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FACULTY OF CHEMICAL TECHNOLOGY

BACHELOR THESIS

Pardubice 2018 **Alisa D‘yachenko**

UNIVERSITY OF PARDUBICE
FACULTY OF CHEMICAL TECHNOLOGY
DEPARTMENT OF PHYSICAL CHEMISTRY

Preparation and dissolution kinetic study of matrix tablets with extended release of pentoxifylline

Bachelor thesis

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ZADÁNÍ BAKALÁŘSKÉ PRÁCE

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Jméno a příjmení:	**Alisa D'yachenko**
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Název tématu:	**Příprava a disoluční kinetika matricových tablet s prodlouženým uvolňováním pentoxifylinu**
Zadávající katedra:	**Ústav organické chemie a technologie**

Zásady pro vypracování:

1. Zpracujte literární rešerši na téma "Pentoxifylin, jeho vlastnosti a terapeutické účinky."
2. Seznamte se s experimentálním postupem přípravy tablet metodou přímého lisování a připravte tablety s pentoxifylinem a různými excipienty.
3. Proveďte disoluční testy připravených tablet.
4. Získané disoluční profily vyhodnoťte a diskutujte vliv složení tablety na množství uvolněného léčiva.
5. Výsledky zpracujte formou závěrečné zprávy.

Rozsah grafických prací:

Rozsah pracovní zprávy:

Forma zpracování bakalářské práce: **tištěná**

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Vedoucí bakalářské práce: **Ing. Alena Komersová, Ph.D.**
Katedra fyzikální chemie

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V Pardubicích dne 28. února 2017

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V Pardubicích 2. 7. 2018 Alisa D’yachenko

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ANNOTATION:

The subject of this bachelor thesis is the study of the kinetics of the release of the active pharmaceutical ingredient pentoxifylline from hydrophilic matrix tablets. In the theoretical part is discussed controlled release, dissolution process and suitable pharmacokinetic models. The experimental part focuses on the dissolution of hydrophilic matrix tablets in a dissolving medium of pH 1.2 and subsequent evaluation of obtained dissolution profiles using appropriate mathematical models. The result of this part is to determine the release rate constants of pentoxifylline from various dosage formulations and assessment of the effect of excipients (especially retardant components) on the dissolution profile of the drug.

KEY WORDS:

hydrophilic matrix tablets, pentoxifylline, dissolution test, controlled drug release.

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PTX – pentoxifylline

GIT – gastrointestinal tract

HPMC – hydroxypropyl methyl cellulose

MC – methyl cellulose

API – active pharmaceutical ingredient

PF – pharmaceutical form/formulation

UV/VIS – ultraviolet and visible area

Tg – glass-transition temperature

CHF – congestive heart failure

IHD –Ischaemic Heart Disease

COPD – Chronic Obstructive Pulmonary Disease

CR – controlled release

SR – sustained release

AUC – area under the concentration curve

V_d – Volume of distribution

CL – clearance

F – biovailability

LD – loading dose

A – Absorbance

1 Introduction

Pharmaceutical forms (PF) with modified release of an active pharmaceutical ingredient (API) are a young group of drugs, characterized by an altered mechanism and nature of the release. As a result, such PFs give a real opportunity to influence the pharmacokinetics of drugs, leading to changes in the parameters of efficacy and tolerability according to clinical needs. Controlling the process of delivery and release of the drug, you can control the therapeutic effect, avoid overdose and inefficiency, increase the duration of the effect and reduce the frequency of medication.

To create PF with modified release different technologies and methods are used: physical (addition of substances slowing down absorption or membranes acting on the basis of diffusion or osmosis, etc.), chemical (modification of the chemical structure by formation of salts with certain solubility parameters, conjugation with chemical groups - pro-drug), technological (special systems of delivery and release - pellets, microgranules or microcapsules, multilayer shells with predetermined dissolution parameters, etc.).

The most used type of modified release pharmaceutical forms are tablets and capsules.

2 Theoretical part

2.1 Modified release dosage

The first patent of modified release dosage made Israel Lipowski in 1938. He coated pallets to prolong the release of a drug. That work gave start to another development in 1950s that included usage of coated particle approach to sustained drug delivery.[1]

The modified release dosage forms can be divided into groups:

1) Extended release

2) Delayed release

3) Targeted released

4) Repeat action dosage form/pulsating release

5) Prolonged action dosage form[2,3]

2.1.1 Extended release dosage

It is a prolonged dosage form that provides the creation of a stock of a drug and its subsequent slow release in the body. They are used mainly orally, some retard dosage forms are intended for rectal administration.

There are 2 main types of extended release: controlled released (CR) and sustained release (SR). The difference between them is that CR is characterized by a constant release rate of the drug and SR doesn't have that ability.[2,3]

2.1.2 Delayed release dosage

When delayed release dosage form administers to the body, the release of the drug begins later and lasts longer than of the usual dosage form. Medicinal forms with delayed release provide a delayed onset of action of the drug substance.[2,3]

An example of delayed-release dosage forms are ultra-long, ultra-lent suspensions with insulin.

2.1.3 Targeted released dosage

It is a dosage form that release drug near the site of action so the majority of dose interacts with the target tissues. The directing to the target site happens by using the natural conditions of the target organ or tissue; or by using targeting groups for binding to specific receptors on cells. This kind of administration makes the drug specificity more effective and allows minimizing toxicity and site effects.[2,3]

2.1.4 Repeat action dosage form/pulsating release dosage

It is a dosage form, after which administration to the body, the drug substance releases in batches, which essentially resembles the plasma concentrations created by the usual intake of

tablets every 4 hours. This form provides the repeated action of the drug. In these dosage forms a single dose of drug substance is usually separated from the other by a barrier layer that can be film, compressed or coated.[2,3]

Depending on its composition, the dose of the drug substance can be released or after a given time, regardless of the location of the drug in the gastrointestinal tract; or at a certain time in the right part of the digestive tract.

Periodically-released dosage forms include double-layered tablets and double-layered dragees ("duplex"), multi-layer tablets.

2.1.5 Prolonged action dosage form

A dosage forms upon administration of which the initial dose of the drug substance is released into the body and the remaining (maintenance) doses are released at a constant rate corresponding to the elimination rate and ensuring the consistency of the desired therapeutic concentration. Prolonged release dosage forms include wire-frame tablets, tablets and capsules with micro forms, etc.[2,3]

Table 1: Abbreviations that can be used for describing modified drug release

Abbreviations that can be used for describing modified drug release	
EX	Extended release
CR	Controlled release
SR	Sustained (slow) release
DR	Delayed release
TR	Targeted release
PA	Prolonged action
RA/PR	Repeat action/Pulsating release

2.2. Extended release matrix tablets

It is a tablet with continuous, evenly extended release and maintenance action of drugs. For their production auxiliary substances are used, forming a network structure (matrix), in which the drug substance is included. Such a tablet resembles a sponge, the pores of which are filled with a soluble substance (a mixture of a drug substance with a soluble filler-sugar, lactose, polyethylene oxide, etc.).

These tablets do not disintegrate in the gastrointestinal tract. Depending on the nature of the matrix tablets can swell and slowly dissolve or maintain its geometric shape during the entire period of staying in the body, and can output as a porous mass, the pores of which are filled with liquid. Thus, the drug substance is released by leaching.

Dosage forms can be multilayered. It is important that the drug is mainly in the middle layer. Dissolution begins from the side surface of the tablet, while the top and bottom surfaces are initially diffused only by auxiliary substances from the middle layer through the capillaries formed in the outer layers.

The release rate of the drug substance is determined by factors such as the nature of the auxiliary and the solubility of drug substances, the ratio of drugs to matrix-forming substances, the porosity of the tablet, and the process of its preparation. Auxiliary substances for the formation of matrices are subdivided into hydrophilic, hydrophobic, lipid, mineral, and biodegradable.[6]

2.2.1. Hydrophilic matrices

Hydrophilic matrix tablets are the most commonly used tablets for oral administration because of their low cost, easy preparation by direct compression of the powder with use of simple formulation and technologies.[4]

The hydrophilic matrix is able to absorb a large amount of water without dissolving. When hydrophilic matrices are exposed to dissolution fluid, steep water concentration gradients are formed between the dissolution fluid and the outermost surface of matrix tablet. This results in - water imbibition into the polymer matrix network. Inside of the pill happen, both axial and radial directions of mass transport can be manifested which dependence on the water diffusion coefficient and the matrix swelling. When dry tablets are administrated into the liquid system, the diffusion coefficient is very low, whereas in highly swollen gels, it is of the same magnitude as pure water. So, the liquid acts as a plasticizer and the glass transition temperature (Tg) reduces from somewhere between 154 – 184 °C to around the system temperature, 37 °C. Once the Tg equals the temperature of the system, the polymer chains relax and eventually disentangle increasing the molecular surface area. This phenomenon of polymer chain relaxation is termed ‘swelling’ and the continuous inward ingression of liquid breaks the hydrogen bonds formed during tablet compaction and can lead to the development of new hydrogen bonds accommodating water molecules. Therefore, the reduction in Tg and formation of new hydrogen bonds results in the swelling of polymer chains. As a consequence, a thick gelatinous layer appears on the surface of matrix tablets, commonly known as a gel layer, as Methyl Cellulose (MC) and Hydroxypropyl Methyl Cellulose (HPMC) pass from the amorphous glassy state to the rubbery state.[4]

The hydrophilic matrix tablet can be divided into three different regions (Figure 1). The highly swollen outer region (erosion front) has the highest amount of water molecules but it is mechanically weak. It acts as a diffusion barrier preventing water penetration into the other two

regions. The middle region (dissolution front) is moderately swollen and is relatively stronger than the outer one. The core of the matrix tablet which actually forms the innermost region (swelling front), remains essentially dry and holds its glassy state for a longer period of time. Moreover, there is evidence that a fourth front (penetration front) is also present, between the swelling and dissolution fronts, adding further complexity to the system.[4,5]

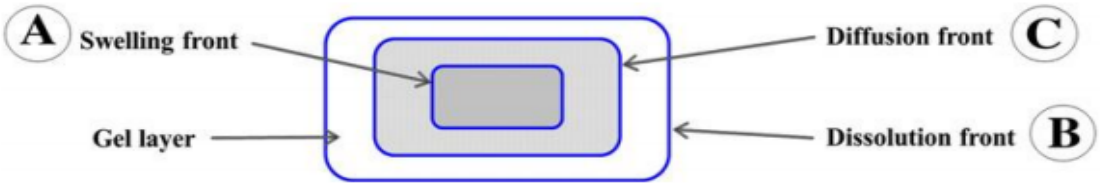

Figure 1: Scheme of the Hydrophilic Matrix after Entry of the Dissolution Medium.[5]

The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups[6]:

1) Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.
2) Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.
3) Polymers of acrylic acid: Carbopol-934, the most used variety.

2.2.2. Hydrophobic matrix

The drug substance is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. The polymer forms the channels in which the drug is dispersed. The release of the drug happens by diffusion from the tablet through the porous network of already existing pores and pores that are created by dissolution of the drug particles.[7]

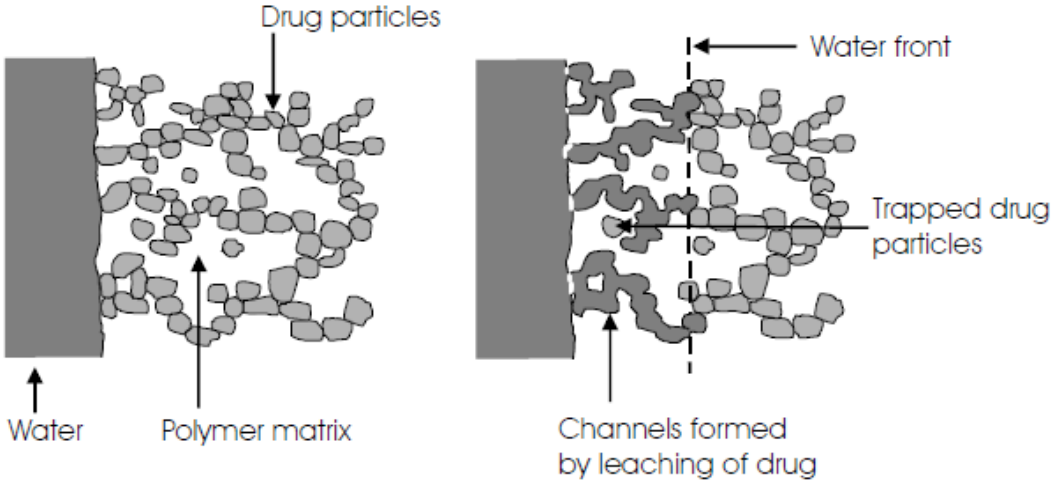

Figure 2: Schematic representation of a leaching-based release mechanism.[7]

As materials for the hydrophobic matrix can be used insoluble polymers polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. To create

channels in the polymer layer insoluble in water are added water-soluble substances (Polyethylene glycol, polyvinylpyrrolidone, lactose, pectin, etc.) are added. Washing out of the pill skeleton, they create conditions for the gradual release of the drug. Such types of matrix tablets can become inert in the presence of water and gastrointestinal fluid.

2.2.3. Lipid matrix

These matrices are made from natural lipid waxes or from synthetic mono/di/triglycerides, hydrogenated vegetable oils, fatty higher alcohols, etc. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.[6]

2.2.4. Mineral matrix

Mineral Matrices consist of polymers which are obtained from various weeds. Example are Alginic acid which is hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.[6]

2.2.5. Biodegradable matrix

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and polyanhydrides.[6]

2.3. Pentoxifylline

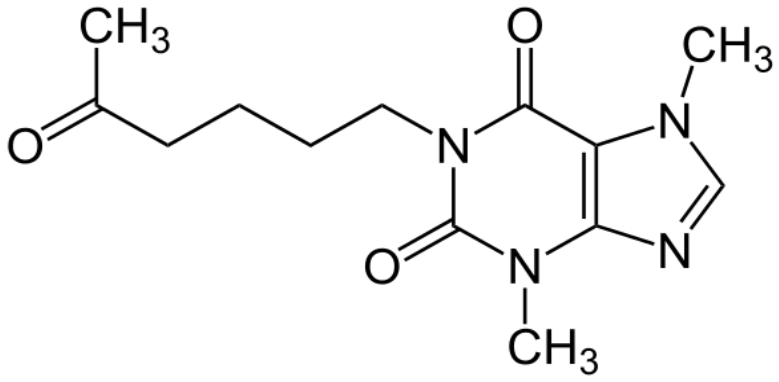

Figure 3: Structural formula of Pentoxifylline.[8]

Pentoxifylline is a derivate of theophylline and caffeine. It is white crystalline powder that is well soluble in water and ethanol, and sparingly soluble in toluene. PTX (pentoxifylline) was developed by Werke Albert.[8]

Chemical name: 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione

Molecular formula: $C_{13}H_{18}N_4O_3$

Molecular mass: 278.3 g/mol

2.3.1. Indications and usage

1) Disorders of cerebral circulation:

- ischemic and post-apoplexy states; Cerebral atherosclerosis (dizziness, headache, memory impairment, sleep disturbances), discirculatory encephalopathy, viral neuroinfection (prevention of possible microcirculatory disturbance);
- IHD, condition after a myocardial infarction;
- Acute circulatory disorders in the retina and choroid of the eye;
- Otosclerosis, degenerative changes on the background of the pathology of the vessels of the inner ear with a gradual decrease in hearing;
- COPD, bronchial asthma.

2) Violation of peripheral circulation (Raynaud's disease, endarteritis, trophic tissue disorders (post-thrombotic syndrome, varicose veins, shin sores, gangrene, frostbite).

3) Diabetic nephroangiopathy and other diabetic angiopathies.

2.3.2. Contraindications

Pentoxifylline should not be used in patients who has:

- acute myocardial infarction;
- massive bleeding;
- hemorrhage in the brain;
- extensive hemorrhage in the retina of the eye;
- pregnancy;
- lactation;
- hypersensitivity to pentoxifylline, other methylxanthine derivatives or drug components.

Should be used with caution:

- lability of blood pressure (tendency to arterial hypotension);

- CHF;
- stomach ulcer and 12 duodenal ulcer (for oral intake);
- state after recent surgery;
- hepatic and / or renal failure;
- age to 18 years (efficacy and safety are not studied).

2.3.3. Site effects

Pentoxifylline can cause the violations of the following systems:

- Nervous system: headache, dizziness, anxiety, sleep disturbances, convulsions.
- Skin and subcutaneous fat: hyperemia of the face skin, "hot flashes" of blood on the face skin and upper chest, swelling, increased nails brittleness
- Digestive system: dry mouth, decreased appetite, intestinal atony, exacerbation of cholecystitis, cholestatic hepatitis.
- Sensory organs: blurred vision, scotoma.
- Cardiovascular system: tachycardia, arrhythmia, cardialgia, progression of angina pectoris, lowering blood pressure.
- Hematopoiesis and homeostasis systems: thrombocytopenia, leukopenia, pancytopenia, hypofibrinogenemia.

Allergic reactions: itching, skin hyperemia, urticaria, angioedema, anaphylactic shock.

Overdose Pentoxifylline. Symptoms: weakness, dizziness, decreased blood pressure, fainting, tachycardia, drowsiness or agitation, loss of consciousness, hyperthermia, areflexia, tonic-clonic convulsions, signs of gastrointestinal bleeding (vomiting like "coffee grounds"). Acute toxicity is shown in Table 2.

Treatment: gastric lavage followed by the introduction of activated charcoal, symptomatic therapy (including measures aimed at maintaining respiration and blood pressure), emergency measures for bleeding.

Table 2: Acute toxicity (LD_{50}) of Pentoxifylline.[9]

SPECIES	ROUTE	LD_{50}(MG/KG)
Mouse	p.o	1385
	i.v.	197
	i.p	239
Rat (SD)	p.o	1772
	i.v.	231

2.3.4. Pharmacodynamics properties / Mode of action

The API is a methylxanthine derivative, an angioprotector, improves microcirculation.

The mechanism of action of pentoxifylline is associated with the inhibition of phosphodiesterase and with the accumulation of cyclic adenosine monophosphoric acid in the vascular cells of the smooth muscles, in blood cells and in other tissues and organs. PTX blocks adenosine receptors.

It inhibits platelet aggregation, increases the elasticity of erythrocytes, reduces the increased concentration of fibrinogen in the plasma and strengthens fibrinolysis, which reduces the viscosity of blood and improves its rheological properties. In addition, PTX has a weak myotropic vasodilator effect, somewhat reduces the overall peripheral vascular resistance and has a positive inotropic effect, improves oxygen supply (the most - of the limbs and central nervous system, to a moderate extent - in the kidneys). The drug slightly dilates the coronary vessels.[9]

2.3.5. Pharmacokinetics

Metabolism mainly occurs in the liver, where a number of pharmacologically active metabolites are formed, the main ones being 1- (5-hydroxyhexyl) -3,7-dimethylxanthine (metabolite I) and 1- (3-carboxypropyl) -3,7- Dimethylxanthine (metabolite V). C_{max} of the pentoxifylline and main products of its biodegradation are achieved within 1 hour and the concentration of metabolites in blood plasma is 5 to 8 times higher than the concentration of the starting substance.[10]

Elimination:

Elimination half-life of the pentoxifylline is 1.6 hours. It is eliminated mainly by kidneys in the form of metabolites (more than 90%), less than 4% of the administered dose is excreted with feces, can be excreted by lactating mammary glands.[10]

Pharmacokinetics in special clinical cases

The elimination of metabolites is slowed in patients with severe impairment of renal function.

Elimination half-life of the PTX elongation was noted in patients with impaired liver function.[10]

2.4. Commercial drugs

In the middle of the 20th century, myotropic antispasmodics were the main medicines for the treatment of angiopathy of the central and peripheral vessels. But these drugs eliminated only spasm, and practically did not affect the rheological properties of the blood. Everything changed when in 1972 the employees of the German pharmaceutical company “Hegst” synthesized Pentoxifylline, which was given the original name Trental. Nowadays Pentoxifylline is an active

substance of many drugs and can be expressed in different pharmaceutical form, such as solution for injection, prolonged-release tablet, modified-release tablet, capsule and enteric-released tablet.

2.4.1 Pentoxifylline brands in Czech Republic

Pentoxifylline as an active compound of the following drugs which are common in the market of Czech Republic (Table 3).

Table 3: List of drugs containing PTX in the Czech market.[11]

Name of the product	Pharmaceutical form	Package
Agapurin 20MG/ML	Solution for injection	5X5ML
IAGAPURIN SR 400 MG	Prolonged-release tablet	100; 50; 20
AGAPURIN SR 600 MG	Prolonged-release table	100; 50; 20
PENTOMER RETARD 400 MG	Prolonged-release tablet	100; 50; 20
PENTOMER RETARD 600 MG	Prolonged-release tablet	100; 50; 20
TRENTAL 20MG/ML	Solution for infusion	25X5ML; 5X5ML
TRENTAL 400 MG	Modified-release tablet	100; 20
TRENTAL 400 MG	Prolonged-release tablet	100; 20

2.4.2. Pentoxifylline brands in world

The next drugs containing PTX can be found in the world market (Table 4).

Table 4: List of some drugs containing PTX in the world market.[12]

Name of the product	Pharmaceutical form	Package
FLEXITAL 200 MG	Capsule/tablet	10
FLEXITAL 400 MG	Capsule/tablet	10
FLEXITAL 20MG/ML	Solution for injection	5X15ML
KINETAL 400 MG	Capsule/tablet	10
TRENTAL 300 MG	Infusion	5X15ML
TRENTAL 400 MG	Modified-release capsule/tablet	100
TRENTAL 300GM/15ML	Solution for injection	15ML
TRENTAL 400 MG	Enteric release tablet	15

2.5 Mathematical description of the drug release from the dosage form

The goal of pharmacotherapy is to achieve the desired therapeutic effect with minimal side effects. The concept of "rational use of medicines" includes both the selection of the necessary drugs and the determination of its dose. A rational approach is to combine the principles of pharmacodynamics and pharmacokinetics, and if pharmacodynamics characterizes the "concentration-effect" relationship, the pharmacokinetics studies the dose-concentration relationship. The "standard" dose of a drug, determined in clinical trials, is some average value that is not always suitable for all patients due to physiological, pathological and other factors, so knowledge of pharmacokinetics and basic pharmacokinetic parameters is necessary for an individual approach for choosing the drug and dose of it.

Pharmacokinetics is the section of pharmacology that studies the kinetic patterns of chemical and biological processes occurring with a drug in the body. It is the science of chemical transformations of a drug in the body.

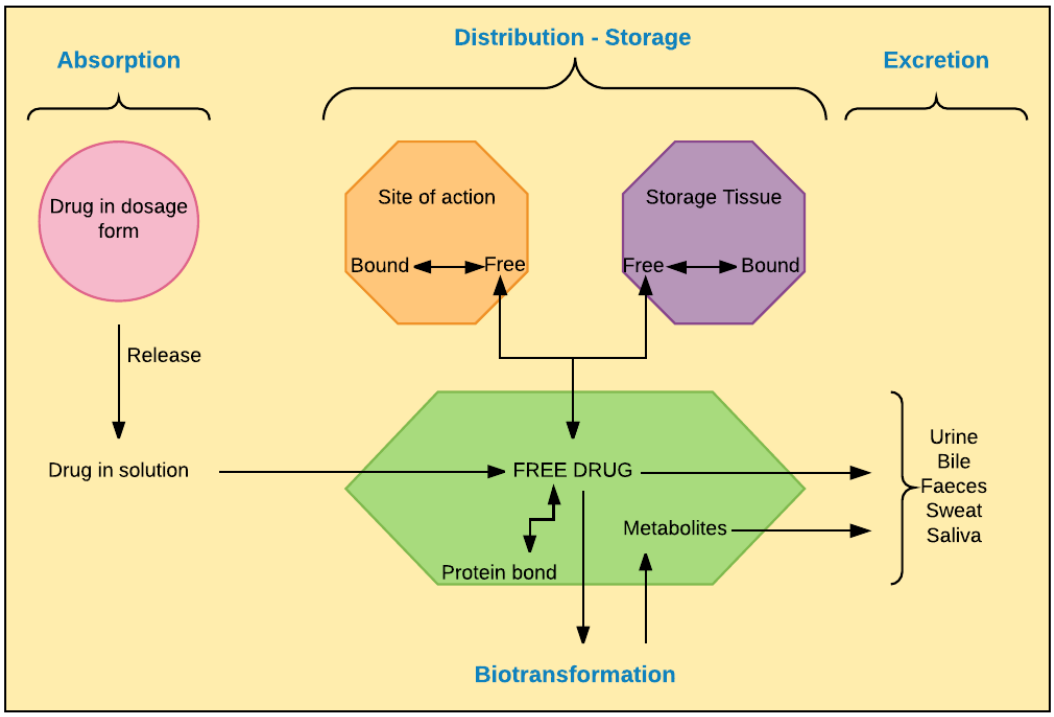

Figure 4: The pharmacokinetics process [13]

2.5.1 Pharmacokinetics action (ADME)

The four cornerstones of pharmacokinetics (Figure 4):

- Absorption (input)
- Distribution (drug in tissues)
- Metabolism (metabolites in tissues)
- Elimination (excretion/output)

Absorption and distribution depend on pharmaceutical formulation.

2.5.2 Pharmacokinetics parameters

In order to quantify the distribution processes of a drug in the body, a mathematical description of pharmacokinetics and different pharmacokinetics metrics are used. These parameters can be divided into primary, derived and secondary.

The primary parameters - V_d, clearance CL

Derived parameters - the elimination rate constant, elimination half-life $t_{1/2}$

Secondary parameters - bioavailability F, area under the concentration curve (AUC)

Volume of distribution (V_d)

This is the hypothetical volume of body fluid that is necessary for the uniform distribution of the entire amount of a drug (dose) in a concentration that is similar to the

concentration in the blood plasma. High values of the volume of distribution indicate that the drug actively penetrates into biological fluids and tissues. If the drug is actively associated, for example, with fat tissue, its concentration in the blood can almost instantaneously become very low, and the volume of distribution will reach several hundred liters, exceeding the actual volume of body fluids. The volume of distribution depends on various factors: the physicochemical properties of the active compound (molecular weight, ionization level and polarity, solubility in water and fats), physiological factors (age, sex, total body fat). The volume of distribution is used in the selection of the dosing regimen for the calculation of LD (loading dose) required achieving the desired concentration of the drug in the blood.[14]

Clearance CL

Clearance is volume of plasma or blood, which is completely cleared from the drug per unit of time. Due to the fact that the main way of elimination are the kidneys and liver, the total clearance is the sum of the renal and hepatic clearances. The main physiological factors determining the clearance are: the functional state of the main physiological systems of the body, the volume of blood flow and the rate of blood flow in the organ. [14]

Elimination rate constant (*k*)

It is a percentage reduction of the concentration of the substance in the blood per unit of time (reflects the proportion of the drug withdrawn from the body per unit time). Elimination consists of the processes of biotransformation and excretion. The rate constant of elimination is characterized by elimination in the framework of a single-chamber model with a linear character of the elimination process.[14]

Biological half-life ($t_{1/2}$)

Biological half-life (elimination half-life) is the time necessary to reduce the concentration of the drug in the blood by 50% as a result of elimination. The relationship between the biological half-life and the elimination rate constant is important for the choice of the interval between doses, and also for determining the time interval necessary to achieve an equilibrium concentration with repeated administration of drugs.[14]

Bioavailability (F)

Bioavailability is part of the drug dose that has reached the systemic blood flow after an extravascular injection (in this case, not a whole amount of the drug reaches the systemic blood flow). It is expressed in values from 0 to 1 or in percent.**[14]**

Area Under the Curve (AUC)

AUC is directly proportional to a single dose of drugs and is inversely proportional to the overall clearance of the drug. It represents the extent of drug absorption.[15]

2.5.3 Mathematical models of drug release from drug forms

Unlike the immediate release of drug, extended release forms must be predicted to show that the new dosage form of the drug dissolves in the proper manner. For this, different mathematical models are used. These models describe the amount of a drug that has been released per unit of time; can help in choosing the right geometry of a pill; are needed in optimization of the release kinetic; improve overall therapeutic efficacy and safety of these drug.

A large number of mathematical models were developed to describe the release rate of drugs from different drug delivery systems. Some of important models are:[16]

1. Diffusion model
2. Zero order kinetic model
3. First order kinetic model
4. Higuchi model
5. Korsemeyer-peppas model (the power law)
6. Hixson-crowell model
7. Weibull model
8. Baker-Lonsdale model
9. Hopfenberg model
10. Gompertz model
11. Sequential layer model

First order kinetic model

The model is used to describe absorption and elimination of drug *in vivo*. The release of the drug which follows first order kinetics can be expressed by the equation:

$$\frac{-d[A_s]}{dt} = k_1[A_s] \qquad (1)$$

Where k_1 is first order rate constant expressed in units of 1/time, $[A_s]$ is the current drug concentration in the solid dosage form and t is time.

Rearranging and integration both sides of the equation give the dependence of the concentration (amount) of the drug in the dosage form A_s on the time in exponential view.

$$A_s = A_0 e^{-k_1 t} \qquad (2)$$

After logarithmization of the equation (2) above we get:

$$\ln A_s = \ln A_0 - k_1 t \qquad (3)$$

Where A_0 is the maximum amount of released drug from dosage form at time $t = \infty$.[16,17]

To describe the amount of the released drug during the dissolution of the tablet (A_l), the following formula is used:

$$A_l = A_\infty \left(1 - e^{-k_1 t}\right) \quad (4)$$

Weibull model

This model can be successfully applied to almost all kinds of dissolution curves and is used to explain the release of drug. The Weibull model is described by following equation:

$$A_l = A_\infty - e^{\frac{-(t-T)^b}{\alpha}} \quad (5)$$

Where *m* is the accumulated fraction of the drug in time, *t*; the scale parameter, α, represents the time. The location parameter, *T*, determines the lag time in various cases zero. And *b* is a shape parameter that characterizes the curve. When (b=1) the curve has an exponential look, (b>1) represents a S-shaped curve with upward curve followed by turning point, and (b<1) parabolic with the higher initial slope after that consistent with the exponential.

Weibull model, unlike the first-order kinetic model, is not based on fundamental physical law or kinetic fundament. It is a statistical model and it does not characterize the dissolution kinetic properties of the drug exactly.[18,19]

2.6 Dissolution tests

The quality of medicines and their interchangeability can be assessed using the dissolution test, designed to assess the release rate of the active ingredient from solid dosage forms, such as tablets and capsules. Solid dosage forms have many advantages: easy in use, accuracy of dosing, and the possibility of localizing the action of a drug substance in a particular section of the gastrointestinal tract. The effectiveness depends on the rate of dissolution of the drug substance. The Dissolution test allows determining how quickly the drug dissolves in the body, and theoretically to predict after what time its therapeutic effect will begin to manifest.[20]

Table 5: Recommended dissolution mediums

pH	Dissolution buffer
1,2	NaCl; HCl
2,5	NaCl; HCl
3,5	Glycine; NaCl; HCl
4,5	KH_2PO_4; HCl/NaOH
6,8	KH_2PO_4; NaOH
7,2	KH_2PO_4; Na_2HPO_4;

The test conditions are the closest to the physiological parameters. The dissolution test is carried out on the devices "Rotating basket", "Blade stirrer" and "Flowcell", the speed of rotation of the blade or basket and the flow rate are selected during the experiment. As a dissolution medium, solutions are used whose pH values correspond to pH values in different parts of the gastrointestinal tract (Figure 5, Table 5). If the drug's release from the tablet or capsule should occur in the stomach, this tablet/capsule will dissolve well in a low pH buffer solution. However, the medicinal substances that make up the drug have different physicochemical properties, therefore, for each drug. A dissolution medium is selected according to its chemical structure and the composition of the auxiliary substances. As the dissolution medium, artificial gastric and intestinal juice without the addition of enzymes can be used.[21]

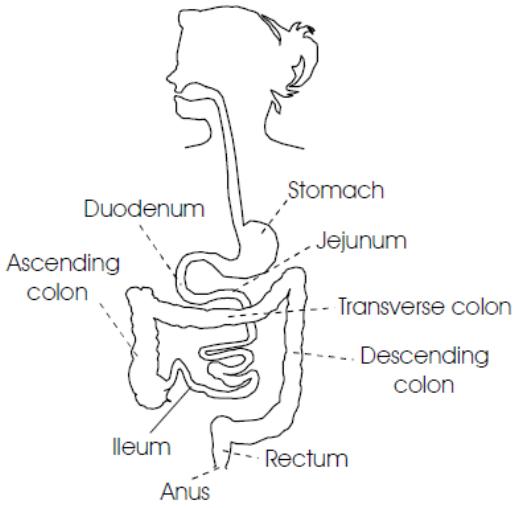

Figure 5: The gastro-intestinal tract and potential sites for drug delivery.[7]

The volume of the dissolution medium corresponds to the volume of the contents of the stomach in a state of fasting plus a glass of water. Usually, the tablets or capsules are dissolved in 500 ml of a buffer solution, but the 900ml volume is used as well. The temperature of the dissolution medium should be the same throughout the experiment and correspond to the body fluid temperature of 37 °C. Sampling is carried out at regular intervals depending on the duration of action of the drug substance. Thus, for immediate release dosage forms, the dissolution time is 45 minutes, and for prolonged-release tablets or capsules, the test is carried out for 24 hours (Table 6).[20,21]

Table 6: Average GI transit time for solid dosage forms.[7]

	Transit time (h)		pH	
	Pellets	**Tablets** [a]	**Fasted**	**Fed**
Stomach	0,5-1 3,6 (1,5-5)	0,5 9,6 (3,3-14)	3-4	1,5-3
Small intestine	3,1 (1,5-5,7)	2,0 (1,0-3,3)	± 5 proximal part ± 7,5 ileocecal junctions	
Colon	28 (10-55)	15 (3,8-26)	± 6,4 ascending colon ±7 descending colon	
Total	35 (10-55)	26 (9,5-42)		

[a] for non-disintegrating tablets with diameter 9mm.

2.6.1 Apparatuses

The performances of dissolution apparatuses are highly dependent on hydrodynamics due to the nature of dissolution testing. The designs of the dissolution apparatuses and the ways of operating dissolution apparatuses have huge impacts on the hydrodynamics, thus the performances. Hydrodynamic studies in dissolution apparatuses were carried out by researchers over the past few years with both experimental methods and numerical modeling such as Computational Fluid Dynamics (CFD).

Paddle

It is the most common method of studying solubility. The dissolution test is performed inside the vessel of a certain geometry and volume. The sample is placed directly in the medium, which during the experiment is agitated by the agitator blades. The method provides highly reliable results in the analysis of virtually all types of solid dosage forms, with the exception of sparingly soluble tablets. Including, it can be used for research of light pop-up samples, which are supplied with special weighting agents.[22,24]

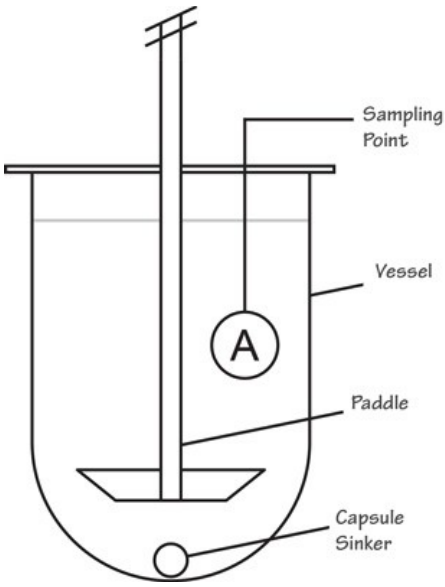

Figure 6: Schematic description of paddle method.[23]

Rotating basket

The device is arranged and operates as follows: There is a water bath or heating jacket on the basis. The water bath keeps a constant temperature of the solvent medium in a vessel made of glass or other inert, transparent material. A reticulated, cylindrical basket with the testing drug is placed into the vessel. The basket is connected to metallic drive shaft that is rotated by the stirring element connected to the electric motor.[24,25]

The method is used to test capsules and other samples that tend to float to the surface. Not suitable for testing the solubility of disintegrating tablets: the flakes can clog the cells of the basket, so the reliability of the test results is reduced.[24,25]

Figure 7: Rotating basket for dissolution tests [26]

Flow through cell

The device consists of a vessel for the dissolution medium, a pump with a sinusoidal velocity profile of 120 ± 10 pulses/min, a flow cell and a water bath that keeps the temperature within the test within the required limits. The flow through cell dissolution method is performed to dissolve prolonged and sparingly soluble drugs, powders, active pharmaceutical ingredients, suppositories, suspensions, liposomes, microspheres, gels and medical implants. Can operate in two different modes:[24,27]

1) **An open system.** Open system mode has been used to test hardly soluble compounds (in a flow cell, the concentration of the test compound is 2-5 times lower than the saturation level) and modeling the dissolution of these compounds in conditions of physiological transit in the gastrointestinal tract. Open systems are also well suited for testing extended-release and modified-release drug compounds due to the possibility of successively changing the dissolution medium, which also makes it possible to vary the pH during testing.[27]

   A closed system. Closed system modes are the most used. They allow to flexibly regulate the volume of the dissolution medium from 15 to 4000 ml, and allow to test dosage forms that is difficult to reproduce in the usual vessel of the dissolution test (powders, suspensions, implants, gels, ointments, microspheres, suppositories forms, etc.)[27]

Reciprocating Cylinder

The device consists a cylindrical glass vessel with a flat bottom, a glass swing cylinders, the inert fittings, upper and lower cylinder screens made of non-absorbent inert material, an electric motor and a drive element that drives the cylinders inside the vessels. The vessels are putted in a water bath, which allows maintaining the temperature during the test in the range 37 ± 0.5 ° C. The device is designed in such a way that no part of the assembly has a significant effect on vibration. Vessels are supplied with caps, which protect the dissolution medium from evaporation during the test. The cylinders perform reciprocating movements, passing a distance of 9.9-10.1 cm. At this time interval or time point, the swinging cylinder is lifted and a part of the medium is taken approximately midway between the surface of the medium and the bottom of the vessel.[24,28]

The reciprocating cylinder is used for testing delayed-release drugs and for analysis of poorly soluble immediate-release drugs.

2.7 Excipients for preparation of hydrophilic matrix tablets

2.7.1 Prosolv® SMCC 90

PROSOLV® SMCC (silicified microcrystalline cellulose). It is a product of two components: microcrystalline cellulose (MCC) (98%) and colloidal silicon dioxide (CSD) (2%). A high functionality and multifunctional excipient, it requires less complex processing, has high inherent functionality, and passes that functionality on to the drug formulation. PROSOLV® SMCC is unique in that it imparts both optimum compaction and superior flow to formulations, and has a great balance between flowability and compressibility. It also exhibits both brittle fracture and plastic deformation characteristics, leading to superior binding properties. The production process of PROSOLV® SMCC leads to homogeneous and much finer CSD particle size distribution. This results in a five-fold specific surface area increase, as well as in a 30-50% compaction increase compared to traditional MCC. The increased surface area enables superior flow and increased compaction and results in improved content uniformity and stability in the formulation.[29]

Silicified microcrystalline cellulose is used as a binder and filler to produce complex dosage forms. It has better compaction than conventional microcrystalline cellulose and is designed for both wet granulation and direct compression.[29]

When used for direct compression, PROSOLV® SMCC has many advantages when used as a filler for capsules, or can replace granulations, while significantly reducing the number of required excipients and use levels. PROSOLV® SMCC formulations produce distinctive, uniform, and cost-effective tablets.[29]

2.7.2 Disintequik™ MCC 25

It is a co-processed dry binder containing 75% of α-lactose monohydrate and 25% microcrystalline cellulose. Disintequik MCC 25 is designed for direct tableting operations where hard tablets and fast disintegration is required. The combination of α -lactose monohydrate and microcrystalline cellulose allows microcrystalline cellulose. And the fast disintegration is ensured by the presence of microcrystalline cellulose.[30,31]

2.7.3 Magnesium stearate

The main representatives of lubricants are stearic acid and its salts of calcium or magnesium. Magnesium stearate is used in a powdered and granular state. The granule of stearate is an agglomerate of thin primary particles, which, due to shear, gradually, by layers, are distributed along the wall of the matrix. Thus, the resulting film provides a long lubricating

effect, extends the disintegration time of the compressed tablet and reduces the dissolution rate. [32,33]

While the developing the formulation, it should be noted that magnesium stearate can interact with API. For example, with aspartame, acetylsalicylic acid, some vitamins and most alkaloids.[32,33]

2.7.4 HPMC

Hydroxypropylmethylcellulose, or hypromellose has a wide range of applications: can be used as a viscosity-increasing agent, film-former, stabilizing agent, dispersant, emulsifier, coating agent, rate-controlling polymer for sustained release, suspending agent, tablet binder. It is economically advantageous in use as an auxiliary substance to produce oral, ophthalmic and topical pharmaceutical formulations. The role of MHPC as an excipient depends not only on a type of hypromellose, but also on it amount in a PF. For example, methocel in concentration 2%-5% w/w may be used as a binder;10%-80% w/w may be added as a high-viscosity grades in retard release forms; 2%-20% w/w is available for film-forming; 0,45%-1% w/w is used as a thickening agent to vehicles for eye drops.

First of all, it should be noted the versatility hypromellose as a binder. Due to the fact that several types of HPMC were synthesized, having different viscosity of the solution, it became possible to use it in the synthesis of dosage forms different, not only in consistency, but also on ways of application (for example: manufacture of capsules, plastic bandages or wetting agent for hard contact lenses).[33]

METHOCEL™ Hypromellose as the controlled-release agent in hydrophilic matrix systems offers a wide range of properties. In the Table 7 are shown characteristics of *Methocel™ K4M Premium CR* and *Methocel™ K100M Premium CR*, that were used in experiment.[34]

- A letter (E, F or K) identifies hypromellose; substitution type K has gelation temperature = 70°C in 2% aqueous solution.
- Number identifies viscosity; 4M type has viscosity 4,000 mPa·s 2% solution in H_2O 20°C.
- Premium means that product meets all requirements of the UPS.
- CR is a physical form, controlled-release drug.

Table 7: Typical Properties of selected METHOCEL™ CR Grade Products[34]

METHOCEL™ Premium Product Grade	-	K4M Premium CR	K100M Premium CR
Methoxyl, %	USP	19–24	19–24
Hydroxypropoxyl, %	USP	7–12	7–12
Substitution type	USP/EP	2208	2208
Chlorides, max., %	EP	0,5	0,5
Apparent viscosity, 2% in water at 20°C, cP	USP	3000-5600	80000-120000
Apparent viscosity, 2% in water at 20°C, mPa·s	EP	2308-3755 [2903 Nom]	16922-19267 [18243 Nom]
ID Test A, B, C	UPS	Pass	Pass
ID Test A, B, C, D, E, F	EP	Pass	Pass
Opalescence of solution	EP	Pass	Pass
Solution color, yellowness, 1% in water	EP	Pass	Pass
pH, 1% in water	EP	5.5–8.0	5.5–8.0
Loss on drying, max., %	USP/EP	5	5
Organic impurities, volatile	USP	Pass	Pass
Residue in ignition, max., %	USP	1,5	1,5
Ash, sulfated, max., %	EP	1	1
Heavy metals, as Pb, max., ppm	USP/EP	10	10
% through 40 mesh sieve	None	>99%	>99%
% through 100 mesh sieve	None	>90%	>90%

3. Experimental part

3.1 Laboratory equipment and instruments

- weighing scales PT 210 (Sartorius, Göttingen, Germany)
- analytical scales AA-200 (Denver Instrument Company, Colorado, USA)
- dissolution apparatus SOTAX AT 7 Smart (SOTAX Pharmaceutical Testing LLC, Prague, Czech Republic)
- Agilent 8453 UV/VIS spectrometer (Agilent Technologies Deutschland GmbH, Waldbronn, Germany)
- program: UV – Visible ChemStation (Agilent Technologies 95 – 00)
- manual press (Trystom comany. LLC, Olomouc, Czech Republic)
- ultrasonic cleaner K12 (Ilabo LLC, Kyjov, Czech Republic)
- semi-automatic micro-pipette 0,5 – 5 ml (Transferpette, BrandTech Scientific, Great Britain)
- semi-automatic micro-pipette 20 – 200 µl, 100 - 1000 µl, 500 - 5000 µl, 1 – 10 ml (Eppendorf, Germany)
- phials
- cuvettes d = 0,5 cm (Fisher, Mnichov, Germany)
- ordinary laboratory glass
- weighing boat
- Spatulas Scoop Bars

3.2 Materials

- HCl, 36% (Lach – Ner LLC, Neratovice, Czech Republic; analytical reagent grade)
- NaOH (Penta, Prague, Czech Republic; analytical reagent grade)
- ethanol; analytical reagent grade
- deionized water
- NaCl (Lach – Ner LLC, Neratovice, Czech Republic; analytical reagent grade)
- Pentoxifylline (Sigma – Aldrich Chemie GmbH, Steinheim, Germany)
- A stock solution of HCl

Preparation: 36 ml of 36% HCl were mixed with deionized water in 100ml volumetric flask and was diluted with deionized water to the mark.

Dissolution medium pH 1,2

Preparation: 2 g of sodium chloride was dissolved in 800 ml of deionized water. 7 ml of stock solution HCl was added and the solution was diluted to 1000 ml with deionized water. 900 ml of the dissolution medium were always used per each dissolution vessel.

3.3 Preparation and composition of the hydrophilic matrix tablets

All hydrophilic matrix tablets with the active substance pentoxifylline, which were used in the experimental part of the thesis were prepared by direct compression method at the Department of Physical Chemistry (Faculty of Chemical Technology - University of Pardubice). The exact composition of the individual formulations is shown in Table 8.

Each tablet was compressed on a manual pressing machine (Trystom Ltd., Czech Republic (Figure 8)) for 5 minutes at a constant press force of 8-9 kN. Thus, cylindrical shape tablet was produced (Figure 9). The total weight for the individual tablets was 0.5 g ± 0.005 g. 6 tablets of the same composition with the active ingredient PTX and 1 blank with no active substance were always prepared for each dissolution test.

Figure 8: Manual pressing machine

Figure 9: Studied tablets

Table 8: Composition of formulations F1 – F4 (in mg)

Formulation	F1	F2	F3	F4
Prosolv® SMCC 90	245	245		
Disintequik™ MCC 25			245	245
Methocel™ K4M Premium CR	150		150	
Methocel™ K100M Premium CR		150		150
Magnesium stearate	5	5	5	5
Pentoxifylline	100	100	100	100

3.4 PC programs

- GraphPad Prism 7
- Microsoft PowerPoint 2016
- Microsoft Excel 2016

3.5 Dissolution test of tablets with the active substance pentoxifylline

For the dissolution test a rotating basket method was chosen. The glass cylindrical vessels were filled with 900 ml 1.2 pH dissolution medium. The filled vessels together with the water bath were heated to 37 ± 0.5 °C. The mixing speed was set at 125 revolutions per minute. Total dissolution time (24 hours) and frequency of sample selection were set on the dissolution device control panel (Figure 10).

During the test, 3 ml of the sample were taken at the following time intervals:

- The first 8 samples were taken every 15 minutes
- Another 4 samples were taken after 30 minutes
- The following 8 samples were taken after 60 minutes
- The last six samples were taken after 120 minutes

The total dissolution time was 1440 minutes/24 hours. For all taken samples taken the concentration of released PTX was determined by UV/VIS spectrometry by the calibration method. Absorbance values were read at the wavelength of 274 ± 1 nm. At this wavelength there is no interference of most excipients.

Figure 10: Dissolution apparatus Sotax AT 7 Smart [35]

3.6 UV/VIS spectrometry

UV/VIS spectrometry combines the optical (visible) wavelength range from 400 to 800 nm and the ultraviolet wavelength range from 200 to 400 nm. This method gives information about how the substance is arranged at the atomic and molecular level, how atoms and molecules behave when combined into condensed matter, and also gives accurate data on the concentration of matter.

A feature of optical spectroscopy in comparison with other types of spectroscopy is that most structurally organized matter (larger than atoms) reacts resonantly with the electromagnetic field in the optical frequency range. Therefore, optical spectroscopy is currently used very widely to obtain information about matter. The absorbency range for commercially available devices ranges from 0.2 to 2 units. If the absorbance values cross this limits a testing sample should be diluted.

3.7 Measurement of the calibration of pentoxifylline

To a 100ml volumetric flask was weighed 10 mg of PTX active substance. The volume was supplemented with a buffer solution of pH 1.3. From the prepared stock solution, a sample was taken and a calibration series of solutions (100 mg/l - 6.25 mg/l) was assembled using a binary dilution. Samples were measured on a UV/VIS spectrometer against the buffer alone at pH 1.2 at a wavelength of 274 nm. Prior to the determination, the Lambert - Beer Act was validated within the appropriate concentration range.

4. Results

4.1 UV/VIS calibration of pentoxifylline

The maximum absorbance values were subtracted from the taken PTX solutions at different concentrations of API in the corresponding dissolution medium (pH 1.2) at the wavelength of 274 nm. After, the concentration of absorbance dependence was constructed. The calibration line obtained is shown in Figure 11.

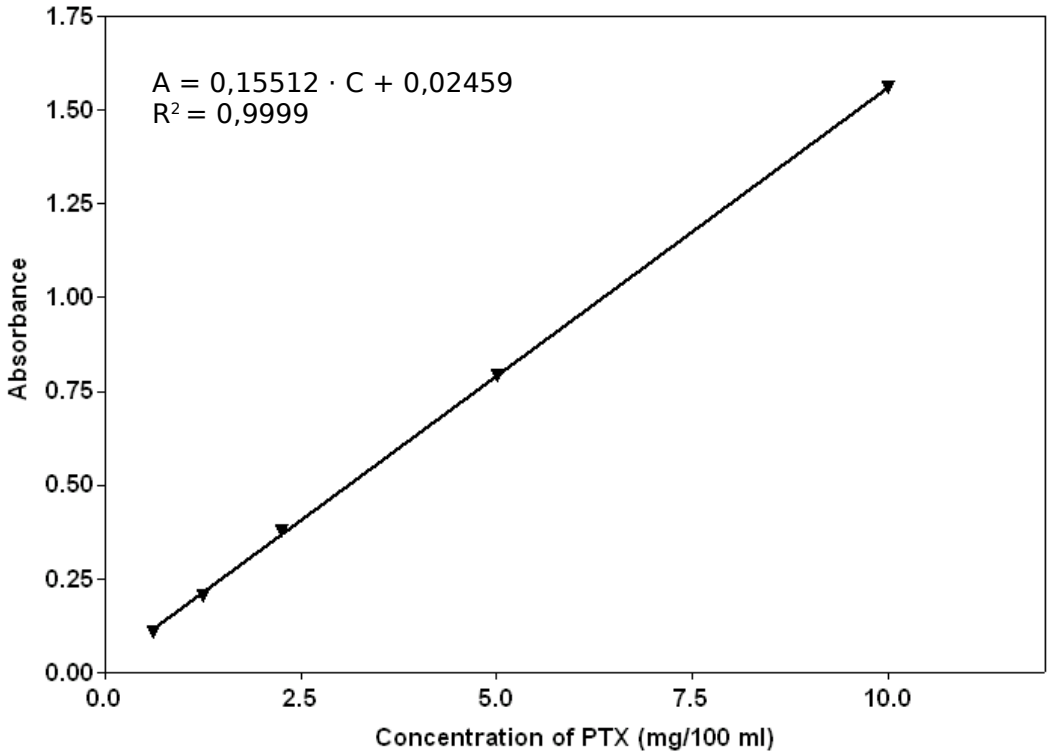

Figure 11: Calibration dependence of PTX in dissolution medium pH 1.2

4.2 Dissolution curves

The concentration of pentoxifylline in the dissolution profiles was recalculated to percentages and plotted against time *t*.

Formulation 1

The tablet is composed of API pentoxifylline (100 mg), Prosolv® 90 (245 mg) co-processed dry binder, retarding component Methocel™ K4M Premium CR (150 mg) and Magnesium stearate (5 mg). The dissolution profile F1 at pH 1.2 is shown in Figure 12.

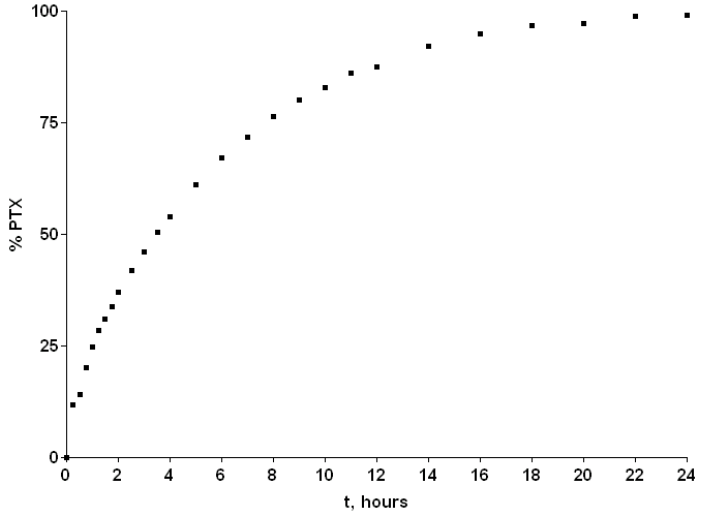

Figure 12: Dissolution profile of F1, pH 1.2.

Formulation 2

The tablet is composed of API pentoxifylline (100 mg), Prosolv® 90 (245 mg) co-processed dry binder, retarding component Methocel™ K100M Premium CR (150 mg) and Magnesium stearate (5 mg). The dissolution profile F1 at pH 1.2 is shown in Figure 13.

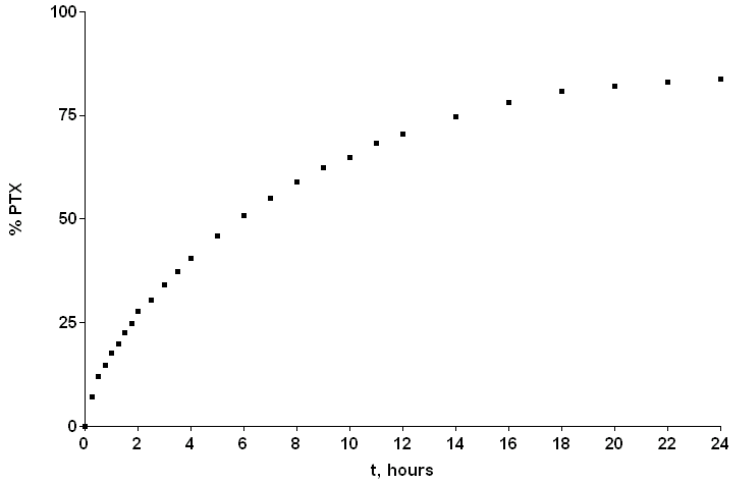

Figure 13: Dissolution profile F2, pH 1.2.

Formulation 3

The tablet is composed of API pentoxifylline (100 mg), Disintequik™ MCC 25 (245 mg) co-processed dry binder, retarding component Methocel™ K4M Premium CR (150 mg) and Magnesium stearate (5 mg). The dissolution profile F1 at pH 1.2 is shown in Figure 14.

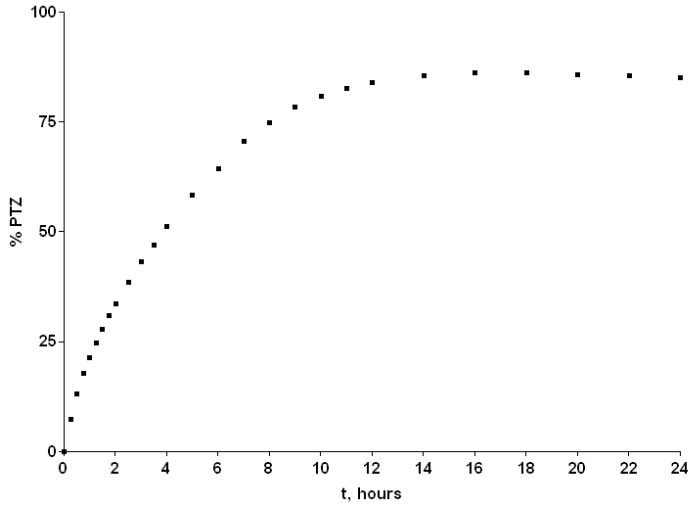

Figure 14: Dissolution profile F3, pH 1.2.

Formulation 4

The tablet is composed of API pentoxifylline (100 mg), Disintequik™ MCC 25 (245 mg) co-processed dry binder, retarding component Methocel™ K100M Premium CR (150 mg) and Magnesium stearate (5 mg). The dissolution profile F1 at pH 1.2 is shown in Figure 15.

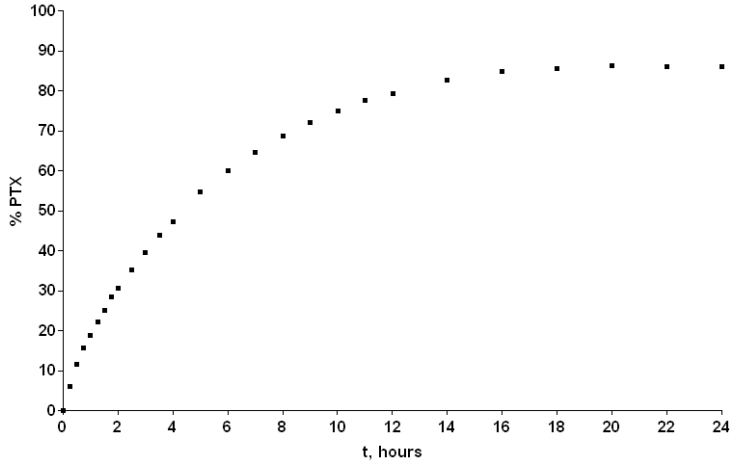

Figure 15: Dissolution profile F4, pH 1.2.

Formulations 1-4

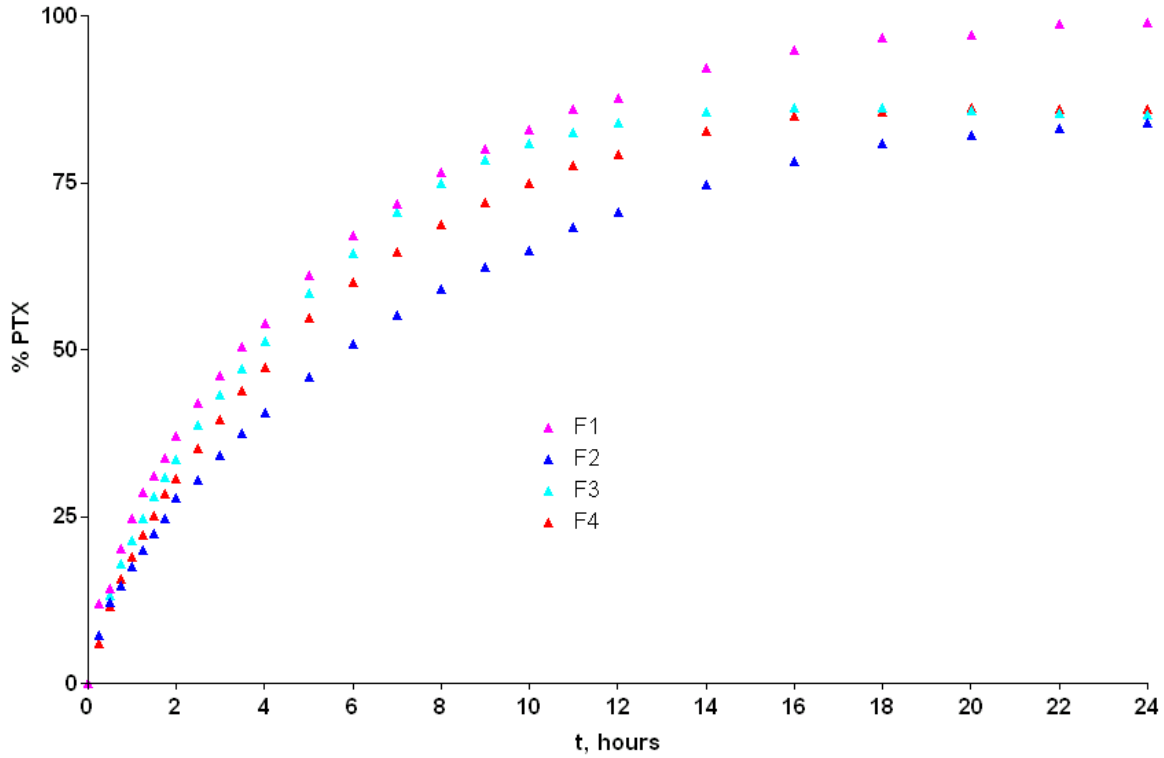

Figure 16: Comparison of the dissolution profiles F1-F4, pH 1.2.

4.3 Nonlinear regression analysis of dissolution profiles

All dissolution profiles of the F1-F4 formulations were further evaluated using the kinetic model of the first order and the statistical Weibull model using non-linear regression analysis.

Formulations 1

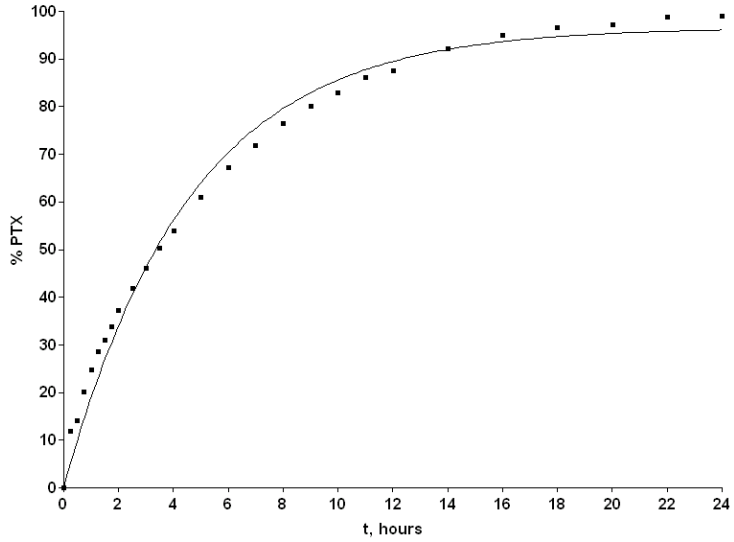

Figure 17: The dissolution profile F1 fitted to the first order kinetic model, pH 1.2

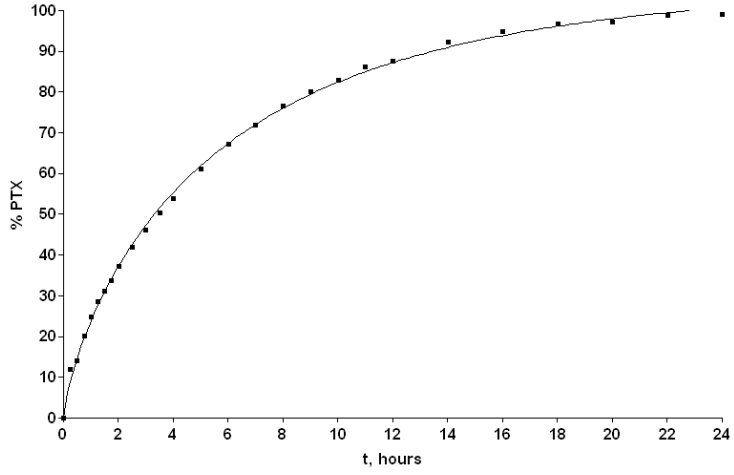

Figure 18: The dissolution profile F1 fitted to the Weibull model, pH 1.2

Formulations 2

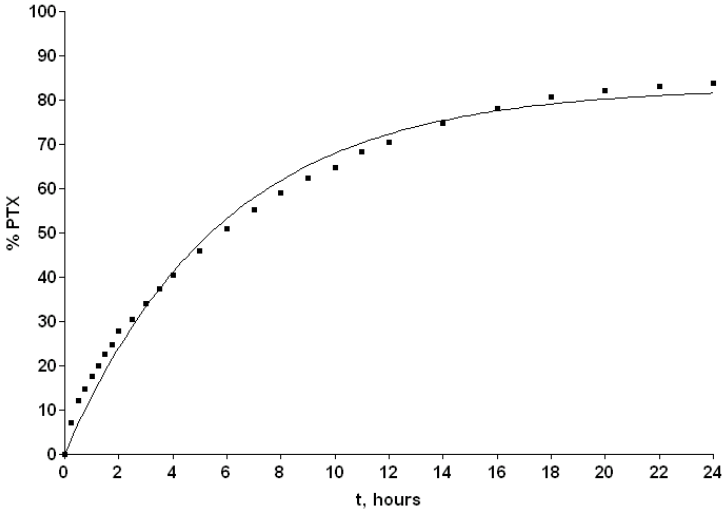

Figure 19: The dissolution profile F2 fitted to the first order kinetic model, pH 1.2

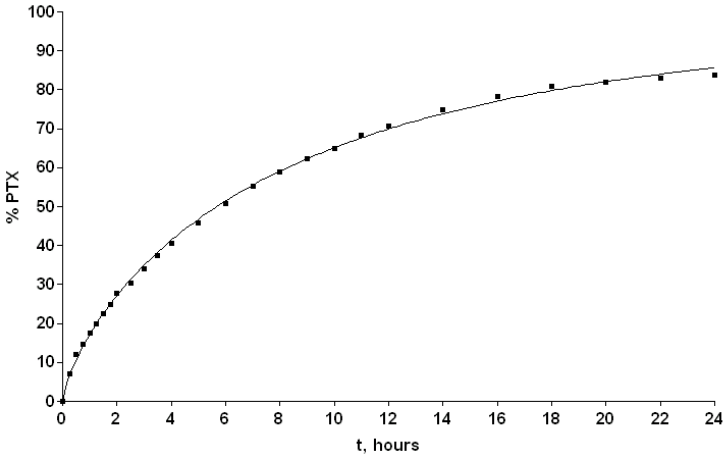

Figure 20: The dissolution profile F2 fitted to the Weibull model, pH 1.2

Formulations 3

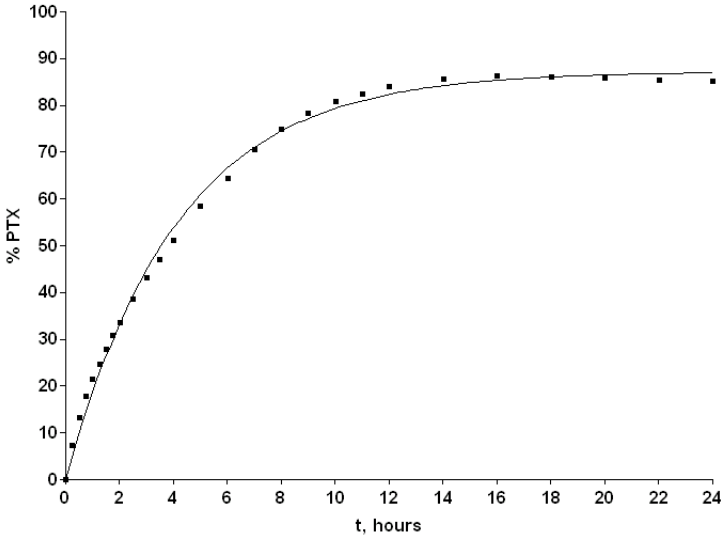

Figure 21: The dissolution profile F3 fitted to the first order kinetic model, pH 1.2

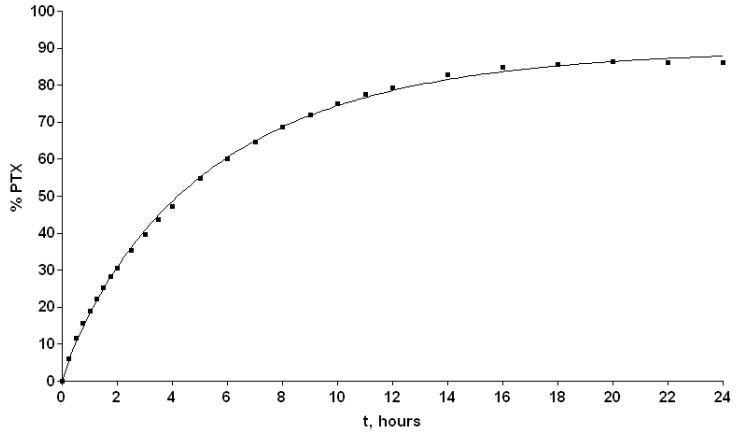

Figure 22: The dissolution profile F3 fitted to the Weibull model, pH 1.2

Formulations 4

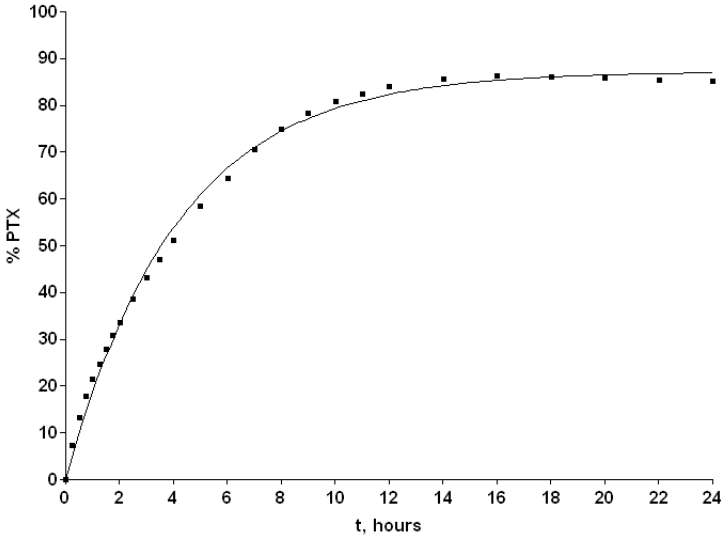

Figure 23: The dissolution profile F4 fitted to the first order kinetic model, pH 1.2

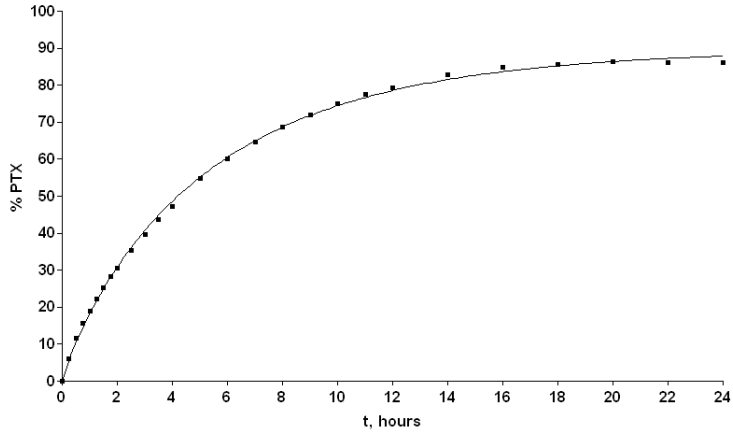

Figure 24: The dissolution profile F4 fitted to the Weibull model, pH 1.2

Formulations F1 – F4 first order kinetic model

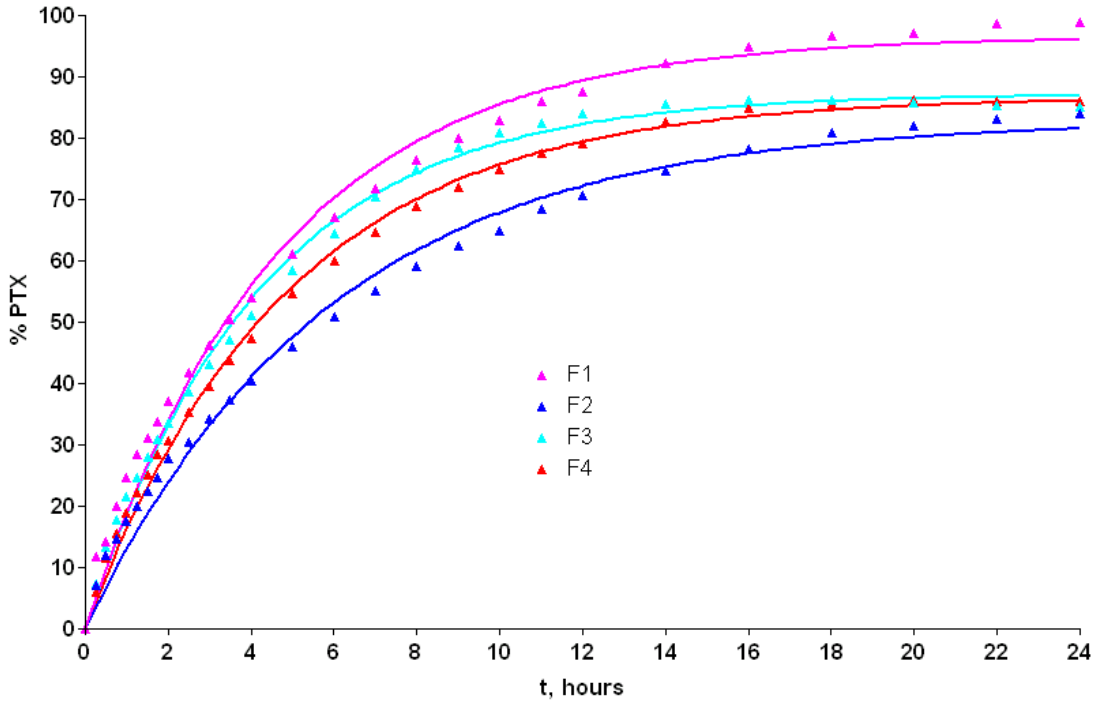

Figure 25: Comparison of dissolution profiles with F1-F4 formulations, fitted to the first order kinetic model, pH 1.2

Formulation F1 – F4 - Weibull model

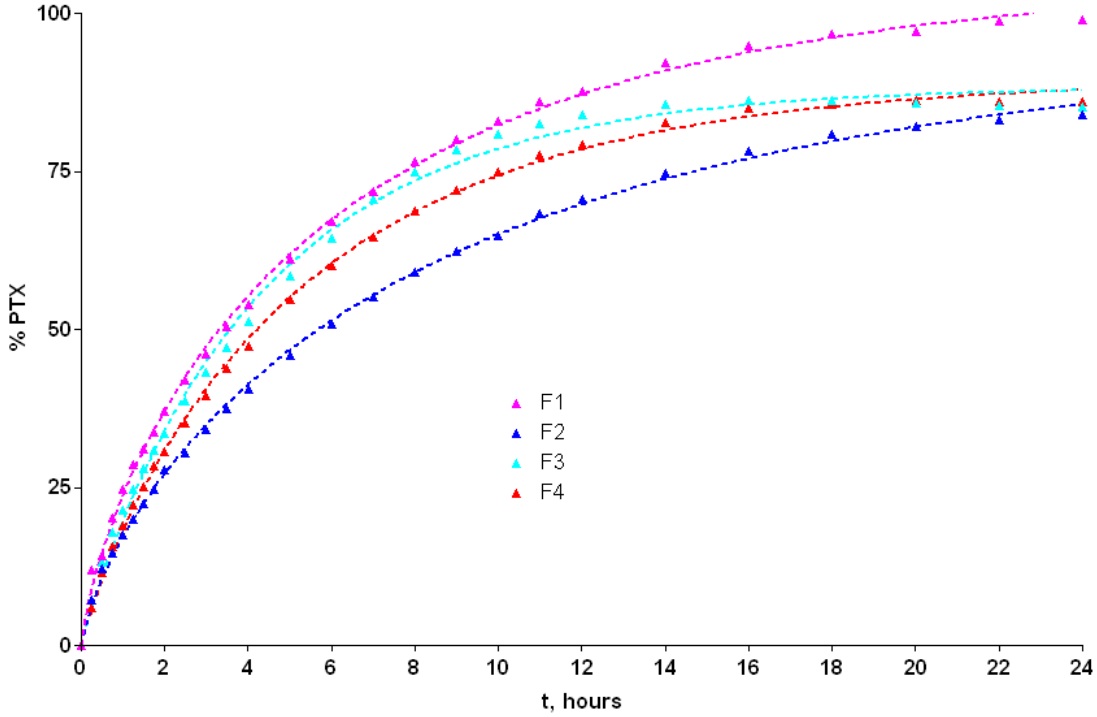

Figure 26: Comparison of dissolution profiles with F1-F4 formulations, fitted to the Weibull model, pH 1.2

Formulation F1 – F4 - Weibull model/first-order kinetic model

The obtained dissolution profiles were evaluated based on first order kinetic model and the Weibull model. The rate constants of the pentoxifylline release process were obtained using the regression analysis. For evaluation and statistically processing of all data was used GraphPad Prism 7. The results were summarized graphically (Figure 27) and in tabular form (Tables 9, 10).

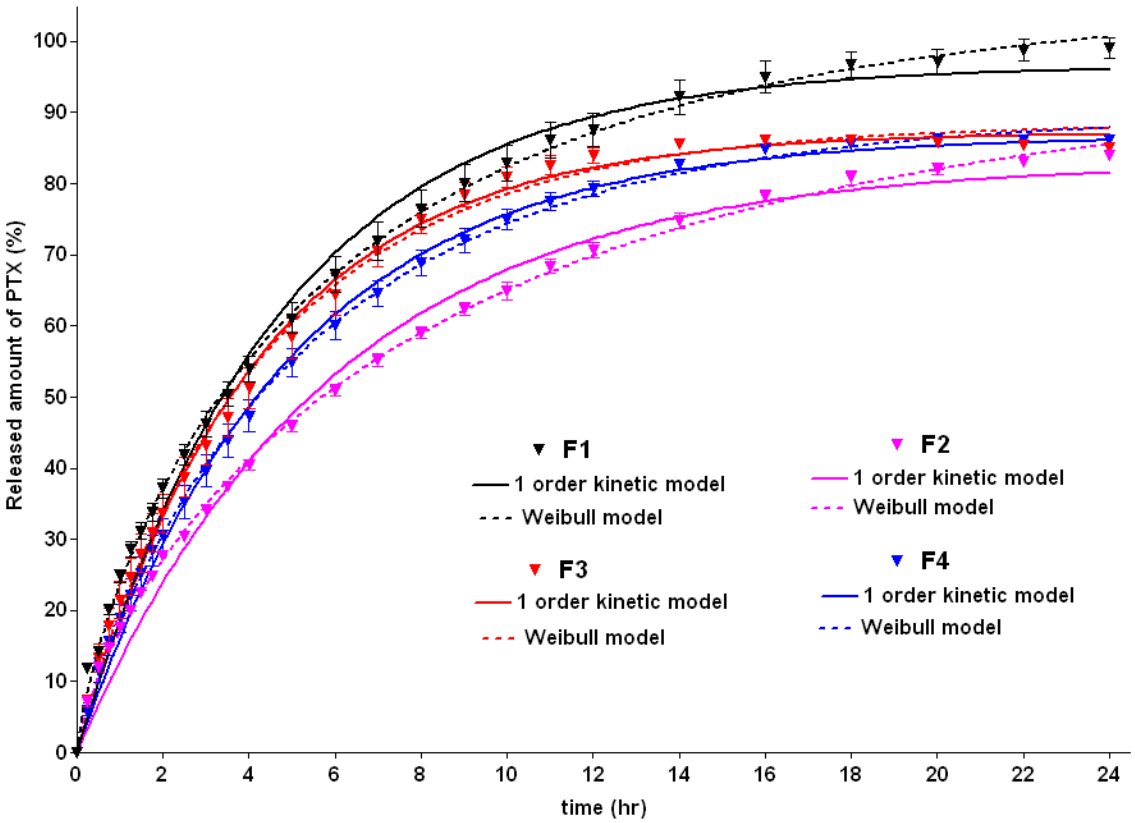

Figure 27: Comparison of dissolution profiles with F1-F4 formulations, fitted to the Weibull model and the first order kinetic model, pH 1.2.

Tabular overview of nonlinear regression analysis results

Table 9: Regression analysis of dissolution profiles F1-F4, pH 1.2, the first order kinetic model

Formulation	First order kinetic $A_t = A_\infty(1-e^{-k_1 t})$			
	$k_1 \pm SD$ (hr^{-1})	$A_\infty \pm SD$ (%)	*ASS*	R^2
F1	0,2169 ± 0,009783	96,62 ± 1,506	297,3	0,9883
F2	0,1711 ± 0,008302	82,93 ± 1,541	207,9	0,9886
F3	0,2398 ± 0,00639	87,23 ± 0,7716	90	0,9956
F4	0,2068 ± 0,004923	86,72 ± 0,7277	64,52	0,9970

Table 10: Regression analysis of the dissolution profiles F1-F4, pH 1.2, the Weibull model

Formulation	Weibull model $A_t = A_\infty - e^{\frac{-(t-T)^b}{\alpha}}$			
	$\lambda \pm SD$	$b \pm SD$	*ASS*	R^2
F1	0,2523 ± 0,004224	0,7709 ± 0,01425	27,66	0,9989
F2	0,1952 ± 0,003505	0,7597 ± 0,01372	615,95	0,9991
F3	0,2534 ± 0,009406	0,9388 ± 0,02773	74,86	0,9966
F4	0,2264 ± 0,003798	0,8918 ± 0,01387	18,88	0,9991

5. Discussion

The aim of this thesis is to study dissolution kinetics of Pentoxifylline and mathematically describe the release of the API from hydrophilic matrix tablets of different composition. The thesis focuses on the determination of the dissolution profiles of formulations containing PTX (F1-F4) in dissolution medium of pH 1.2, and then quantitatively evaluation of these profiles using the first order kinetics and Weibull model. And then based on the results of the regression analysis, assess the impact of selected excipients (retardants and binders) on the different release rate of the active pharmaceutical ingredient pentoxifylline from the prepared matrix tablets.

The formulations F1-F4 prepared on a manual press were subjected to the dissolution test using apparatus SOTAX AT 7 Smart. If I evaluate the physical properties of the excipients, then all the components were perfectly matched, a high level of homogenization was achieved, and the resulting mixture was easily susceptible to pressing.

As dissolution method was chosen a rotating basket method. Concentrations were evaluated using a UV/VIS spectrophotometer with a wave length of 274 nm using a calibration curve method. Linearity of the calibration curve was validated. The calibration dependence (Figure 11) shows a high degree of linearity, where the coefficient of the determination R^2 equals to 0.9999.

For the release of active pharmaceutical ingredient in acidic medium, the first-order kinetics is used for description as a suitable mathematical model. During the experiments this assertion was confirmed by the high values of the determination coefficient R^2. It was also validated by using the Weibull model. The coefficient *b* is equal to 1 in the Weibull model, so the mathematical expression of this model can be considered like the first order kinetic equation.

From the dissolution test results, it is clear those formulations F1 and F3, which contain Methocel™ K4M Premium, release active pharmaceutical compound faster than formulations F2 and F4. The formulations F1 and F3 released most of the substance over 8 hours. While formulations F2 and F4 required about 12 hours to release the same amount of substance. Comparison of the dissolution profiles F1-F4 (Figure 16) shows that formulations with Methocel™ K4M Premium as a retarding excipient release maximum of pentoxifylline more rapidly. It is because Methocel™ K4M Premium has lower apparent viscosity than Methocel™ K100M Premium that has a direct influence on release rate. The thicker excipients are responsible for slower hydration and swelling of tablets. Thick hypromelose makes a viscous gel which acts as a diffusion barrier. Since the amount of both hypromeloses were the same in all formulations, gel formation was depended on type of hypromelose.

Another point of the experimental part was the comparison of the effect of the co-processed dry binder Disintequik™ MCC 25 and another co-processed dry binder PROSOLV® SMCC on the release rate of the active pharmaceutical compound pentoxifylline. Comparing the composition of Disintequik™ MCC 25 and PROSOLV SMCC, it is clear that pentoxifylline is faster released from tablets containing Disintequik™ MCC, since it contains 75% of α-lactose monohydrate and 25% of microcrystalline cellulose. These 75% of the α-lactose make the tablet more hydrophilic, which allows it to dissolve and release API faster. This effect is perfectly visible in the results of the experiment and is described graphically (Figure 27) and in the tables (Table 9, 10).

Also, based on the results, it can be seen that the release rate is mainly affected by the type of retardant and not by the type of binder.

6 Conclusions

The bachelor thesis focused on quantitative description of the kinetics of pentoxifylline release from the hydrophilic matrix tablets of different composition. From the results of the nonlinear regression analysis of the dissolution profiles of the drug formulations, we can conclude that the use of Methocel™ K100M Premium CR as a retardant component significantly retards the release of PTX compared to formulations containing Methocel™ K4M Premium CR. The slower release of the active substance from the matrix is caused due to the higher viscosity of the gel layer formed when the tablet is swollen.

The comparison of two co-processed dry binders shows that PROSOLV® SMCC 90 gives slower release of the drug than Disintequik™ MCC 25.

From *in vitro* perspective the optimal formulations are F2 and F3 that release the most of the drug over a period of 10 hours.

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