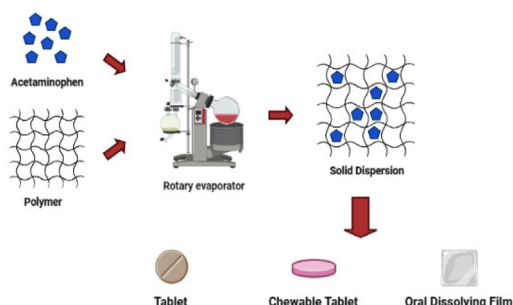


Improvement of Medication Adherence and Controlled Drug Release by Optimized Acetaminophen Formulation

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Received December 16, 2020 / Revised March 18, 2021 / Accepted March 23, 2021

Abstract: Acetaminophen (paracetamol, APAP) is a major component of Tylenol, Penzyl Q, and Panpyrin, and is the most commonly used antipyretic analgesic in children. The conventional oral drug delivery systems of APAP are pills and tablets. However alternative drug delivery methods are desirable in case of pediatric or geriatric patients, especially for drugs like APAP that must be taken in large doses at once. Another requirement for a good drug delivery system is the rapid dissolution to ensure a rapid therapeutic action as pain reliever. In this study Acetaminophen (paracetamol, APAP) was encapsulated in a water-soluble polymer. After the preparation of the solid dispersion by encapsulating acetaminophen in polyvinylpyrrolidone, the resultant granules were used in three formulations: tablets, chewable tablets, and oral dissolving films (ODF). Solid dispersions and prepared formulations were evaluated by Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffractometer (XRD), and universal tensile machine (UTM), and the release behavior was compared. As a result, it was confirmed that the oral dissolving films can be taken easily because it has the advantages of both tablet and liquid dosage form accurate dosage, easy administration, easy swallowing, and fast bioavailability. Furthermore, the drug absorption rate can be effectively increased by changing the formulation.



Keywords: acetaminophen, chewable tablet, oral dissolving film, formulation, drug release, medication compliance.

1. Introduction

Acetaminophen (commonly known as Paracetamol, APAP) is among all drugs one of the most widely used. APAP is in fact the standard antipyretic and analgesic for mild to moderate pain states and is considered a safe medication that can be administered also to children without severe side effects.¹ The popularity of APAP has grown since the discover of the side effects of its main competitor, Aspirin. APAP is metabolized in the liver to sulfate and glucuronide compounds and excreted in the urine,¹ its main side effect appeared only in case of overdosage that has been proved to cause acute centrilobular hepatic necrosis without early symptoms. However, APAP is usually well tolerated even in high dosage. The adult therapeutic dose of APAP is

1 g single dose or a dosage of 4×1 g daily at 4–6 h intervals.² On pediatric patient aged between 2 and 12 years the therapeutic dosage is usually calculated on the weight (10–15 mg/kg) and administrated every 4–6 h. The APAP analgesic effect begins approximately after 10 min from the oral administration, and its half-life is approximately 1–4 h.³

Oral drug delivery is the most used administration method among all available systems because its ease to use and cost effective. Furthermore, it has a high patient compliance to the therapy and fewer side effects compared to other methods.^{3,4} Most of commercially available oral drug carriers are capsules and tablets. However, these carriers could be problematic both for pediatric and geriatric patient with fear of choking and when swallowing is inconvenient as in the case of cough or throat diseases. In addition, APAP has to be taken in a fairly large amount at a time. Therefore easy-to-swallow formulations with suppressed bitterness could be suitable for improve the patient compliance to the therapy. In this direction several formulations, beside the traditional pills, have been developed in literature to make APAP appealing.

Recently, alternative oral drug delivery systems, like films and

Acknowledgments: This research was supported by the bilateral cooperation Program of the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2019K2A9A1A06098563).

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chewable tablets have started gaining popularity among the consumers because of the rapid disintegration or dissolution, and the possibility to self-administration, even without water. Therefore, the pharmaceutical industry is designing and developing new types of drug delivery systems capable to achieve a rapid dissolution inside the mouth to avoid the requirement of ingestion.^{5,6} Buccal drug delivery has become an important alternative to the conventional route of drug administration. Since the drug is absorbed through the oral mucosa with this route of administration, it is possible to bypass the primary metabolism of the liver and avoid drug degradation or metabolism in the gastrointestinal tract.^{7,8}

Among the various bio-adhesive mucosal dosage that has been developed, the use of polymeric films for buccal delivery (also known as oral dissolving films) has the advantage that the drug is localized in a particular region and, as consequence, the overall bioavailability is increased by prolonged retention time.⁹⁻¹² In addition, the possibility to easily control the film fabrication makes the oral films a flexible system in which the dimension and the shape of the film. It can be controlled to tune the degradation of the film and, as direct result, the absorption of the drug.⁹ The oral dissolving films have all the advantages of a tablet (accurate dosage and easy administration) and a liquid dosage form (easy swallowing and fast bioavailability).^{13,14} All these proprieties have prompted many pharmaceutical companies to convert their products from tablets to rapidly thin oral dissolving films (ODF).¹⁵ Chewable tablet is also a good alternative to the traditional tablets and pills. It is particularly pleasant in case of pediatric patients because it can be used to effectively cover the drug taste as an oral film, it has the advantages of the good stability, the accurate dosage, the portability, and the ease of delivery. Several of this drug delivery system have been also developed for APAP. In the specific case of pediatric users, jelly¹⁶ and ODF¹⁷⁻²⁰ are well optimized systems for the administration of APAP. However, a comparative study among their performances has never been reported.

In this work we studied and compared three typology of oral delivery systems for APAP using as reference the formulation in tablets. In particular, tablets, chewable tablets, and rigidity-regulated films were prepared. The solubility of APAP was improved by an encapsulation in polyvinylpyrrolidone (PVP) K30 using a rotary evaporation method, which is suitable for large production.^{21,22} Mannitol, glycerin, magnesium stearate, and sodium starch glycolate were added to the different compositions based on the desired formulation (tablets, chewable films, and rigidity-regulated films). The drug release rate was then evaluated to

verify its tunability according to the formulation. X-ray diffraction (XRD) and Fourier transform-infrared (FTIR) spectroscopy, mechanical compression, and high-performance liquid chromatography (HPLC) were carried out to evaluate the crystallinity, the chemical composition, the elasticity of prepared samples, and the solubility, respectively. On the drug release a study on the release kinetics have been done both with commonly used kinetics models (Korsmeyer-Peppas, Zero-order model, Higuchi model, first order model and Hixson-Crowell model) and with a response surface method (RMS) that allowed to introduce in the kinetics the effect due to the pH variation.

2. Experimental

2.1. Materials

APAP (Acetaminophen P., Hwail Pharmaceutical, Republic of Korea), sodium starch glycolate (SSG, Hwawon Pharmaceutical, Korea), and magnesium stearate (Mg-st, Junsei Chem Co. Ltd, Japan) were used in this study. Polyvinylpyrrolidone (PVP) K30, mannitol, glycerin and Hydroxypropyl cellulose (HPC) were purchased from Sigma-Aldrich (USA). All other chemicals and organic solvents used HPLC-grade products. The structure of APAP is shown in Figure 2.

2.2. Preparation of solid dispersion of APAP

To increase the solubility of APAP, a solid dispersion encapsulated with PVP K30 as a water-soluble polymer was prepared (The weight ratio of APAP and PVP K30 = 1:5). After dissolving APAP and PVP K30 in methanol, a solid dispersion was prepared using a rotary evaporator (N-1000, EYELA, Japan) under the constant condition of 50 rpm speed and 75 °C temperature. The solvent was completely removed with a freeze dryer (FD8508, IIShin, Republic of Korea), and a freezer mill (Freezer mill 6750, SPEX, USA) was used to obtain a fine powder.

2.3. Thermodynamic analysis of solid dispersion

The encapsulation of APAP within the PVP K30 was confirmed by DSC (DSC 4000, Perkin Elmer, Japan). Four mg of the solid dispersion were placed in an aluminum pan, and then the DSC was conducted in the range from 0 to 200 °C with a temperature rate of 30 °C/min.

2.4. Crystallographic analysis of solid dispersion

The XRD spectra (MAX 2500 X-ray diffractometer, Rigaku, Japan) were analyzed to confirm the encapsulation of APAP. Samples were sufficiently laminated on a 0.3 mm transparent glass sub-

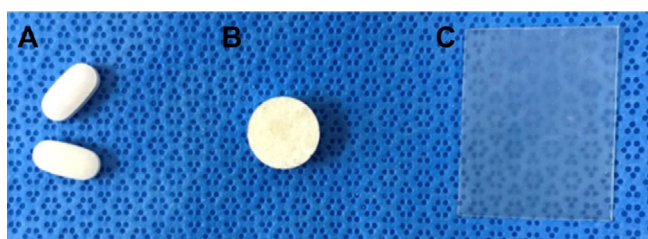


Figure 1. Different formulations tested: (A) normal tablet, (B) chewable tablet, and (C) film.

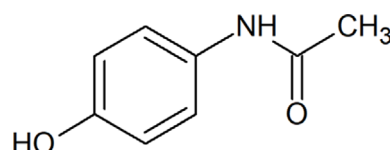


Figure 2. Chemical structure of acetaminophen.

Table 1. Formulation of normal tablets, chewable tablets, and films of acetaminophen (unit: mg). Encapsulation efficiency in percentage

			Normal tablet	Chewable tablet	Hard film	Soft film
Solid Dispersion	API	APAP	50	100	100	100
	Polymer	PVP K30	250	500	500	500
Diluent		Mannitol	125	250	250	250
Disintegration agent		SSG	50	100	100	100
Binder	Hydroxypropyl cellulose		20	0	40	0
Plasticizer	Glycerin		0	40	0	40
Lubricant (1%)		Mg-st	5	10	10	10
Dosage			*2	*1	*1	*1
Total (100%)			1000	1000	1000	1000
Encapsulation efficiency (%)			95.52 ± 0.42	96.35 ± 0.72	98.46 ± 0.98	97.78 ± 1.02

strate, and then analyzed under the conditions of a gap size of 0.02°, a speed of 4°/min, a measurement range of 5–60°, a current of 30 mA, and a voltage of 40 kV.

2.5. Fabrication of normal tablets, chewable tablets, and films

Tablets, chewable tablets, and films were prepared by mixing the different additives according to Table 1. Mannitol, SSG, HPC, and glycerin were used as a sweetener and excipient, a disintegrant agent, a binder, and a plasticizer, respectively. The tablets were designed to take 2 tablets per day due to the volume limitation. The oral films and the chewable tablets were designed to decrease the dose to 1 tablet per day. Chewable tablets were prepared in the same way as tablets, but glycerin was added instead of HPC because of its viscosity and strength. The solid dispersion, mannitol, SSG, HPC, glycerin, and Mg-st were mixed well by a vortex mixer (DAIHAN Scientific, Republic of Korea). Tablets were prepared placing the mixture into a mound in a single tablet punch press applying a pressure of 50 MPa. Hard films were prepared by a heating press (Dae Heung Science, Republic of Korea). To increase flexibility of films, sweetener was added instead of a binder and glycerin as a plasticizer was diluted to 50% in distilled water, prior to its addition. In the same way as the hard films, soft films were prepared using a heating press.²³ To obtain films with a thickness of 0.35 mm, the heating press conditions was set at 170 °C for 5 min under the pressure of 10 MPa.

2.6. Structural analysis of solid dispersion and each formulation

The structural changes in the process of preparing solid dispersion and making it into tablets, chewable tablets, and films were analyzed by FTIR (GX, Perkin Elmer, Waltham, Massachusetts, USA) in the 4000–600 cm^{−1} range with a resolution of 1 cm^{−1}, 16 spectra were collected for each sample and mediated to increase the signal to noise ratio.

2.7. Mechanical strength of hard film and soft film

To analyze the mechanical strength of the films, tensile strength was measured using a universal tensile machine (Quasar 30, Galdabini, Italy). The stress range was 0–1.0 MPa, and elongation was

measured within the range of 0–0.4%. The measure was conducted until fracture of samples. The ultimate strength and strain were evaluated when the fracture occurred. The Young's modulus was calculated as the angular coefficient in the initial linear part of the stress-strain curve, where the mechanical behavior was elastic.

2.8. Dissolution test and HPLC analysis

Dissolution test was conducted by HPLC analysis to compare the dissolution rates of each formulation. The dissolution test was based on the first method (rotary specimen tube method) among the 12th edition of the Korean Pharmacopoeia.²⁴ A first solution, to simulate the gastric acid, was prepared by dissolving 2.0 g of sodium chloride in 7.0 mL of hydrochloric acid and adding water to reach the volume of 1,000 mL. This solution was colorless and transparent with a pH of 1.2. A second solution at pH 4.0 was prepared by mixing with 4L of water, 9.4 mL of acetic acid and 4.9 g sodium acetate triol. A third solution to simulate the saliva was prepared by mixing a phosphate buffer solution (pH 6.8) and water in a 1:1 volume ratio. The dissolution of each formulation was tested using a dissolution tester (DST-610, Labfine, Republic of Korea) at a rotation speed of 100 rpm, a solution volume of 900 mL, and a temperature of 37±0.5 °C. Two mL of each sample was taken at each time point (0, 5, 10, 15, 30, 45, 60, 90, and 120 min), and the same amount of eluate was refilled. The taken eluate was filtered through a 45 µm syringe filter and analyzed by HPLC. HPLC (NS-4000 HPLC, Futecs, Republic of Korea) was performed with an autosampler (S6300 SAMPLE INJECTOR, Futecs, Germany) and a silica gel column (Intersil® OSD-3 C18, GL Science Inc, South Korea). The analysis was performed by injecting 100 µL of sample at a flow rate of 1.0 mL/min and a temperature was 35±5 °C. The mobile phase was prepared by mixing 400 mL of distilled water, 40 µL of phosphoric acid (85% aqueous), and 80 mL of acetonitrile. A wavelength of 254 nm was used. On the release behaviour five different drug release kinetic models have been tested: Korsmeyer-Peppas, Zero order, Higuchi, First order, and Hixson.^{25,26} These models are briefly described in the following list:

1. Korsmeyer-Peppas model: $(M_t/M_\infty) = Kt^n$, where M_t is the fraction of APAP released at the time t , M_∞ is the total amount of drug, K is the release rate constant, and n is the release exponent.

2. Zero-order model: $M_t = K_0 t$, where M_0 is the zero-order release constant.
3. Higuchi model: $M_t = K_H \sqrt{t}$, where K_H is the Higuchi dissolution constant.
4. First-order model: $\log(M_t) = K_0 t / 2.303$, where M_0 is the zero-order release constant.
5. Hixson-Crowell model: $\sqrt[3]{W_0} - \sqrt[3]{W_t} = K t$, where W_0 is the initial amount of APAP, W_t the remaining amount of DCF at time t and K a constant.

The Parson's index (R^2) has been used to evaluate the goodness of fit and select the best fitting model. To consider also the effect of the pH an additional approach has been used. The empirical equation has been extrapolated to describe the release kinetics of the drug according to the pH and the formulation by the use of a RMS.²⁷⁻³⁰ Using this method we were able to verify the eventual presence of statistically relevant effect due to the mixed effect³¹⁻³³ of the two considered factors (pH and time). Both factors were considered continuous, an ANOVA test followed by a Turkey multi-comparison was conducted to verify the significance of each term to include in the model. Only the terms with a significant effect ($p \leq 0.01$) were included in the model. The model was considered significant with a p-value ≤ 0.05 . The drug upload efficiency was calculated by evaluating the mass of the APAP inside the formulation after the complete dissolution by the use of HPLC (m_1). Knowing the initial weight of APAP (m_0) insert in each formulation the upload efficiency has been then calculated by the Eq. (1).

$$E(\%) = m_1 / m_0 \times 100 \quad (1)$$

3. Results and discussion

3.1. Thermodynamic and crystallographic analysis of solid dispersion (SD)

DSC and XRD analysis were performed to verify the encapsulation of APAP inside the PVP K30. It is very important because the degree of interaction between drug and polymer in a solid dispersion system has the greatest effect on taking the completely amorphous drug formation or reducing the particle size.²¹ The DSC analysis results are shown in Figure 3. The endothermic peak shown by the thermography of the APAP at 170 °C is compatible with the fusion of its crystal structure, as reported in literature.²¹ PVP K30 had no endothermic peak because of its amorphous structure. Also, the solid dispersion which encapsulated the APAP in PVP K30 did not show an endothermic peak. The solid dispersion in which APAP was well encapsulated with PVP K30 was confirmed through the loss of crystallinity of APAP. The XRD analysis results were shown in Figure 4. A clear set of well-defined peaks in the 11–26° range indicates that the APAP was crystalline. PVP K30 showed very broad diffraction peaks around 10–20° indicating an amorphous structure. Similar broad peaks were visible in the solid dispersion spectrum. The efficient encapsulation of APAP was then proved both by DSC and XRD analysis. The encapsulation of the active pharmaceutical ingredient (API) in PVP K30 was expected to further improve the solubility of the API.

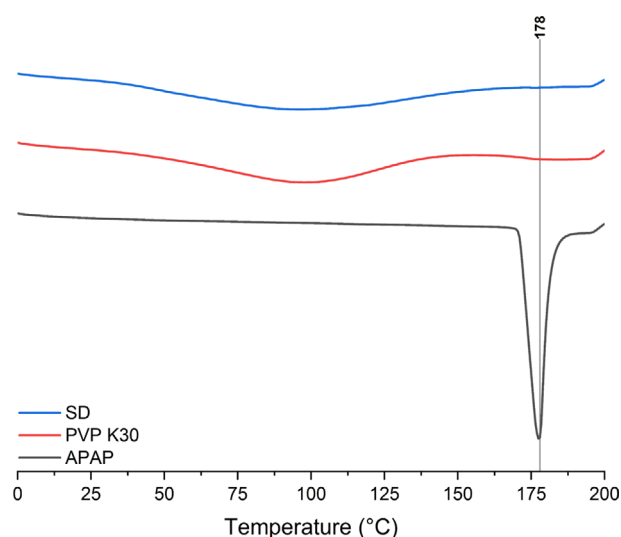


Figure 3. DSC thermograms of acetaminophen, PVP K30, and solid dispersion. The acetaminophen showed an endothermic peak around 170 °C, PVP and solid dispersion did not show endothermic peak.

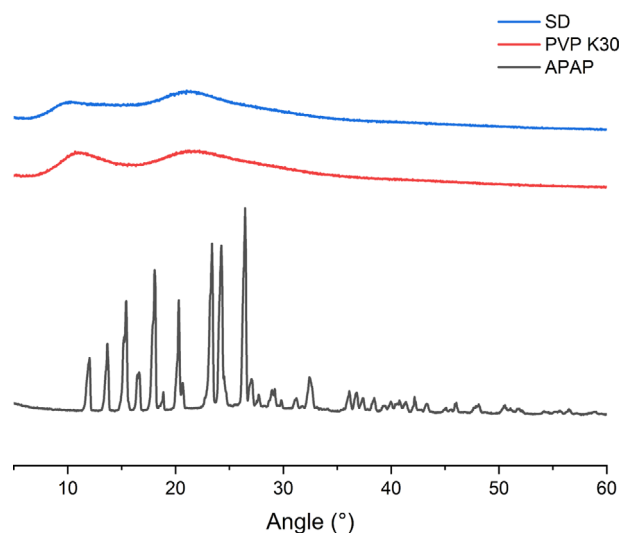


Figure 4. Powder X-ray diffraction spectra of acetaminophen, PVP K30, and solid dispersion.

3.2. Structural Analysis of solid dispersion

The encapsulation efficiency was calculated and reported in the last row of Table 1, we were able to effectively encapsulate more than 95% of the initial drug in all the formulations proving that the process was reliable. The structural analysis was conducted by FTIR analysis which results are shown in Figure 4. Several peaks present in the APAP spectrum were also recognizable in the solid dispersion obtained by encapsulating the drug into PVP K30 (Figure 5(a)) this confirmed that no chemical changes occurred during the process. In the APAP spectra the vibrational frequency at 3321 cm^{-1} was assigned to the C-H stretching of the aromatic ring,^{34,35} the band at 2878 cm^{-1} to the vibration of ethyl and methyl groups.^{34,35} The Vibrational peaks at 1650 cm^{-1} , 1609 cm^{-1} were attributed to the amide group. The prominent peaks at 1562 cm^{-1} and 1505 cm^{-1} were attributed to the C-C stretching of the aromatic group.^{34,35} The methyl group was

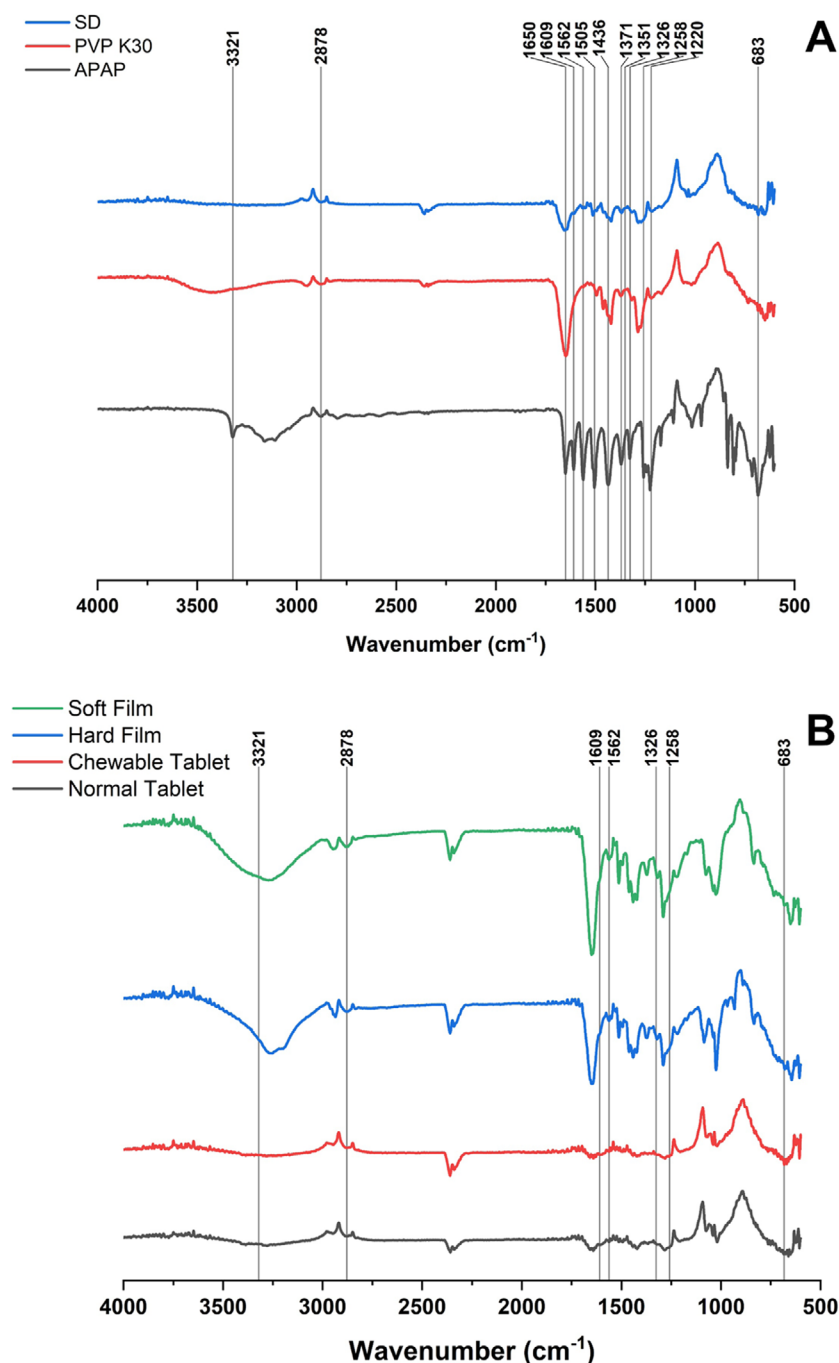
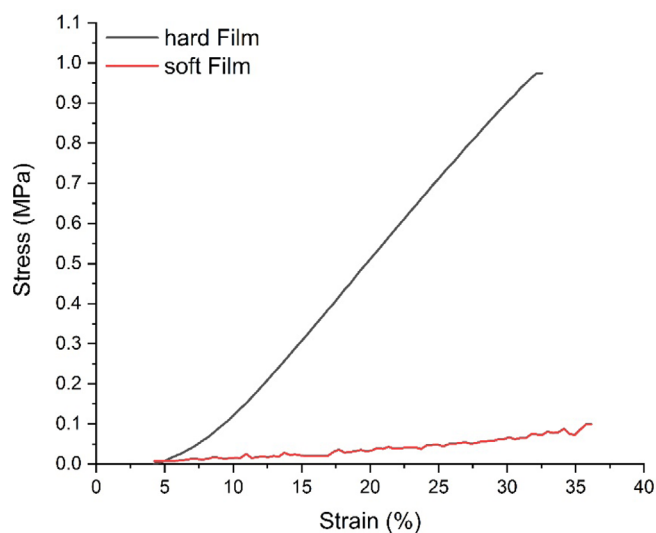


Figure 5. FTIR spectra of (A) Acetaminophen, PVP K30, and solid dispersion (B) Normal tablet, chewable tablet, hard film, and soft film. No denaturation or loss occurred during processing.

recognized by the presence of a peak 1436 cm^{-1} .^{34,35} Peaks at 1371 cm^{-1} , 1351 cm^{-1} and 1326 cm^{-1} were assigned to the $\text{H}_3\text{C}-\text{C}=\text{O}$ stretching, the symmetrical C-H bending and the symmetrical CH_3 bending, respectively.^{34,35} Peaks at 1258 cm^{-1} and 1220 cm^{-1} were both assigned to the C-N (aryl) stretching.^{34,35} All the peaks between 680 cm^{-1} and 900 cm^{-1} were attributed to the presence of the benzene ring.³⁶ Only some of these listed peaks were diagnostic of the presence of APAP in the solid dispersion, in particular we could recognize in the solid dispersion the peaks at 2878 cm^{-1} , 1609 cm^{-1} , 1562 cm^{-1} , 1326 cm^{-1} , 1258 cm^{-1} and 683 cm^{-1} . The same peaks were partially recognizable in the four-formulation pre-

pared by adding additives to the solid dispersion (Figure 5(b)). As could be expected, tablets and chewable tablets showed similar peaks with the solid dispersions because they were formed by physically mixing the solid dispersion and additives. However, different peaks from the previous formulation were observed in films prepared by application of heat and pressure. We hypothesized that the large peak centered around 3200 cm^{-1} may be due to the hydrogen bonds formed between the hydroxyl groups of APAP and the carbonyl group of PVP K30 when the films were manufactured. In addition, hydrogen bonds between APAP and PVP K30 were also affected to increasing peak intensity of the



	Ultimate Strain	Ultimate Strength	E
	%	MPa	MPa
Hard Film	32.55216	0.97425	3.9486
Soft Film	36.15168	0.09911	0.17054

Figure 6. Tensile strength of hard film (in black) and soft film (in red) within the value of the ultimate strain, ultimate strength and Young's modulus.

carbonyl bond ($C=O$; $1600\text{--}1800\text{cm}^{-1}$), also this phenomenon could be explained by the application of heat and pressure in the fabrication process.

3.3. Tensile strength of hard and soft films

Figure 6 shows the stress-strain curve obtained by testing the two film formulations. Soft films showed a behavior similar to a ductile bulk material with small deformation in uniaxial tensile test, whereas hard films showed the typical behavior of brittle materials. Brittleness is a characteristic of a material that is damaged when stressed but is less prone to deformation before fracture.³⁷ The addition of glycerol and plasticizer can explain the difference in the mechanical strength of the two films. For the hard film the ultimate strength and the young modulus resulted to be 0.974 MPa and 3.95 MPa, respectively. In case of the soft film the plasticizer caused a significant decrease in ultimate strength and Young's modulus that resulted to be 0.099 MPa and 0.17 MPa, respectively.³⁸ This effect can be effectively used to prevent the products easily broken by external shocks during distribution or storage as previously reported in several work.³⁹⁻⁴¹

3.4. Dissolution test and HPLC analysis

In Figure 7, the results of dissolution rate for each formulation under the simulated gastric juice (pH 1.2), the simulated gastric juice in the digestion phase (pH 4.0) and saliva (pH 6.8) are shown. At pH 1.2, both tablets and chewable tablets were completely dissolved after approximately 45 min. Both hard and soft films showed rapid dissolution completely dissolved within 5 min. At higher pH (both 4.0 and 6.8) tablets and chewable tablets were dissolved in 30 min, on the other hand, hard and soft films were dissolved within 5 min. The dissolution rate of the films

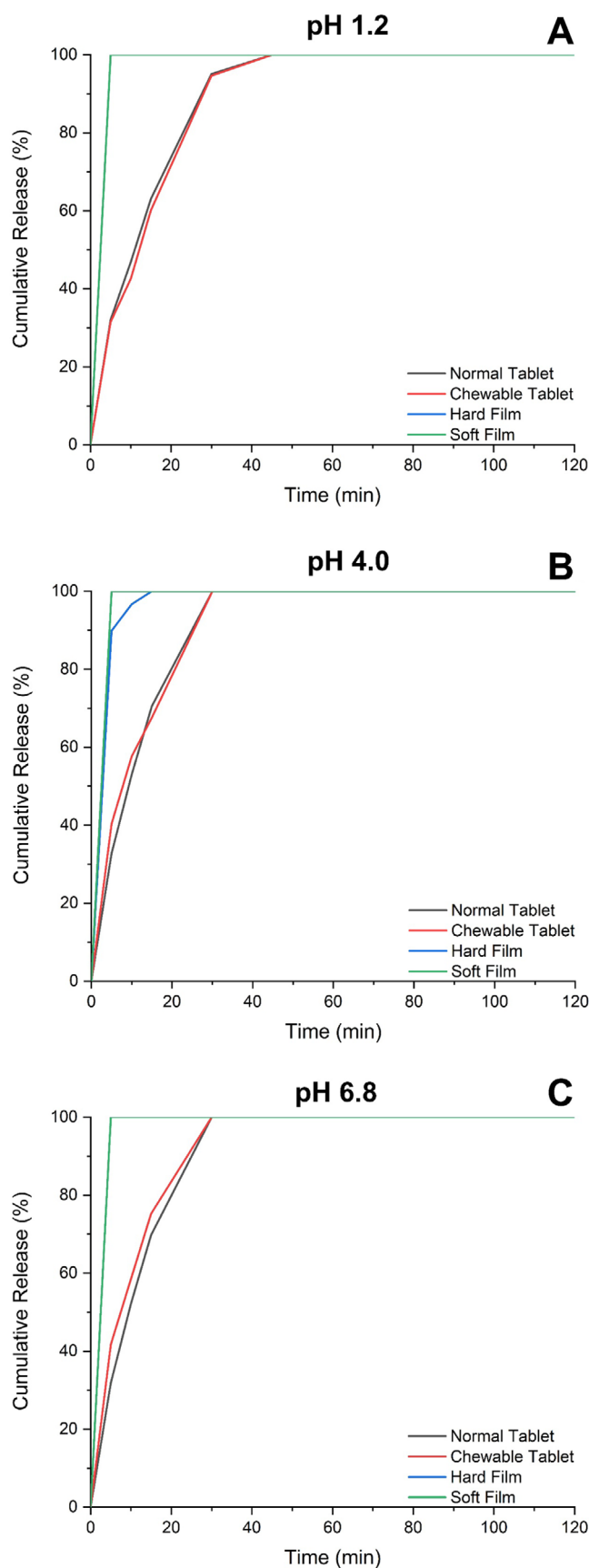


Figure 7. Cumulative release behavior of 4 formulations (normal tablet, chewable tablet, hard film, and soft film) in (A) pH 1.2 (simulated gastric juice), (B) pH 4.0 (simulated gastric juice in digestion phase) and (C) pH 6.8 (simulated saliva).

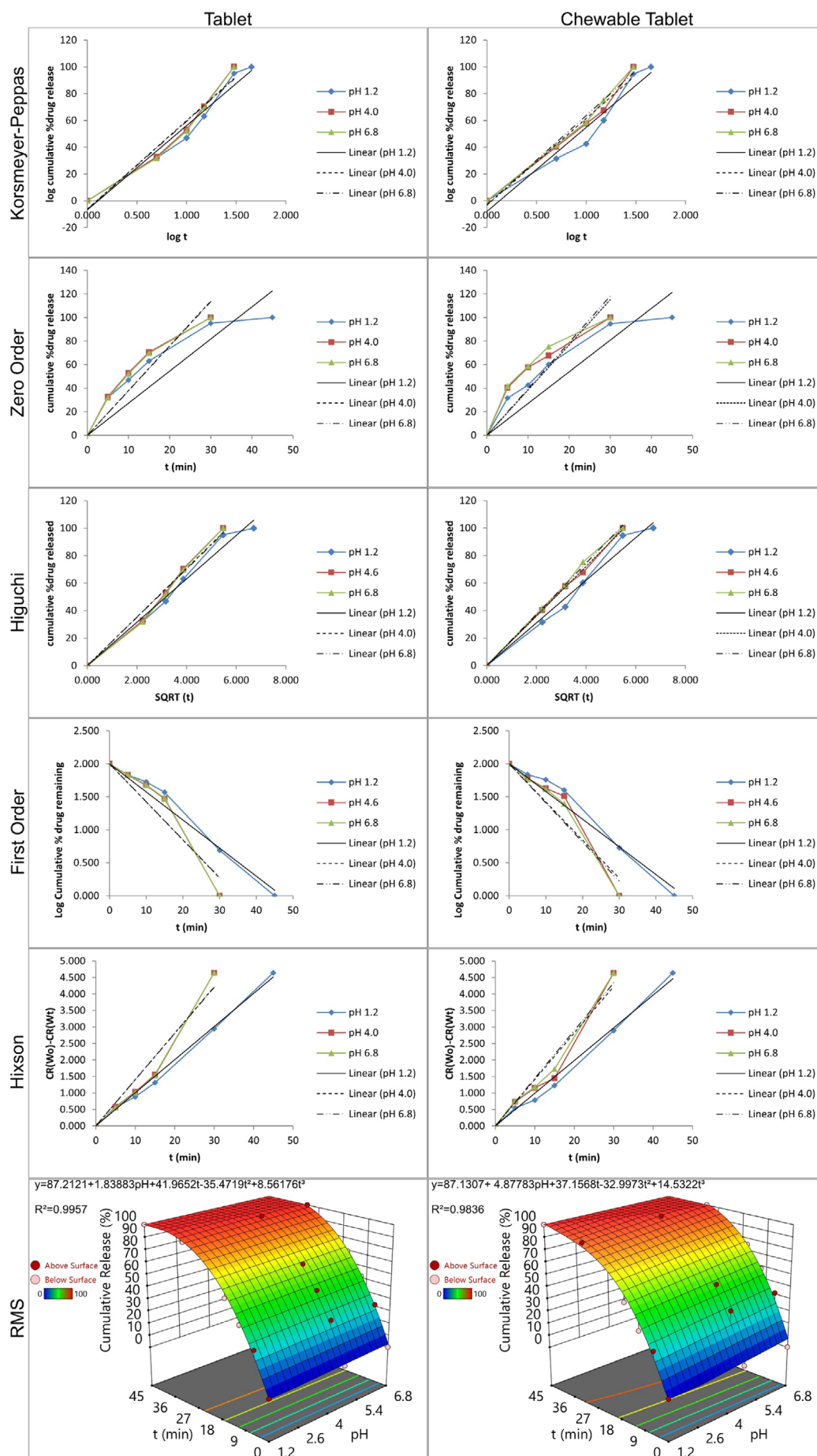


Figure 8. Kinetic models of the APAP release from the tablet and the chewable tablet formulations.

was faster than tablets and the chewable tablets in all the pH conditions. A slightly faster release rate can be expected through the formulation change. In addition, the decrease in the crystallinity of APAP obtained in the presence of PVP K30 may also have contributed to a higher dissolution rate. The dissolution had a too fast dissolution to allows the collection of enough timepoint. The films were completely dissolved as soon as they were placed into the solution. We evaluated five different kinetics models which results are shown in Figure 8. We compared the Korsmeyer-Peppas, Zero order, First order, Higuchi and Hixson model. The coefficient of the models within the R^2 values are reported in Table 2. Interestingly the model that best fit the release behaviour depends on the pH. For both the formulations (tablets and chewable tablets) dissolved at pH 1.2 the Hixson model had the

higher R^2 while in case of higher pH (4.0 and 6.8) the Higuchi model was the best fitting. It should be noticed that in literature all these models have been used to model the release kinetics of APAP in different context,⁴²⁻⁴⁵ in fact choice of the best fitting model seems to strongly depends on the drug formulation and the technique used to produce it. However, none of the proposed models studied the co-dependance with the pH while some literature studied the effect of the pH alone.^{46,47} We decided to include the dependance on the pH in a model by using a RMS have been used to fit a polynomial surface on the collected data and to obtain an empirical equation that also consider the effect of the release due to the pH. The model equations in this case are reported directly above the surface plots in Figure 8. Both the surfaces well fitted the collected data. In this case both the first

Table 2. Coefficient of the release models tested within the R^2 . Five different models have been tested, for each pH the best fitting model (with the higher R^2) has been selected and indicated by an asterisk

Model	pH	K	Tablet		Chewable tablet		
			n	R^2	K	n	R^2
Hixson	1.2	0.1003	-	0.9977*	0.0991	-	0.9953*
Hixson	4.0	0.1406	-	0.9745	0.141	-	0.9736
Hixson	6.8	0.1401	-	0.9725	0.1446	-	0.9864
Zero order	1.2	2.7265	-	0.9272	2.6948	-	0.9369
Zero order	4.0	3.08011	-	0.9579	3.8337	-	0.9411
Zero order	6.8	3.7827	-	0.9809	3.9282	-	0.9307
Higuchi	1.2	15.773	-	0.995	15.499	-	0.9936
Higuchi	4.0	17.694	-	0.9964*	18.034	-	0.9996*
Higuchi	6.8	17.574	-	0.9955*	18.626	-	0.9993*
First order	1.2	-0.0426	-	0.9854	-0.042	-	0.981
First order	4.0	-0.0577	-	0.933	-0.0578	-	0.9239
First order	6.8	-0.0575	-	0.9303	-0.0593	-	0.9499
Peppas	1.2	62.972	-6.8271	0.9641	62.644	-7.9024	0.9432
Peppas	4.0	65.964	-6.1639	0.9628	64.707	-3.2022	0.9789
Peppas	6.8	65.831	-6.5242	0.9584	66.467	-2.7536	0.9895

Table 3. ANOVA tables for the RMS empirical model of the release for the tablet and chewable tablet. The significance levels were assigned as follows: $p \leq 0.1$ (.), $p \leq 0.05$ (*), $p \leq 0.01$ (**), $p \leq 0.001$ (***).

Source	Sum of squares	df	Tablet			
			Mean square	F-value	p -value	
Model	18764.86	4	4691.22	631.65	< 0.0001	***
t	34.36	1	34.36	4.63	0.0546	.
pH	1703.92	1	1703.92	229.42	< 0.0001	***
t^2	1950.29	1	1950.29	262.60	< 0.0001	***
t^3	47.79	1	47.79	6.43	0.0276	*
Residual	81.70	11	7.43			
Cor total	18846.56	15				
Source	Sum of squares	df	Chewable tablet			
			Mean square	F-value	p -value	
Model	18125.77	4	4531.44	165.23	< 0.0001	***
A-Time	241.76	1	241.76	8.82	0.0128	*
B-pH	1335.82	1	1335.82	48.71	< 0.0001	***
B^2	1687.67	1	1687.67	61.54	< 0.0001	***
B^3	137.68	1	137.68	5.02	0.0467	*
Residual	301.67	11	27.42			
Cor total	18427.45	15				

order terms t and higher order terms t^2 and t^3 were included in the model as statistically significant as reported in the ANOVA Table 3.

4. Conclusions

Various formulations have been designed to facilitate the administration of APAP, improve dosage compliance, and obtain a rapid drug dissolution thus a rapid efficacy. After the preparation of the solid dispersion by encapsulation of the API in a water-soluble polymer, the chemical and physical properties were evaluated. As results of DSC and XRD analysis, it was confirmed that APAP was mainly in the crystalline form and PVP K30, and prepared solid dispersion were amorphous. It was possible to confirm the efficient encapsulation of the APAP in the PVP K30. The FTIR analysis showed that the APAP was not denatured neither in the process of preparing the solid dispersion nor in the preparation of the different oral delivery systems. Films were classified according to the presence or absence of plasticizers and their mechanical strength was evaluated. Films with plasticizers were damaged when subjected to stress but exhibited the characteristics of a material less prone to deformation before fracture. Finally, the dissolution rate of each formulation was tested by HPLC analysis. The dissolution rate of each formulation followed the same tendency regardless the pH of the solution. Specifically, in both the simulated gastric juice and saliva, the films were faster to reach the complete dissolution compared to the chewable tablets and the tablets. The ODF was effective in improving the dissolution rate when compared with the others oral delivery systems. The study on the release kinetics revealed a dependance on both the time and pH.

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