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Development of multi-unit pellet system tablets containing acyclovir: Effect of fillers on drug release and tablet quality

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ABSTRACT

The study aimed to formulate multi-unit pellet system (MUPS) tablets containing the antiviral drug acyclovir (ACV) and investigate the impact of different tablet fillers on the quality parameters and drug release profiles. Acyclovir-loaded pellets were prepared using the extrusion-spheronization method and then compressed into MUPS tablets with one of the following fillers: starch, Avicel® or lactose. The results showed that the choice of filler significantly affected the mechanical properties of the MUPS tablets. Tablets containing Avicel® exhibited the highest hardness and longest disintegration time, while those with lactose had the lowest strength. Only the Avicel®-containing tablets met all the pharmacopeial quality requirements. However, the type of filler did not have a significant effect on the *in vitro* dissolution profiles of acyclovir from the MUPS tablets. Regardless of the filler, the drug release was faster in the simulated gastric fluid (pH 1.2) compared to the simulated intestinal fluid (pH 6.8). Kinetic modeling revealed that the Weibull model best described the drug release mechanism for all three formulations. The findings underscore the importance of selecting appropriate excipients when formu-

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lating MUPS tablets to achieve the desired mechanical properties and drug release characteristics.

Keywords: multi-unit pellet system, acyclovir, *in vitro* dissolution, chitosan, Avicel®

INTRODUCTION

In the pharmaceutical industry, the continuous pursuit of advanced oral drug delivery systems is paramount for enhancing patient compliance, improving therapeutic efficacy, and achieving optimal drug bioavailability. Among these systems, multiple unit pellet systems (MUPS) have garnered significant attention due to their ability to merge the advantages of both pellets and tablets. MUPS tablets, composed of drug-loaded pellets compressed into a single dosage form, offer numerous benefits such as uniform distribution of the active pharmaceutical ingredient (API), minimized risk of dose dumping, and potential for controlled and sustained release profiles. The mentioned attributes are essential for maintaining consistent therapeutic drug levels and improving patient adherence to prescribed medication regimens[1,2].

Acyclovir (ACV), an antiviral drug extensively utilized in the treatment of herpes simplex virus and varicella-zoster virus infections[3], serves as an exemplary model drug for MUPS formulation. Categorized under the biopharmaceutical classification system (BCS) as a class III compound[4], ACV is characterized by adequate aqueous solubility but low intestinal permeability. However, in some countries, 800 mg tablets are also available, placing them within BCS as a class IV[5]. This presents a notable challenge for oral delivery, as the drug's bioavailability is limited by its inability to be efficiently delivered through the gastrointestinal membrane. Therefore, innovative formulation strategies are crucial to improve the bioavailability and effectiveness of acyclovir, thus meeting the clinical need for effective antiviral treatment.

The process of pelletization through extrusion and spheronization is a well-established technique in the pharmaceutical industry for producing spherical pellets with high mechanical strength and uniform size distribution[6]. The pellets can be either filled into the capsules or compressed into the MUPS tablets[7], offering the advantage of multiparticulate dosage forms that combine the benefits of immediate and controlled release mechanisms. The formulation of MUPS tablets is preferred over capsules for several reasons. Tablets have a higher production rate and rapidly disintegrate into primary microparticles. Additionally, MUPS tablets are less likely to stick to the esophageal

lining when swallowed and are more difficult to tamper with, addressing major concerns associated with hard capsules[8,9]. Taking tablets with food, especially high-calorie food, can cause them to remain in the stomach for too long. This can be disadvantageous, particularly for enterosolvent tablets, because their onset of action may be significantly delayed. MUPS tablets rapidly disintegrate in the stomach into individual pellets, which are less affected by the emptying of gastric contents. As a result, they pass freely through the pylorus into the small intestine[10]. The speed at which pellets move from the stomach to the small intestine is determined by their density. Pellets with a density of around 1.5 g/cm^3 exit the stomach more quickly than those with a density greater than 2 g/cm^3. Pellets that are smaller than 2 mm and have a density of less than 2 g/cm^3 pass through the pyloric sphincter as rapidly as liquids, whether the stomach is empty or after a meal[11].

The selection of excipients, particularly binders and fillers, plays a critical role in the formulation process, influencing the physical and mechanical properties of the pellets and the resulting MUPS tablets. Chitosan, a naturally derived biopolymer with favorable biocompatibility and mucoadhesive properties, is employed in this study as a binder. Chitosan's unique characteristics, including its ability to form a gel-like matrix and facilitate drug release through matrix erosion and diffusion[12], make it an ideal candidate for modulating the release profile of ACV from the pellets. The incorporation of chitosan in pellets can modify the drug release profile. It can slow down the drug release by forming a gel layer around the pellets, hindering drug diffusion[13]. A decisive influence also has molecular weight of chitosan. Higher molecular weight chitosan tends to retard drug release more effectively compared to lower molecular weight chitosan[14]. Using chitosan in combination with other oppositely charged polymers can further modulate the drug release from pellets. The interaction between the oppositely charged chitosan and alginate can create a more controlled release profile[15]chitosan and sodium alginate, alone and in combination, on the ability of formulations containing a model drug (paracetamol. Increasing the chitosan content in pellets can lead to lower porosity and a rougher surface, which can also influence the drug release kinetics[16].

Additionally, the choice of filler - potato starch, lactose, or Avicel® - is crucial, as it can significantly affect the mechanical integrity, disintegration time, and drug release kinetics of the MUPS tablets[8]. Each filler exhibits distinct properties that can influence the overall performance of the tablet, necessitating a comprehensive evaluation to determine the optimal formulation[13]. In addition to ensuring the quality of MUPS tablets, it is important to choose correct shape

and size of tablets because it can affect the tolerability and swallowability of the dosage form by the patient[8].

The study aims to formulate acyclovir-loaded MUPS tablets and investigate the impact of different fillers on the tablets' quality parameters and drug release profiles. The study encompasses a detailed assessment of the physical characteristics of the tablets, including weight variation, hardness, friability, and disintegration time, adhering to pharmacopeial standards. *In vitro* dissolution testing evaluating the release profiles of ACV in simulated gastric or simulated intestinal fluid, provides insights into the drug's release behavior under physiological conditions. Understanding the mechanisms of drug release from MUPS tablets is essential for optimizing their formulation. Drug release from MUPS tablets can be influenced by several factors, including the physical properties of the pellets, the type of binder and filler used, and the compression force applied during tablet formation. The findings from this study have significant implications for the pharmaceutical industry, particularly in the formulation of oral drug delivery systems. By optimizing the formulation of acyclovir-loaded MUPS tablets, this research addresses key challenges associated with the oral delivery of BCS class III drugs. The insights gained can guide the development of robust, patient-friendly dosage forms that enhance therapeutic efficacy and improve patient compliance.

METHODOLOGY

Material

ACV was obtained from Union Quimico Farmaceutica S.A. (Barcelona, Spain). Chitosan (medium molecular weight 90–310 kDa, degree of deacetylation 82%) was purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Methocel K100M; co-processed microcrystalline cellulose with lactose monohydrate and natrium carboxymethyl cellulose (Specicel®140) were supplied by Dow Chemical Company (Midland, Michigan, USA). Microcrystalline cellulose (Avicel® PH 102), acetic acid, sodium chloride, hydrochloric acid and magnesium stearate were purchased from CentralChem s.r.o (Bratislava, Slovakia). Potato starch was from Lyckeby Amylex, a.s. (Horažďovice, Czech Republic). Lactose was from Lyckeby Culinar a.s, (Hražďovice, Czech Republic). Aerosil 200 was purchased from Chemex (Prague, Czecg Republic). The purified water was prepared by distillation apparatus Kavalier (Prague, Czech Republic).

Preparation of pellets

The powdered components of the mixture, which are ACV and a special filler, Specicel® 140, containing microcrystalline cellulose, lactose monohydrate, and croscarmellose sodium salt, were homogenized together and then wetted with a binder solution. 2% w/w chitosan solution acidified with a 3% w/w acetic acid solution was used as a binder. The wet mixture was then extruded using a Pharma extruder DE-120 (Gabler Engineering GmbH, Malsch, Germany) with 0.8 mm diameter holes, while being set in motion by augers rotating at 40 rpm. The extrudate was broken and pelletized in the spheronizer R-600 (Gabler Engineering GmbH, Malsch, Germany) at 1200 rpm. The entire process took 3 minutes. The resulting pellets were dried in a fluidized bed dryer (Glatt GPCG2 Lab System, Binzen, Germany) at 50°C until the moisture content was less than 3%. The moisture content was continuously monitored using a halogen moisture analyzer (Mettler-Toledo Halogen Moisture Analyzer HG63, Greifensee, Switzerland).

Preparation of MUPS tablets

The prepared pellets were mixed with one of the tested fillers (potato starch, lactose, or Avicel®) in a 1:1 ratio (w/w). Magnesium stearate (0.6%; w/w) as an anti-adhesive agent and Aerosil (0.3%; w/w) as a lubricant was added to their mixtures. The mixture was homogenized for 15 min in a homogenizing device (Turbula, Basel, Switzerland). The flow rate of the prepared mixtures was then compared by pouring 10 g of material freely into a closed glass funnel with a hopper diameter of 6.4 cm and outlet diameter of 0.6 cm, measuring the time taken for the entire volume of material to flow through the funnel until it was completely emptied. From the prepared mixtures, tablets weighing 0.500 g were compressed using single tablet press machine (Korsch, Berlin, Germany) at uniform pressure (120 MPa). The cross-sectional images of the MUPS tablets were taken with a Canon 2000D (Canon Inc., Tokyo, Japan) camera in macro mode. The differences in tablet quality due to the type of filler were evaluated by the following pharmacopeial test.

Quality assessment of pellets and MUPS tablets

Weight Variation Test: 20 randomly selected tablets were weighed to three decimal places by analytical scale HZY A200 (Libra, Bratislava, Slovakia) to see if their weights were within the permitted limits. For tablets weighing more than 250 mg, the Ph. Eur. 10[17] permits a deviation of 5% percent. A maximum of two tablets may differ by more than the permitted variation, but this vari-

ation must not exceed twice the permitted variation. At the same time, the dimensions of the tablet (height, diameter) were verified by a digital caliper, type 14016458 KS (Somet, Hradec Králové, Czech Republic).

Hardness: 10 tablets were inserted radially between the jaws of the hardness tester (Schleuniger 2E, Solothurn, Switzerland). The force required to crush the tablets was measured by the device, indicating the tablet hardness in Newton (N)[18]

Friability: 10 tablets were dusted off on a 250 μm sieve. Afterward, they were weighed and placed into a rotating drum with an internal diameter of 286 mm and a width of 39 mm, which is made of translucent synthetic polymer (Tablet Friability Tester from Erweka GmbH, Heusenstamm, Germany). The tablets were then rotated 100 times. Following the rotations, the tablets were dusted off and weighed again. The percentage weight loss of 10 tablets corresponds to their friability[18].

Disintegration: Six tablets were placed in the basket of the disintegration tester - apparatus type A (PIS SPOFA, n.p. VVZ, Kroměříž, Czech Republic), which was then immersed in a container filled with 800 mL of purified water at a temperature of 37 ± 1°C. The basket was continuously moved up and down for 15 minutes at a rate of 20 oscillations per minute. The time taken for all tablets to disintegrate was recorded, and the test was repeated three times for each formulation[19].

Dissolution test

The *in vitro* dissolution testing was conducted using Erweka DT 6 basket-type dissolution tester (Erweka GmbH, Langen, Germany). Dissolution medium contained either simulated gastric or simulated intestinal fluid. Simulated gastric juice (1 L) was made of 2 g of sodium chloride, 7 mL of hydrochloric acid, and the remaining volume of purified water (pH approximately 1.2). Simulated intestinal juice (1 L) was prepared by dissolving potassium dihydrogen phosphate in water. To this solution, 0.2 M sodium hydroxide solution was added, and purified water was added to make up to 500 mL. After adjusting the pH to 6.8, water was added up to 1000 mL. For dissolution testing, the MUPS tablet was placed in the basket, which was then dipped into the dissolution medium (900 mL) and rotated at a speed of 50 rpm. The testing was carried out for 6 hours at a constant temperature of 37 ± 0.5°C. Samples from the dissolution containers were taken at specific time intervals (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 hrs). The amount of ACV released in the solutions was measured spectrophotometrically either at 255 nm (testing in the simulated

gastric fluid) or 272 nm (testing in the simulated intestinal fluid) [13] using a Genesys™ 10S UV-Visible Spectrophotometer (Thermo Scientific, Waltham, MA, USA) against a blank (the dissolution medium). A linear regression analysis was performed to obtain the equation, which was used for subsequent concentration determinations: c = (A-0.0149)/0.065 (dissolution in the simulated gastric juice); c = (A-0.0756)/0.0615 (dissolution in the simulated intestinal fluid), where c is concentration (μg/mL) and A is absorbance.

Kinetic models

The *in vitro* drug release data was fitted to various kinetic models to determine the drug release mechanism: Zero order kinetics ($Q=k_0t$), First order kinetics ($\ln(100-Q)=-k_1t$), Higuchi model ($Q=k_ht^{1/2}$), and Weibull model ($\log[-\ln(1-Q/100)]=\beta \log(t-Ti) - \log(\alpha)$)[20]. The best fitted model was selected based on the highest correlation coefficient (R^2).

Statistical analysis

The data was analyzed using Microsoft Excel 2016 (Microsoft Corporation, Washington, U.S.) for statistical processing. The results were presented as mean ± standard deviation (SD). Data differences were assessed for significance using one-way ANOVA with Daniel's XL Toolbox add-in. The graph shows significant (*) or non-significant (NS) differences.

RESULTS and DISCUSSION

Pellets are often formulated to release drugs at specific rates, providing a more controlled and sustained release of the drug[21]. Due to pellets are easier to dose-divide via their compression into a tablet than by dosing into a capsule, our primary objective was to formulate MUPS tablets and investigate the impact of the choice of tablet filler on the quality parameters of MUPS tablets, as well as the drug release from them. In our study, we utilized ACV as the model drug, which belongs to BCS class III exhibiting adequate water solubility but low intestinal permeability[22]. The drug-containing pellets were prepared using the traditional extrusion and spheronization method, resulting in spherical pellets[13]. Through sieve analysis, the average pellet size was found to be 0.6 mm. Hamman et al.[23] conducted a study on the compression of pellets into tablets, finding all size fractions from 0.2 to 2.5 mm to be suitable.

Flow rate of pressing material

Before actual compression of the material, we compared the flow rate of the pellets mixed with filler and lubricant/anti-adhesive agent to the flow rate of pure pellets (reference sample). Figure 1 shows that adding filler reduced the material flow rate by 49.3 to 58.1%.

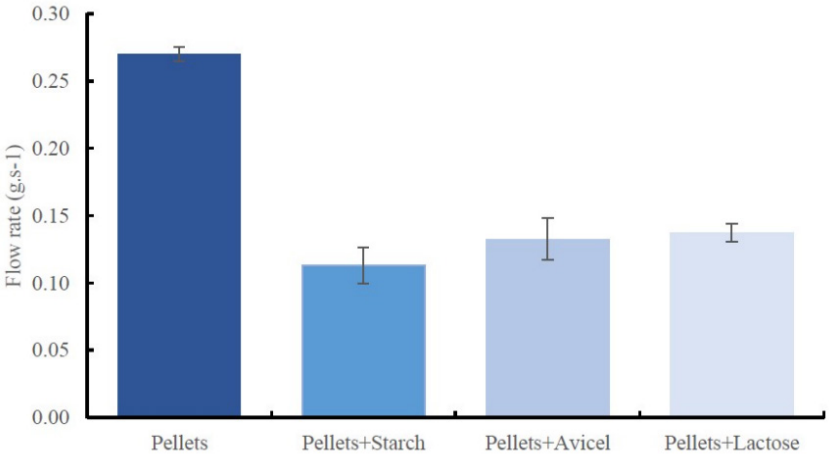


Figure 1. The influence of the filler on flow rate of the pellets; pellets without filler, pellets and starch (1:1, w/w), pellets and Avicel® (1:1, w/w), pellets and lactose (1:1, w/w).

Quality assessment of pellets and MUPS tablets

The fillers perform several functions in MUPS tablets. The filler particles have to occupy the space around the pellets, function as a cushioning agent to mitigate the impact of the compressive force during the compression, and ensure a uniform blend with the particles. Furthermore, even under relatively low compression force, the inert excipient must yield a sufficiently firm tablet, characterized by rapid disintegration time and no influence on the release of the API from the particles[24].

The basic physical characteristics of MUPS tablets are summarized in Table 1. The weights of the MUPS tablets are near the average value and do not exceed the permitted 5% deviation (Figure 2). The lowest variability in weights was observed when lactose was used as a filler in the MUPS tablets, but the RSD values were also low using the other two types of fillers. The size (height and diameter) of the MUPS tablets remains consistent due to the low RSD. The hardness of the tablets is significantly influenced by the choice of filler. Tablets containing Avicel® exhibited the highest hardness at 85 ± 11.3 N, while those containing lactose had the lowest strength. The differences in tablet hardness were also evident in their mechanical resistance when tested for friability. Tablets with a strength ranging from 50 to 90 N are considered to have optimal quality. The results from the friability and disintegration tests of MUPS tablets correlate with the hardness and disintegration test. Stronger tablets are more mechanically resistant and take a longer time to disintegrate in the dissolution medium. Only MUPS tablets containing Avicel® meet the pharmaceutical

requirement for friability when the result is rounded to one decimal place. All three types of MUPS tablets disintegrated in water within 15 minutes, meeting the required time limit for uncoated tablets as per the pharmacopoeia.

The MUPS tablets containing Avicel® showed the longest disintegration time at 10 minutes and 57 seconds. It was observed that these tablets were the only ones that met the required pharmacopoeial limits for tests predicting the general quality parameters of uncoated tablets.

Table 1. Physical characteristics of MUPS tablets

	F1 (with starch)	F2 (with Avicel®)	F3 (with lactose)	Note
Mass (g)	0.495 ± 0.002	0.502 ± 0.002	0.500 ± 0.002	Mean ± SD; n=20
RSD (Mass variability)	0.005	0.004	0.003	
Height (mm)	4.050 ± 0.015	4.028 ± 0.016	4.047 ± 0.012	Mean ± SD; n=20
Diameter (mm)	11.986 ± 0.013	12.012 ± 0.013	12.018 ± 0.006	Mean ± SD; n=20
Hardness (N)	53.4 ± 9.7	85.0 ± 11.3	33.9 ± 5.1	Mean ± SD; n=10
Friability (%)	7.73	1.02	19.96	10 tablets
Disintegration time (s)	164 ± 34	657 ± 23	109 ± 4	Mean ± SD; n=3

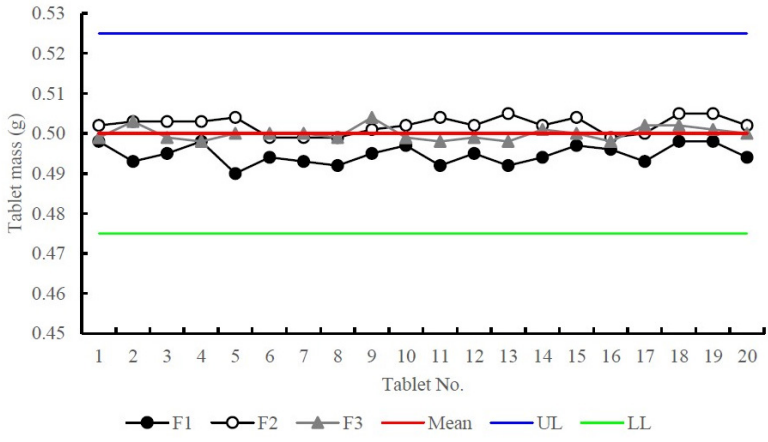
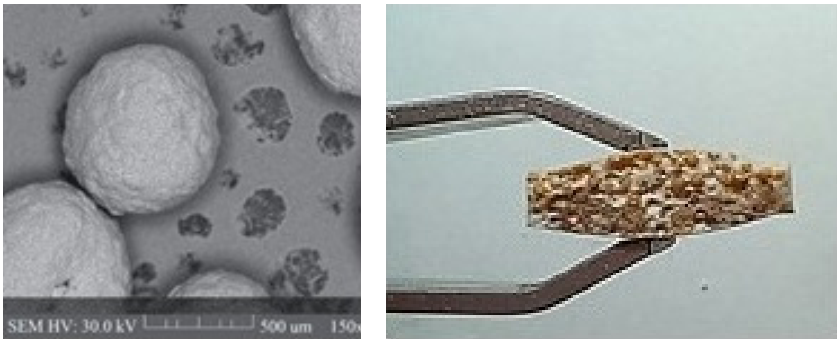


Figure 2. The weight variance of MUPS tablets: F1 with starch, F2 with Avicel®, F3 with lactose (UL illustrates upper limit, LL illustrates lower limit).

The pellets were physically characterized through several tests, and their morphology was analyzed using SEM. The results are part of another scientific study[13]. In Figure 3A, a pellet is shown by SEM at 150x magnification. Figure 3B illustrates a cross section of the MUPS tablet (F2), which was created using a scalpel. F1 and F3 were too fragile to make a uniform cut. Although this technique may not be the most convenient, as it can lead to empty voids at the cut site after some pellets have fallen out, it does allow for the direct assessment of the tablets' mechanical resistance. It is evident that F2 appears the most compact and least damaged even after incision.



A) B)

Figure 3. A) SEM image of the pellets at 150-fold magnification; B) Photographic image of a cross-section of MUPS tablet (F2).

Avicel® is frequently employed as an excipient in both tablet compression and pelletizing processes[24]. Tablets containing Avicel® generally have higher mechanical strength and better disintegration characteristics[25]. Certain Avicel® grades, like PH-113 and CE-15, can enhance the organoleptic properties of tablets and provide a smoother, creamier mouthfeel. This is advantageous mainly for chewable tablets and orally disintegrating tablets.

An important consideration when manufacturing MUPS tablets is the particle size distribution of the filler and the pellets themselves. As a result, we conducted a sieve analysis to evaluate the particle size distribution of the individual fillers. The potato starch used was found to be the finest material among the evaluated fillers, with an average particle size of d=40.95 μm (calculated according to[26]). Avicel® had a slightly higher average particle size (d=73.46 μm), and lactose had a particle size almost three times higher (d=116.68 μm) compared to starch. The strength of the MUPS tablets was optimized by the presence of starch. This is because the small powder particles effectively fill the

spaces between the individual pellets during the compression, and they also contribute to the rapid disintegration of the tablet in the dissolution medium, reverting it back to its original microparticles.

It is clear that the filler is crucial in the formulation of MUPS tablets. This is highlighted by the fact that attempting to compact MUPS tablets directly from the pellets under the same pressing conditions was unsuccessful. The resulting tablets were found to be brittle and crumbly.

The filler particle size can impact tablet processing. For instance, Carpin et al.[27] found that smaller lactose particles led to increased moisture sorption and caking tendency compared to larger ones.

Dissolution test and drug release kinetics

The rate and extent of drug release from tablets and its passage into the biological tissue impacts the drug's bioavailability and therapeutic effect. The dissociation test simulates physiological conditions in order to predict the efficacy and safety of the drug.

As the Figure 4 indicates, the course of drug dissolution is greatly influenced by dissolution medium. While in acidic medium almost 80% drug release was achieved after 15 minutes, neutral pH slowed down the drug release. This phenomenon may be due to the use of chitosan in the pellets as a binder.

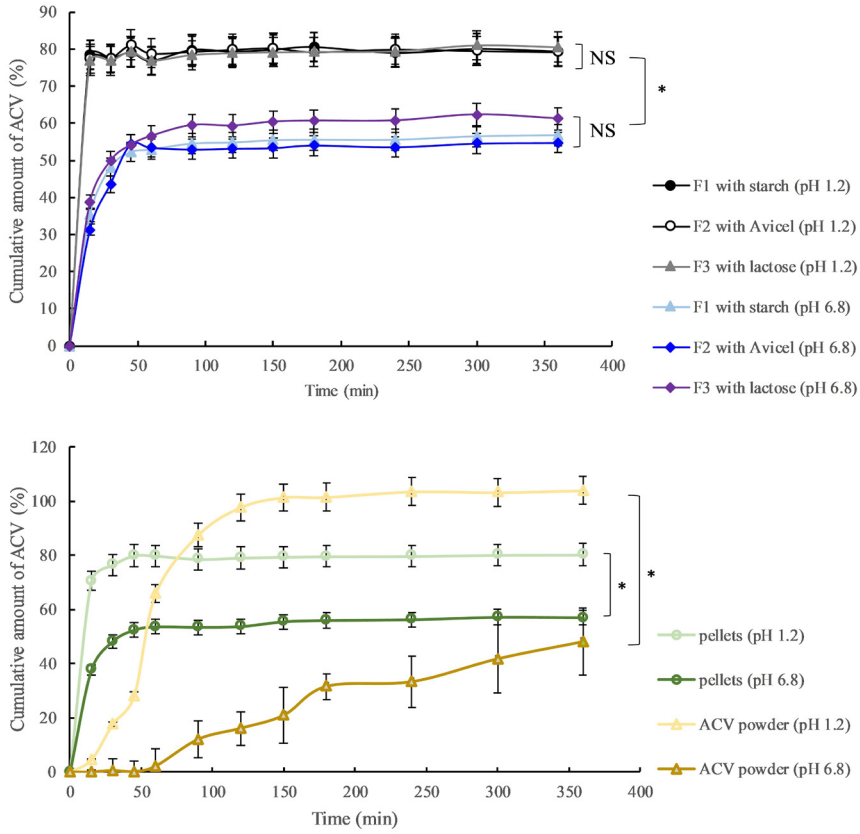


Figure 4. Dissolution profiles of ACV from MUPS tablets, pellets and capsules in different media, simulated gastric fluid (pH 1.2) vs. simulated intestinal fluid (pH 6.8) indicating significant (*) and non-significant (NS) differences.

Chitosan exhibits excellent swelling properties in acidic environments. It contains primary amino groups ($-NH_2$) along its backbone. In acidic conditions, these amino groups become protonated ($-NH_3^+$), resulting in an increase in the positive charge density of the polymer. Further, acidic media can disrupt the intramolecular and intermolecular hydrogen bonds within the chitosan structure, allowing for greater water penetration and swelling[28,29]. When the pellets come into contact with an aqueous medium, water diffuses into the interior of the particle, causing the drug to dissolve and diffuse out. Drug release rate in artificial gastric juice can vary significantly depending on the formulation design and the specific mechanisms governing drug release, such as polymer swelling, pH-responsiveness, and gastric emptying kinetics.

In our case, there was no significant effect of the filler in MUPS tablets on the rate of drug release in an acidic environment. The dissolution profiles are almost identical. Non-significant differences were also confirmed by statistical analysis.

Chitosan is a weak base, and in neutral and basic environments, the chitosan molecules will lose their charge. As Ferrari et al.[30] refer, chitosan is ineffective as an absorption enhancer at these higher pH values when the chitosan molecules exist in a more coiled conformation.

The MUPS tablets formulated in this study are designed primarily for controlled release. The use of specific binders, such as chitosan, aims to modulate the drug release profile over an extended period, thus enhancing therapeutic efficacy. To provide a comprehensive understanding of how tablet formation affects drug release, we include data on the dissolution profiles of un-compressed pellets. The data, illustrated in Figure 4, demonstrate that an acidic pH significantly enhances the release of ACV across all formulations (ACV powder, pellets, MUPS tablets). In contrast, a pH of 6.8 slowed down the drug release. For the dissolution tests, we utilized a basket apparatus to maintain consistency in our comparison. Therefore, we weighed the ACV powder into a gelatin capsule to ensure that it does not fall through the basket to the bottom of the container. The packaging formed by the gelatin capsule caused the delay of the drug's actual release until the capsule dissolved. As the capsule swelled, it became more permeable to the drug, resulting in an increase in the cumulative amount of drug released after one hour. In the acidic medium, nearly all the drug was released within two hours. However, in the dissolution medium at pH 6.8, only 48.13 ± 12.43% of the drug was released after six hours. The standard deviations indicate that the variability in ACV release from the capsule is significant, suggesting a less predictable and non-uniform drug release pattern. This highlights a major advantage of pellet formulations, particularly MUPS tablets, over conventional powders, or granules. With pellets, it is possible to achieve a consistent and sustained release of the drug at a steady rate over an extended period. Based on the dissolution profiles it can be concluded that the pellets compression into the MUPS tablets has no significant effect on drug release. Additionally, presented data of the dissolution profile of ACV in its powder form serve as a baseline for evaluating the effects of formulation changes. This comparison clarifies how processing into MUPS tablets alters the dissolution characteristics relative to raw ACV.

Drug release kinetics is a crucial aspect of pharmaceutical science that describes the rate and pattern of drug release from a dosage form. Understand-

ing the drug release kinetics helps to ensure the desired therapeutic effect, improve bioavailability, and minimize side effects. Table 2 records the coefficient of determination (R^2) values and rate release constant (c) for the zero order, first order, Higuchi, and Weibull kinetic models of the drug release from the MUPS tablets (F1, F2, and F3) either in acidic or near-neutral environments. The Weibull model provide the best fit for all three formulations regardless of the pH environment, with R^2 values around 0.96. This finding is consistent with other research papers, e.g., Dévay et al.[31] declared that theophylline was released from the pellets.

Table 2. The coefficient of determination (R2) and rate release constant (c) for the kinetic models

	pH 1.2			**pH 6.8**		
Model	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
Zero Order						
R^2	0.6305	0.6627	0.6627	0.6653	0.6743	0.6748
k_0	1.7	1.7	1.7	1.7	1.7	1.7
First Order						
R^2	0.6494	0.6748	0.6748	0.6743	0.6743	0.6748
k_1	0.0079	0.0080	0.0080	0.0080	0.0080	0.0080
Higuchi						
R^2	0.8621	0.8787	0.8787	0.8803	0.8803	0.8787
k_H	26.41	26.68	26.68	26.76	26.76	26.68
Weibull						
R^2	0.9582	0.9652	0.9652	0.9663	0.9663	0.9652
α	0.0014	0.0014	0.0014	0.0014	0.0014	0.0014
β	1.5	1.5	1.5	1.5	1.5	1.5

The Weibull model is an empirical model that can fit a variety of release patterns, including monophasic, biphasic, triphasic and complex multiphasic profiles. MUPS tablets composed of uncoated pellets exhibit complex release kinetics that the flexible Weibull model is well-suited to describe. It uses two parameters - α (scale parameter) and β (shape parameter)[33]. The β value provides information about the release mechanism. Lower β values (<0.75) point to diffusion-controlled release, while higher values indicate more complex release kinetics involving swelling, erosion, or wear-out phenomena[34].

The drug release profiles are similar across the three formulations, with the percentage of drug released ranging from around 77-81% in acidic environment over the 6-hour time period studied. There is an initial burst release of the drug within the first 0.5 hours, followed by a more gradual release over the remaining time.

When comparing the drug release in artificial gastric fluid *versus* artificial intestinal fluid, the data shows a higher percentage of drug released under acidic conditions for all three formulations. A similar observation was made by Partheniadis et al.[32] studying the release of piroxicam from chitosan pellets, who explain this phenomenon through extensive dissolution/erosion of the gel matrix observed at pH 1.2 but not at pH 5.6.

This would mean that this dosage form formulated from pellets in which the function of the binder is performed by chitosan, subsequently pressed into MUPS tablets, is suitable for drugs that are to be released immediately in the stomach, where they are to act therapeutically, and after passage into the intestine, the drug release from pellets will be slowed down due to the higher pH, i.e., the drug will be released outside the stomach to a minimal extent, which is facilitated by the pH dependence of the solubility of the chitosan. However, the pellets must also have sufficient density (at least 2 g/cm^3)[11] to remain in the stomach as long as possible after the MUPS tablet disintegrates into subunits.

The decrease in MUPS tablet weight during the dissolution test at time t=0h *vs*. the pellets weight at time t=6h was variable depending on the filler used in MUPS tablets. The MUPS tablets containing lactose (F3) showed the lowest pellet residues after disintegration, with minimal impact of the pH. At pH 1.2, the residue was 31.33 ± 2.20% and at pH 6.8, it was 29.98 ± 7.10%. This result aligns with the high solubility of lactose compared to other fillers. For MUPS tablets with starch (F1), there was a noticeable pH effect. The residue at pH 1.2 was 74.12 ± 1.95%, while at pH 6.8, it was 44.49 ± 4.41%. This is consistent with the lower solubility of starch in acidic environments. Microcrystalline cel-

lulose (MCC) in F2 caused the least weight loss after dissolution, the residue at pH 1.2 was 75.22 ± 4.40% and at pH 6.8 was 77.23 ± 2.13%, as MCC is insoluble in both acidic and neutral mediums. Despite the loss on weight, the pellets retained their spherical shape during the dissolution testing in most cases.

There are numerous factors that affect drug release, absorption, and stability. Apart from the physical and chemical properties of an API, pH, viscosity, ionic strength, and the hydrophilic-lipophilic balance of digestive juices in specific parts of the GIT have a significant impact.

Variables such as the volume of these juices, passage time in specific segments of the GIT, and the intensity of stomach and bowel movements must be considered[35].

ACV due to its pKa (2.27) is soluble in acidic environment therefore, is preferable absorbed in an upper GIT[36]. Bejgum et al.[37] analyzed the degradation products of acyclovir in an acidic environment. In addition to the previously identified guanine, they also found other degradation products such as methyl acetal ethylene glycol, formaldehyde, ethylene glycol, ACV-formaldehyde adduct, and guanine-formaldehyde adduct. This implies that the determined concentrations of ACV released during dissolution into gastric juice are at their highest level and that the remaining portion consists of these degradation products. Due to the unstable nature of ACV in acidic environments, it is recommended to incorporate the drug in a more basic micro-environment with basic excipients. Additionally, MCC (Avicel®) properties depend on pH. At lower pH values, the electrostatic repulsion force between MCC particles decreases[38], which may also contribute to the higher amount of drug released in the acidic environment.

MCC is a common cushioning excipient used in MUPS tablets. The results of our study confirm its effectiveness and indispensability in this role. Generally, cushioning material protect the pellets from compaction-induced damage[39]. Traditional cushioning material include MCC, starch, lactose, dicalcium phosphate and mannitol. They reduce mechanical stress on the pellets, maintaining their stability and efficacy, enhance the overall mechanical strength of the tablet and ensure consistent and reliable tablet production by minimizing defects during compression[24]. In order to avoid processing problems caused by the large dispersion of particle size between the cushioning excipients and the pellets themselves, cushioning pellets have also started to be formulated[39,40] to prevent a risk of segregation during production. These are often formulated from MCC.

According to the obtained results from our experiment, following summary and recommendations can be postulated:

- The choice of filler in MUPS tablets had a significant effect on the quality parameters. The best results were found for MUPS tablets containing Avicel®.
- The type of filler in MUPS tablets did not significantly affect the dissolution of ACV from them.
- ACV is better released in acidic environments, possibly due to the use of chitosan as a binder in the pellets, which dissolves well in acidic environments.

The choice of filler significantly affected the mechanical properties and drug release profiles of the formulated MUPS tablets containing ACV. Tablets with Avicel® exhibited the highest hardness and longest disintegration time, while those containing lactose had the lowest strength. Only the MUPS tablets with Avicel® met the required limits of all pharmacopoeial tests. The fillers in the MUPS tablets did not have a significant effect on the dissolution profiles. However, there were notable differences in the dissolution profiles due to the pH of the dissolution medium. ACV was released more quickly in the acidic medium, and in all cases, the release followed Weibull kinetics. The findings underscore the importance of selecting appropriate excipients in the formulation of MUPS tablets to achieve desired therapeutic outcomes. This research provides valuable guidance for the pharmaceutical industry in developing robust, patient-friendly oral drug delivery systems.

STATEMENT OF ETHICS

This study does not require ethical permission to be carried out.

CONFLICT OF INTEREST STATEMENT

The author declares that there are no conflicts of interest regarding the publication of this manuscript.

AUTHOR CONTRIBUTIONS

The study was designed by Martina Papadakos and Miroslava Špaglová. Data were acquired by Martina Papadakos and Miroslava Špaglová. Miroslava Špaglová and Dominika Žigeayová performed the data analysis. The manuscript was drafted by Miroslava Špaglová and Dominika Žigrayová. Juraj Piešťanský and Martina Papadakos contributed to the critical revision of the manuscript. Statistical analysis was carried out by Miroslava Špaglová. Technical or financial support was provided by Juraj Piešťanský and Dominika Žigrayová. The study was supervised by Juraj Piešťanský.

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