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The application of povidone in the preparation of modified release tablets

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ABSTRACT

The aim of the study was to investigate the modified release of a model substance, of tablets containing different types of Kollidon and particular additives. Additionally, the release kinetics and mechanism of prolonged release of certain tablet preparations were investigated. In this work, tablets containing different types of povidone (Kollidon CL, Kollidon 30, Kollidon SR and other excipients) were prepared by the direct compression technique. The results showed that tablets with fast disintegration and release should contain in their composition, Kollidon CL, lactose and Avicel, however, the use of β-CD instead of lactose or Avicel brings about a slight prolongation in the disintegration time of tablets and the release of an active substance. Furthermore, while other tablet compositions generated within this study must be considered as being prolonged release types, only two of these showed the best fitted mathematical models. The *in vitro* dissolution data reveal that the dissolution profiles of the two formulations, one containing Kollidon SR with the addition of Kollidon 30, and the second with HPMC K15M, Kollidon 30, Kollidon CL and lactose, best fitted the Higuchi model. Moreover, the release mechanism of these two formulations plotted well into Korsmeyer-Peppas, indicating a coupling of drug diffusion in the hydrated matrix, as well as polymer relaxation – the so-called anomalous transport (non-Fickian).

INTRODUCTION

Povidone (polyvinylpyrrolidone, PVP) is a widely used excipient in preparing solid dosage forms. It is employed as a suspending and dispersing agent and as a tablet binding, granulating and coating agent. Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerisation which results in polymers of various molecular weights. Different types of povidone are characterized by their viscosity in aqueous solution, relative to that of water, expressed as a K-value [15,26,31]. Soluble Povidone K-30 (Kollidon 30) is used as a binder in wet granulation and in direct compression applications. In wet granulation, Kollidon 30 generally gives hard and compact granules with good flow properties. The substance can be used for direct compression as a binder and can also slow the drug release. Soluble types of povidone can form hydrogen bonds with compounds of complementary structures for improved dissolution. Many direct compression auxiliaries or grades of active substances suitable for direct compression already contain a binder such as povidone [4]. In the case of direct compression, the moisture content of the tableting mixture is important, and under normal conditions, the usual quantity of water in povidone already provides a binding effect between the particles [9,39].

Crospovidone is a cross-linked homopolymer of 1-ethenylpyrrolidin-2-one [26]. An insoluble cross-linked form of povidone known as crospovidone (Kollidon CL) is used as a tablet disintegrant. Kollidon Cl is a highly cross-linked version of PVP, making it insoluble in water, though it still absorbs water and swells very rapidly without forming a gel, hence generating a swelling force [15,26,31]. This property makes it useful as a disintegrant in tablets. Kollidon CL, being a superdisintegrant, is often added to orally disintegrating tablets (ODT) [11,27,38].

Copovidone is a copolymer of 1-vinylpyrrolidin-2-one and vinyl acetate in the mass proportion 3:2. It is used as

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a tablet binding and coating agent [26]. The formulation consisting of 80% polyvinyl acetate (PVAc), 19% polyvinyl pyrrolidone (PVP), sodium lauryl sulfate and colloidal silicon dioxide in powder form is known as Kollidon SR. It has been shown to be a highly suitable matrix former in controlled release tablets [5,19,23,35,37]. The drug release from the matrix tablets is increased by the addition of water-soluble excipients such as lactose, in contrast to preparations containing the water-insoluble calcium phosphate [23].

From an economical point of view, the production of sustained release tablets by direct compression is of a great promise. In this respect Kollidon SR, a convincing excipient, is expected to be easily applicable for a broad selection of different drugs [33]. In preparations containing Kollidon SR, the geometric shape of the tablet is maintained until the end of a dissolution test due to presence of the water insoluble polyvinyl acetate, while the minor water soluble constituent, polyvinylpyrrolidone, is responsible for pore formation and for engendering a diffusion controlled release [13]. Kollidon SR is a directly compressible [32]. Direct compression is the preferred method for the preparation of tablets, because this requires fewer unit operations besides it is a simple and economic method [17]. However, when using a direct tabletting system to obtain ODT tablets, a few problems come about, among these being low compactibility of the filler and achieving adequate disintegration time lower than 30 s [22,30]. However, the ODTs have produced an efficient substitute to the conventional oral dosage forms, particularly for dysphagia patients [2,11,22,30]. Current sustained-release technologies may be exploited and incorporated into an ODT to provide greater therapeutic value by reducing the need for multiple daily dosing regimens and improving patient adherence [14].

The release of the drug from a sustained release dosage form is controlled by various factors through different mechanisms such as diffusion, erosion or osmosis [10,36]. There are many factors involved in the release of a soluble drug from an insoluble matrix tablet. These include drug solubility, concentration in the tablet, drug diffusivity, and the porosity and tortuosity of the tablet [6,10]. The Higuchi model describes drug release through the diffusion mechanism and it is used to assess drug dissolution from systems such as matrix tablets containing water-soluble drugs. The Hixson-Crowell model assumes that drug release is limited by the dissolution rate of the particles rather than by diffusion through the polymer matrix [10]. The Korsmeyer-Peppas model can be used to characterize the drug release mechanisms as Fickian diffusion [34]. A water-soluble drug incorporated into a hydrophilic matrix is released mainly by a diffusion-controlled process, whereas for a poorly water-soluble compound, the principal mechanism of release is a function of the erosion of the matrix that carries the drug [10].

In our study, papaverine hydrochloride as a model drug was proposed. Papaverine has a direct relaxant effect on smooth muscles. It is used in bile, intestinal, and renal spikes [26]. Papaverine hydrochloride is well-soluble in acidic medium and its solubility increases proportionally with the decrease in pH of the medium [26,28].

The use of different types of povidone is known, however, there are no studies describing different compositions of tablets with a wide range of release from fast to prolonged profile. Therefore, the aim of the work was to study preparations of tablets containing different types of Kollidon displaying modified release of a model substance, made by way of the direct compression method. Additionally, the release kinetics and mechanism of certain prolonged release forms of these tablets were ascertained and compared.

MATERIALS AND METHODS

The employed papaverine hydrochloride (PAP) was the product of Farm-Impex Sp. J., Poland. Microcrystalline cellulose (Avicel PH 102) was the product of FMC BioPolymer, Belgium. β-lactose (lactose) was purchased from Sigma Aldrich. Kollidon CL, Kollidon SR, Kollidon 30 were received as a gift from BASF, Germany. Methocel K15M (HPMC K15M) was received as a gift from Colorcon, England. Kleptose DC-Beta cyclodextrin (β-CD) was a gift from Roquette, Lestrem. Magnesium stearate was purchased from POCH Gliwice, Poland. All other reagents and solvents were of analytical grade, distilled water was freshly distilled.

Preparation of tablets

The composition of tablets formulations is given in Table 1.

Papaverine hydrochloride and other components were premixed in a cube mixer (Erweka, Germany) for 15 minutes and the mixture was passed through mesh no. 40 and then

Table 1. Composition of tablets T1-T8

Name of component	Quantity (mg) per Tablet							
	T1	T2	T3	T4	T5	T6	T7	T8
PAP	50	50	50	50	50	50	50	50
Kollidon SR	-	-	-	80	80	80	50	-
HPMC K15 M	-	-	-	-	-	-	-	50
Kollidon 30	-	-	-	-	68	-	68	68
Kollidon CL	2	2	2	-	-	-	2	2
Lactose	76		70	68	-	-	28	28
Avicel PH 102	70	70	-	-	-	-	-	-
β-CD	-	76	76	-	-	68	-	-
Magnesium stearate	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200

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lubricated with magnesium stearate for another 5 minutes. The magnesium stearate level was fixed at 1% for all the formulations. Tablets were compressed at 200 mg weight on a Single Punch Tablet Press – EP1(Erweka, Germany) fitted with a 9-mm round-shaped punch with compression force 4 kN.

Evaluation of powders of tablets

According to pharmacopoeial requirements [15,31], the flowability of powders F1-F8 was determined and assessed based on angle of repose and compressibility values.

Angle of repose. The powder mixtures, deemed F1-F8, were prepared according to the formulations of tablets T1-T8 given in Table 1. The angle of repose was measured by passing the prepared powders through a funnel of internal diameter 10 mm on the horizontal surface. The angle of repose was measured automatically by way of use of the Apparatus Erweka typ GTB in triplicate.

Compressibility (Carr's index). Such a study was made through employing the Erweka Apparatus typ SVM 222. Herein, an accurate weight of formula tablets was poured into a volumetric cylinder to occupy a volume (V_0) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (V_f). The Carr's index was calculated using Eq. 1 [31]:

$$\text{Compressibility index} = 100\,(V_0 - V_f)/V_0 \quad \textbf{Eq. 1.}$$

The angle of repose and compressibility values as presented in Table 2.

Table 2. Micromeritics properties of the powders F1-F8

Formula	Angle of repose	Carr's index	Flow character
F1	39.2±1.12	20.0±0.92	Fair
F2	39.0±0.64	20.0±1.59	Fair
F3	34.9±1.62	17.1±1.16	Good and fair
F4	32.6±0.74	12.0±1.43	Good
F5	33.5±0.83	17.1±0.50	Good and fair
F6	34.8±2.13	16.1±0.96	Good and fair
F7	33.3±1.05	16.1±2.25	Good and fair
F8	40.0±0.16	20.0±1.51	Fair

Physical properties of tablets

Physical properties of tablets were tested according to pharmacopoeial requirements [15,31].

The tablets were evaluated for weight variation (n=20) using a weighing balance (Mettler AT 201, Switzerland). From each batch, 20 tablets were randomly selected and weighed together. Their mean weight was calculated and then they were weighed individually.

Tablet thickness (n=20) was measured using a Vernier Caliper (Digital Caliper 0-150 mm, Comparator).

Hardness of tablets (n=10) was evaluated using the hardness tester (AEG Type AP 56 N2, Germany). Here, ten tablets were randomly selected from each series. The breaking force needed to crush the tablet was observed.

Friability test was conducted using a friabilator (Erweka TAR 120, Germany). Twenty tablets from each series were weighed and placed into the friabilator. The machine was set to 25 rpm for 4 min. After that, they were reweighed.

Tablet Disintegration Time Assay

Disintegration times were determined using the European Pharmacopeia (Ph Eur.) Apparatus [15] (Erweka Type ZT 222, Germany). Six tablets were randomly selected from each batch and were put into a basket-rack in a vessel with water at 37°C which then was covered with a disk. After the apparatus was switched on, the disintegration time of the tablets was observed.

The tablets T1-T3 were evaluated by the time of de-aggregation required to transform a tablet into small fragments, when immersed in water at room temperature, without stirring [16,18]. Herein, a petri dish (10-cm diameter) was filled with 10 mL of water at room temperature. The tablet was carefully put in the center of the petri dish and the time for the tablet to completely disintegrate into fine particles was measured.

Wetting time

The wetting times were determined for series of tablets T1, T2 and T3. The wetting time of the tablets (n = 6) was measured by placing five circular tissue papers of a 10-cm diameter in a glass petri dish with a 10-cm diameter. Ten milliliters of water containing methylene blue (0.1%, w/v) were added to the petri dish [33]. A tablet was carefully placed on the surface of the tissue paper and the time required for the dye to reach the upper surface of the tablet was recorded. The wetting time is that which is necessary for a complete wetting of the tablet. The measurements were carried out in triplicate for the different samples. The wetting time was recorded and water absorption ratio was calculated using the following formula:

$$\text{Water absorption ratio} = (W_a - W_b)/W_b \quad \textbf{Eq. 2.}$$

where, W_b and W_a is weight of the tablet before and after absorption of water, respectively.

Drug content

Ten tablets from each batch were randomly selected and crushed together. Then, 200 mg of powder was transferred into a 100 ml volumetric flask and 50 ml 0.1 M HCl was added. The flask was shaken for 10 min in a mixer (Vortex Genius 3) and the flask was diluted with 0.1 M HCl. Next, the mixture was filtered through a Whatman filter (0.45 μm pore size) and 2 ml of the solution was transferred into a 50 ml volumetric flask and diluted with 0.1 M HCl. The absorbance of this solution was determined by UV spectrophotometry at 251 nm (Omega UV – VIS, Thermo Scientific, England). The PAP concentration in the acidic medium was calculated according to the linear regression equation obtained from a standard curve ($y = 0.1503\,x + 0.0513$; $r^2 = 0.999$; n = 5). This method obeys Beer's Law within the concentration range of 2.5–20 μg/ml for PAP. The experiment was repeated six times (n = 6).

The physical properties of tablets T1-T8 and content of PAP are shown in Table 3.

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Table 3. Physical properties of tablets

Test	Results							
	T1	T2	T3	T4	T5	T6	T7	T8
Weight (mg) mean SD	201±0.84	202±0.55	201±0.90	197±0.59	202±0.57	200±0.88	205±0.53	203±0.61
Thickness (mm) SD	2.58±0.05	2.67±0.02	2.56±0.04	2.75±0.06	3.09±0.05	2.77±0.05	2.94±0.04	2.86±0.02
Disintegration time (s) SD	25±5	45±3	150±5	> 900	> 900	> 900	> 900	> 900
Hardness (kN), SD	7.6±0.1	8.4±0.08	7.6±0.09	8.1±0.1	8.2±0.1	8.7±0.07	7.8±0.09	6.8±0.1
Friability (%)	0.17	0.20	0.35	0.23	0.25	0.20	0.24	0.27
Wetting time	13.4±3	52.2±8	91.6±10	-	-	-	-	-
De-aggregation time (s)	24±6	77±8	245±12	-	-	-	-	-
Drug content (%) PAP, SD	97.48±1.53	97.51±2.71	94.90±3.24	99.41±0.67	96.89±2.98	95.99±3.07	94.55±1.04	94.74±1.83

Drug release of tablets

The dissolution test was carried out by way of utilizing the Ph Eur. Apparatus 2 [15,31] (Erweka, Germany) with a paddle rotated at 75 rpm. For the test, 900 ml of a dissolution medium maintained at 37±0.5°C was used.

For tablets T1-T3, the dissolution test was carried out twice in two dissolution media: the first within 20 min in 0.1M HCl and the second within 20 min in phosphate buffer at pH 6.8. Each tablet was placed in each of the six vessels of the paddle apparatus. After appropriate intervals of time, 2 ml samples were collected and an equivalent amount of a dissolution medium (2 ml) was added to the vessels. Each solution containing the drawn samples was filtered through a Whatman filter paper (0.45 μm pore size), and, after dilution, analyzed spectrophotometrically at 251 nm in acidic medium and 238 nm in phosphate buffer. Approach utilized for PAP concentration assay in an acidic medium can be found in the Drug content section. The PAP concentration in phosphate buffer at pH 6.8 was calculated according to the linear regression equation obtained from a standard curve ($y = 0.1309\ x + 0.0176$; $r^2 = 0.9999$; $n = 5$). This method obeys Beer's Law within the concentration range of 2.5-20 μg/ml for PAP.

All results are presented in Figures 1 and 2.

For tablets T4-T8, the dissolution test was conducted within 24 hours using as a dissolution medium, 0.1M HCl (pH 1.2) for the first 2 h, this was then replaced with the same volume of a phosphate buffer at pH 6.8 maintained at 37±0.5°C. Two milliliters of the sample were subsequently withdrawn at specified time intervals and replaced with the same volume of pre-warmed (37°C±0.5°C) fresh dissolution medium. The samples withdrawn were prepared and assayed as written above. Data are shown in Figure 3.

Statistical analysis

Statistical and kinetic analyses were made using Statistica 8.0 software. The data obtained were subject to statistical analysis using one-way ANOVA and a p value of <0.05 was considered as being statistically significant.

In vitro release kinetics

In this work, model dependent approaches were used for comparison of dissolution profiles. The drug release data were fitted to the various kinetic models, including zero-order (Eq. 3), first-order (Eq. 4), Higuchi's square root of time (Eq. 5), and Hixon and Crowell's cube root of time (Eq. 6) to determine the release rate (K) and coefficient of determination (R^2).

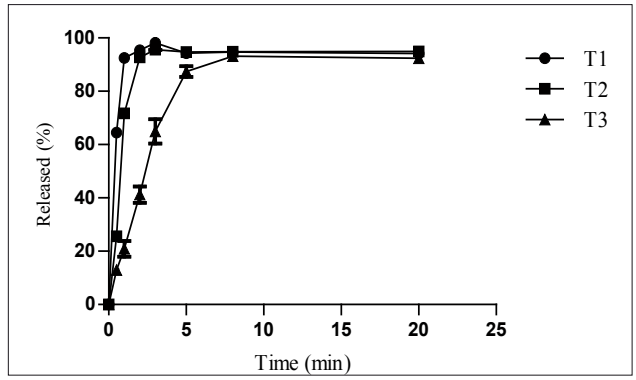

Figure 1. Percentage average release of PAP from tablets T1-T3 from 0.1 M HCl (mean values, n = 6, ± SD, p>0.05)

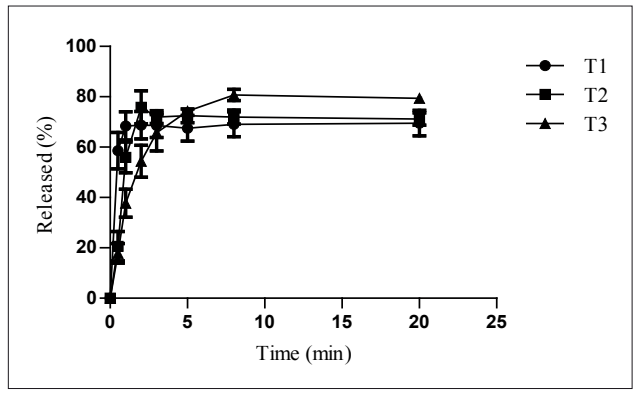

Figure 2. Percentage average release of PAP from tablets T1-T3 from phosphate buffer at pH 6.8 (mean values n = 6, ± SD, p>0.05)

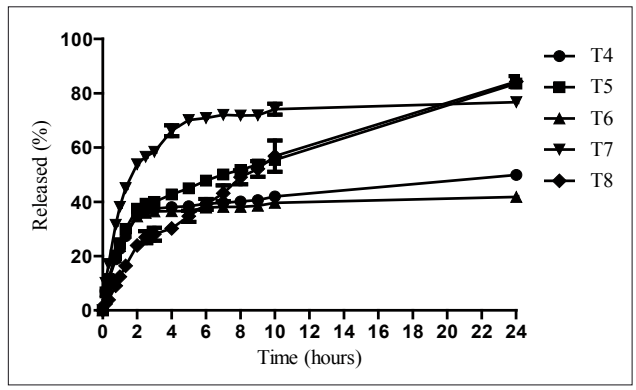

Figure 3. Percentage average release of PAP from tablets T4-T8 (mean values n = 6, ± SD, p>0.05).

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$$Q = K_0 t \quad \textbf{Eq. 3.}$$

$$Log\ Q = Log\ Q_0 - K_1 t / 2.303 \quad \textbf{Eq. 4.}$$

$$Q = K_H t^{1/2} \quad \textbf{Eq. 5.}$$

$$Q_0^{1/3} - Q^{1/3} = K_{HC} t \quad \textbf{Eq. 6.}$$

where Q and Q_0 are the percent of drug released at time t and initial amount of drug, respectively; K_0, K_1, K_H, K_{HC} are the rate constants of zero-order [20], first-order [8], Higuchi [21] and Hixon-Crowell model [10], respectively.

To evaluate the mechanism of the drug release from tablets, the first 60% of the drug release data were plotted by way of Korsmeyer-Peppas equation [34] (Eq. 7) to determine the release exponent (n) and coefficient of determination (R^2).

$$Q_t / Q_\infty = K_{KP} t^n \quad \textbf{Eq. 7.}$$

where Q_t is the percent drug release at time t; Q_∞ the percent drug release after infinite time, usually taken as 100; Q_t/Q_∞ is the fraction of drug released at time t; and K_{KP} in the Korsmeyer's model is a release constant incorporating the structural and geometric characteristics of the system; n is the release exponent, indicative of the drug release mechanism. In addition, for determination of the exponent n, one must use only the initial portion of the release curve ($Q_t/Q_\infty < 0.6$).

For the cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian diffusion. An exponent value of 0.89 is indicative of case II transport or typical zero-order release, $n > 0.89$ is super case-II transport [34]. The data are shown in Table 4.

Quantification of water uptake and erosion determination.

The studies were performed for tablets F4-F8. One tablet of each series was placed in six flat dissolution vessels. These contained the dissolution medium (0.1 M HCl). At time intervals of 60 min and 120 min, the tablets were withdrawn from the acidic medium from two vessels and weighed after excess of the solution and the surface was removed with filter paper. The wetted samples were then dried in an oven at 40°C up to constant weight. The four other vessels containing the acidic medium were changed to phosphate buffer at pH 6.8. During the next further 60, 120, 180 and 240 min, the tablets were taken out, weighed and dried at temp. 40°C as described above. The increase of the weight of the tablets corresponds to the weight of the liquid uptake. This was calculated according to Eq. 8 [7,32]:

$$Q = 100\ (W_w - W_i)/W_i \quad \textbf{Eq. 8.}$$

where Q is the percentage of liquid uptake, W_w and W_i is the mass of the hydrated samples before drying and the initial starting dry weight, respectively.

The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using Eq. 9:

$$E = 100\ (W_i - W_f)/W_i \quad \textbf{Eq. 9.}$$

where W_f is the final mass of the same dried and partially eroded sample.

The entire process was repeated to get three values for each time point, and the average was calculated. Results are shown in Figures 4 and 5.

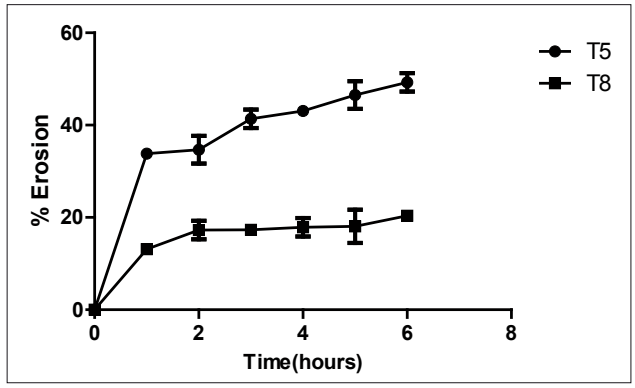

Figure 4. Percentage of erosion (mean values n = 6, ± SD, p>0.05)

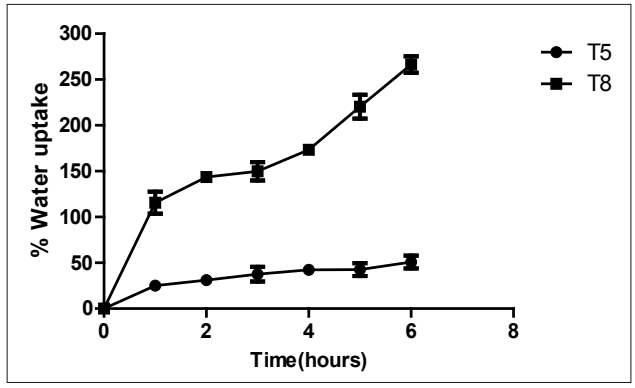

Figure 5. Percentage of swelling (mean values n = 6, ± SD, p>0.05)

Table 4. Kinetic parameters of PAP release from the tablets

	Zero- order Model		First –order Model		Higuchi	Model	Hixon-Crowell Model		Korsmeyer-Peppas Model	
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	n	R^2
T4	1.438	0.5093	-0.0217	0.5866	8.9339	0.7537	-0.0515	0.3936	0.4063	0.8852
T5	2.4967	0.7259	-0.0491	0.8886	14.383	0.9238	-0.0745	0.5356	0.48	0.9362
T6	1.0826	0.3729	-0.0154	0.4104	7.2084	0.6338	-0.0417	0.3031	0.3808	0.8566
T7	2.3764	0.4446	-0.055	0.56	15.505	0.7257	-0.0624	0.3562	0.6251	0.9743
T8	3.2123	0.8448	-0.0615	0.9674	17.695	0.983	-0.1093	0.6247	0.7588	0.9757

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RESULTS AND DISCUSSION

Physical properties of the prepared tablets

Eight formulations of tablets containing 25% PAP prepared by direct compression as a model substance which differ in excipients are presented in Table 1.

As shown in Table 2, the flowability of powders was evaluated based on the results of angle of repose and Carr's index. Compressibility index values up to 15% and angle of repose up to 35 are known to result in good to excellent flow properties [31]. The formulation F4 consisting of Kollidon SR and lactose as excipients had good flow character. However, while the powders F3, F5-F7 presented good flow properties due to angle of repose, compressibility values in the range 16 to 20 revealed only a fair flow character. Only fair, but acceptable flow properties, were also revealed for powders F1, F2 and F8, because the angle of repose values were in the range 36 to 40. Still, all of these results indicate that the powders F1-F8 possessed acceptable flow properties.

The results of the uniformity of weight, hardness and friability of the tablets are in agreement with pharmacopeial requirements (Table 3). The studies of disintegration time showed that three formulations (T1-T3) disintegrated within 15 min and other tablets (T4-T8) had disintegration times longer than 15 min. The disintegration times for tablets T1 amounted to 25 s. Taking the above data into account, tablets T1 can be classified as being ODT, because ODT is defined as a solid dosage form which disintegrates rapidly usually within a matter of seconds when placed upon the tongue [22,29,30]. The tablets T4-T8 did not disintegrate within 15 min., which indicated that they may be classified as being prolonged release tablets. Such classification was predictable because formulations T4-T8 contain the addition of Kollidon SR or Methocel K15M which are used in solid dosage forms with sustained release, and both Kollidon SR and hydroxypropyl methylcellulose are employed as a matrix former in controlled release tablets [23,24,33-35].

The effect of excipients on disintegration time and the wetting time

The assessment of disintegration time for ODT is difficult using only the tests for conventional tablets, because results obtained from the conventional disintegration tests appear not to reflect the disintegration time in the human mouth [1]. The results of the de-aggregation time of the tablets presented in Table 3 show that the shortest disintegrate time (de-aggregation) was that of T1 (24 s), while T2 displayed a time that was just over a minute, and the longest disintegrating interval was that of T3 (245 s). The data of de-aggregation and disintegration time are the same for T1, but that for T2 and T3 were twice longer. The wetting time of tablets changed similarly: it was the shortest for T1 and the longest for T3, which confirmed a shorter wetting time and implies a faster disintegration of the tablet [2]. Upon analyzing the formulations T1-T3, it was noticed that both T1 and T2 were comprised of 35% Avicel PH 102 as a filler and disintegrant, 1% Kollidon CL as a superdisintegrant and 1% magnesium stearate as a lubricant, but differed in the addition of 38% lactose and β-CD in T1 and T2, respectively. Tablets T3 contained a 38% addition of β-CD and a 35% addition of lactose, but was without Avicel. The disintegration time was still longer than T2. This suggested that the addition of β-CD results in a longer tablet disintegration time. β-CD is a cyclic oligosaccharide composed of seven dextrose units joined through one to four bonds. β-CD has good compression characteristic as it has a good compressibility index. Hence, it is considered to be a promising direct compression material [24,25]. In a study conducted by Late and Banga [25], a higher concentration of β cyclodextrin was found to improve tablet hardness without increasing the disintegration time. Thus, β-CD was proposed as a suitable diluent to achieve fast disintegrating tablets with sufficient hardness.

Release rate studies

The release studies carried out in 0.1M HCL showed that at least 80% of PAP is released within 3 min from T1 and T2. Specifically, the data presented in Figure 1 indicate that in a time up to one minute, 92.5% of PAP was released from T1, while for T2, 95.6% PAP was released in an interval up to 3 min. The release study was also carried out utilizing phosphate buffer at pH 6.8 to imitate the conditions of the environment in the human mouth [16]. In this form of the study, the data in Figure 2 indicate that about 70% of the active substance from T1, and for T2, 68.6% and 71.9%, was released within 3 min., respectively.

The release study of PAP from tablets T4-T8 was carried out first in 0.1M HCL up to 120 min. and then in phosphate buffer at pH 6.8. The results in Figure 3 show that in an acidic medium, within 2 hours, 35-37% of PAP was released from T4, T5, T6, 54% from T7 and 24% from T8. After the change of an acidic medium into phosphate buffer at pH 6.8, it was noticed that within 10 h, 40-42% of PAP from T4 and T6; 55-57% from T5 and T8; 74% from T7 was released, respectively. Continuing the study to 24 h, it was observed that from T5 and T8, the amount of the released active substance increased up to above 80%, but from other tablets, that of T4, T6 and T7, only 50%, 42% and 77% of PAP was released, respectively.

The amount of the released PAP during the release study from the tablets depended on the composition of excipients contained in the formulas. Kollidon SR is a substance typically used for prolonged release solid dosage forms [5,19,23,35,37]. Four series of tablets contain the addition of Kollidon SR in amounts of 40% and 25% in T4-T6 and T7, respectively, but the obtained release profiles of PAP were different. Only one of the presented formulas T4-T7 had the desired release profile. This is T5, which contains the addition of Kollidon 30 in an amount that is 34%. From T5, within 6 h, 10 h and 24 h, about 48%, 55% and 80% of PAP was released. This is in comparison with the formula T7 containing, besides Kollidon SR, both lactose (14%) and Kollidon 30 (34%). Herein, in up to 6 h, 10 and 24 h, above 70%, 74% and 77% of PAP was released, respectively. The profile of PAP release from T8 was similar to T5. From F8, within 6, 10, 24 h, 39%, 57% and 80% of PAP was released, respectively. The T8 tablets did not contain Kollidon SR, but this formula was analogous to T7, because it was comprised of lactose (14%), Kollidon 30 (34%) and Kollidon CL (1%),

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yet was different in the addition of Methocel K15M (25%), instead of Kollidon SR. The data in Figure 3 show that the prolonged release of PAP from T8 tablets is due to the the effect of Methocel (25%), with the addition of Kollidon 30 (34%), Kollidon CL (1%) and lactose (14%), while an analogous profile of the release can be obtained from the T5 tablets which contain Kollidon SR (40%) and Kollidon 30 (34%). HPMC is a hydrophilic polymer carrier used for the preparation of oral controlled drug delivery systems [33,35]. It has been employed widely for the development of sustained release dosage forms such as the matrix tablets of high water soluble drugs [32]. In the study conducted by Akbari et al. [3], the effect of two types of Methocel – K4M and K15M – on the release of diclofenac sodium from the matrix tablets was tested. This study has shown that the release rate of the drug decreased with the increasing polymer content, and was dependent on the type of HPMC used.

Release kinetics

The correlation coefficient (R^2) was used as an indicator of the best fitting for each of the models considered (Table 4). The *in vitro* dissolution data of PAP from formulations T5 and T8 (Fig. 3) best fitted all mathematical models, and for T5, ranked in order of Korsmeyer-Peppas > Higuchi > First order, whereas for T8, the kinetics model ranked in order of Higuchi >Korsmeyer-Peppas > First order >Zero order. The *in vitro* release profiles of PAP from formulations T4, T6 and T7 were best explained by the Korsemeyer-Peppas model.

The obtained data were plotted into the Korsmeyer-Peppas model to find out the confirmed diffusion mechanism. Herein, the *in vitro* dissolution data from formulations T5, T7 and T8 exhibited good fitting for the model, with the correlation coefficients (R^2) being 0.9362, 0.9743 and 0.9757, respectively. The values of the exponent (*n*) providing the type of release mechanism were: 0.48, 0.6251 and 0.7588 for formulations T5, T7 and T8, respectively, indicating a coupling of drug diffusion in the hydrated matrix, as well as polymer relaxation, the so-called anomalous transport (non-Fickian).

Water uptake and erosion by the prepared tablets

The rate of swelling and erosion of tablets T5 and T8 up to 6 h were presented in Figures 4 and 5. Here, it can be seen that the percentage of erosion was higher in tablets of T5 containing Kollidon SR, when compared to formulation T8 with Methocel K15M. However, the percentage of swelling was higher in tablets T8 containing HPMC K15M. In the study conducted by Sahoo et al. [32], the percentage of erosion and swelling was higher in the case of tablets containing Kollidon SR, when compared to a formulation with HPMC K15M. This shows that the degree of swelling depends on the concentration and type of polymer occurring in the matrix [32].

CONCLUSION

Tablets with a wide range of release from fast to prolonged release of an active substance containing different types of povidone and other excipients were prepared by direct compression. The tablets with fast disintegration and release contain Kollidon CL, lactose and Avicel, but the use of β-CD instead of lactose or Avicel caused a slight prolongation in the disintegration time of these tablets and the release of the contained active substance. The other compositions of tablets can be considered as being of prolonged release, but only two of these show the best fitted mathematical models. The first formulation containing Kollidon SR (40%) with the addition of Kollidon 30 (34%), and the second which is composed of HPMC K15M (25%), Kollidon 30 (34%), Kollidon CL (1%) and lactose (14%) are those which are best fitted to the Higuchi model. The release mechanism of these two formulations plotted into Korsmeyer-Peppas indicates a coupling of drug diffusion in the hydrated matrix, as well as polymer relaxation, the so-called anomalous transport (non-Fickian).

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