidon® SR, Kollidon® 25 and Kollidon® 17.

Lubricant	Parameter	Kollidon® SR		Kollidon® 25		Kollidon® 17	
		F1	**blank**	**F2**	**blank**	**F3**	**Blank**
Kolliwax® S	**H [N]**	347	437	179,5	301	178,5	264
	D [mm]	13,1	13,1	13,11	3,11	13,1	13,1
	WD [mm]	3,41	3,42	3,465	3,39	3,495	3,38
		F6	**blank**	**F7**	**blank**	**F8**	**Blank**
Kolliphor® P 188	**H [N]**	335,5	498	94,5	259	166,5	204
	D [mm]	13,1	13,1	13,17	13,07	13,1	13,1
	WD [mm]	3,47	3,39	3,685	3,34	3,4	3,44
		F11	**blank**	**F12**	**blank**	**F13**	**Blank**
Kolliphor® P 407	**H [N]**	326,5	469	104,5	218	169	191
	D [mm]	13,1	13,1	13,15	13,08	13,11	13,1
	WD [mm]	3,495	3,36	3,665	3,39	3,5	3,57
		F16	**blank**	**F17**	**blank**	**F18**	**Blank**
Magnesium Stearate	**H [N]**	297	409	37	86	150	193
	D [mm]	13,1	13,11	13,17	13,14	13,11	13,1
	WD [mm]	3,405	3,41	3,78	3,7	3,475	3,48

Table 21: Size and hardness of tablets with Methocel K4M and SheffCel 75HD100CR.

Lubricant	**Parameter**	Methocel K4M		SheffCel 75HD100CR	
		F1	**blank**	**F2**	**blank**
Kolliwax® S	**H [N]**	347	437	179,5	301
	D [mm]	13,1	13,1	13,11	13,11
	WD [mm]	3,41	3,42	3,465	3,39
		F6	**blank**	**F7**	**blank**
Kolliphor® P 188	**H [N]**	335,5	498	94,5	259
	D [mm]	13,1	13,1	13,17	13,07
	WD [mm]	3,47	3,39	3,685	3,34
		F11	**blank**	**F12**	**blank**
Kolliphor® P 407	**H [N]**	326,5	469	104,5	218
	D [mm]	13,1	13,1	13,15	13,08
	WD [mm]	3,495	3,36	3,665	3,39
		F16	**blank**	**F17**	**blank**
Magnesium Stearate	**H [N]**	297	409	37	86
	D [mm]	13,1	13,11	13,17	13,14
	WD [mm]	3,405	3,41	3,78	3,7

4 Summary

Twenty formulations of matrix tablets containing tramadol hydrochloride as the active pharmaceutical ingredient were prepared within this thesis. The prepared matrix tablet formulations were studied by the dissolution test method in a dissolution medium of pH = 1.2 for 12 hours (720 min). The absorbance of the studied samples was measured by UV/VIS spectroscopy. Then obtained values were converted into a concentration curve using the calibration line and its equation. Dissolution profiles were plotted showing the time dependence on the amount of released tramadol hydrochloride. All dissolution profiles were evaluated and estimated using mathematical models: first order, Weibull model, Korsmeyer-Peppas model, and Higuchi model. Prosolv® SMCC 90 was used as a binder for the preparation of all matrices. It is a co-processed dry binder consisting of 98 % microcrystalline cellulose and 2 % of colloidal silicon dioxide. Kollidon® SR (a physical mixture of polyvinylpyrrolidone and polyvinyl acetate), MethocelTM K4M CR (hydroxypropyl methylcellulose with viscosity 4000 cP), and SheffCel 75HD100CR (hydroxypropyl methylcellulose with viscosity 100 cP) were used as a retarding component. Kollidon® 25 and Kollidon® 17 (polyvinylpyrrolidone) were used as matrix forming agents. And tested lubricants were Kolliwax® S, Kolliphor® P 188, Kolliphor® P 407, and magnesium stearate.

It is clear that in the case of hypromellose, with an increase in viscosity, less active substance is released and formulations with Methocel K4M have a slower release rate than formulations with SheffCel 75HD100CR. When using Kollidons®, the release rate is as follows: Kollidon® SR < Kollidon® 25 < Kollidon® 17.

For most formulations, the experimental data better fit the Weibull empirical model. This is especially true for formulations where the API is completely released within an hour. But since the Weibull model is only empirical and not kinetic, it cannot be used to predict drug release. The first order model perfectly describes the drug release from formulations based on Kollidon® SR and Methocel K4M and is suitable for formulations based on SheffCel 75HD100CR. Using the Korsmeyer-Peppas model, it was found that the drug release mechanism of most formulations corresponds to abnormal transport, that is, a combination of diffusion and other processes, while a superposition of transport mechanisms is applied. Since there are several of these mechanisms at the same time, they cannot be characterized by a kinetic model. Formulations F9 and F14 showed a diffuse release mechanism, and their experimental data were plotted with the Higuchi model to test the diffusion mechanism. As a result, the diffuse release mechanism for F9 and F14 was confirmed.

During the dissolution test, various changes in the appearance of the tablets were noted. So, tablets with Kollidon® 17 and 25 completely dissolved within an hour, the formulations with Kollidon® SR kept their shape and the formulations with Methocel K4M and SheffCel 75HD100CR at the end of the dissolution test were round and gel-like. In addition, the Methocel formulations had a dry core inside.

The studied lubricants differ significantly in their physical properties: some are hydrophilic and water-soluble (such as poloxamers 407 and 188), while others are lipophilic and insoluble in water (magnesium stearate and Kolliwax® S). The size of the particles and their shape are also different, Kolliwax® S and both Kolliphor®s have round particles and only in magnesium stearate, they are lamellar.

The disintegration of tablets is more influenced by the nature of the lubricant. Thus, the more hydrophobic magnesium stearate and the less hydrophobic Kolliwax® slow down the release time of the API. On the part of particle size and shape, it is the lamellar structure and the small particle size of magnesium stearate that, when mixed, form a hydrophobic layer that prevents the tablets from wetting and therefore increases disintegration time. The delayed effect of lubricants is best seen on extended release formulations (Kollidon® SR Methocel K4M and SheffCel 75HD100CR groups). It looks as follows: Kolliphor® 407 < Kolliphor® 188 < Kolliwax® S < magnesium stearate.

In addition to disintegration time, the effectiveness of the lubricant is reflected in the strength of the tablets. Both Kolliphor® 188 and Kolliphor® 407 had approximately the same hardness values, but in most cases, Kolliphor® 188 had its values higher. Both of them additionally have a binding effect, which contributes to the formation of tablets with a comparatively higher hardness. A particularly expressive increase in hardness was observed in the formulation with Kolliwax® S. Concerning magnesium stearate significantly reduces the hardness of tablets. Such an effect is associated with the inhibition of intergranular binding forces. So, the comparative hardness series looks as follows: magnesium stearate < Kolliphor® 407 < Kolliphor® 188 < Kolliwax® S. It was also observed that in all formulations tested, the blank had a higher hardness than the API tablet.

For further or similar research in this area, it would be interesting to study the effect of mixing time and intensity of the tableting mixture on drug release and tablet hardness. It will also be useful to study the effect of the amount of lubricant on the tablet properties. And to determine the degree of influence of the above parameters (time and intensity of mixing, the amount of

lubricant) on the degree of homogeneity of the prepared tablets using a scanning electron microscope.

In the case of studying formulations based on Kollidon® 17 and 25, the dissolution test is better to set in a way when samples would be taken every 2 minutes in the first 20 minutes.

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