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Evaluation of Different Types of Paracetamol Active Pharmaceutical Ingredients' Effects on the Release System

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Abstract: The primary purpose of this study was to investigate the effect of active pharmaceutical ingredients (APIs) with varying particle sizes and properties on drug release and to develop matrix-type tablets based on poly(acrylic acid sodium salt) (PAANa) with different gelatin ratios for enhanced paracetamol release. Micronized, superfine, and purified paracetamol APIs were selected as model drugs to assess the impact of these APIs on drug release. Paracetamol is a frequently used medication in healthcare, so it is crucial to select the API with the optimal release rate and an economical, environmentally friendly production method. The direct compression method was employed in the preparation of the tablets due to its simplicity and ease of integration on an industrial scale. The release studies, release kinetics, scanning electron microscope (SEM), Fourier transform infrared spectroscopy (FT-IR), physical properties, and microbial analyses (*Escherichia coli*, total mold, yeast) were investigated. The release studies at pH 1.2 and pH 7.4 revealed that the type of active pharmaceutical ingredient, especially micronized paracetamol API and superfine API, affects the paracetamol release ratio. Microbial analyses showed that produced tablets were convenient for health. In addition, prepared tablets with added gelatine can be used to deliver paracetamol with the desired release profile.

Keywords: Matrix-type tablets, Paracetamol, Release kinetics, Release properties, Antimicrobial properties.

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1. INTRODUCTION

A controlled drug delivery system involves a wide variety of scientific approaches, which are an important part of science and contribute to healthcare. These scientific approaches enhance efficiency, improve patient compliance, and minimize side effects (1-4). Furthermore, designed drug delivery has been progressing for overwhelming problems, including targeting specific sites and controlling drug release rates (5-7). Some drug release systems have major limitations, including poor *in vitro* release and bioavailability, high doses, and adverse side effects (8,9). However, controlled drug delivery systems have been developed to release APIs in a predictable, desired time, release rate, and quantity (10-15).

Controlled-release drug delivery offers a cost-effective solution for formulations, such as swelling matrix-type tablets, which have been widely used in the pharmaceutical industry (16,17). Matrix-type tablets are useful materials for releasing dosage forms and provide the lowest-cost solution for various applications.

Direct compression is one of the selected tablet preparation methods when mixed powders (active pharmaceutical ingredients, or APIs, and excipients) are compressible and stable under high-pressure conditions (18, 19). Additionally, direct compression is favored due to its simplicity, environmental friendliness, time, and cost-effectiveness, which is the most straightforward route for manufacturing matrix-type tablets, offering advantages such as large-scale and continuous production (20-24).

The addition of the drug to the polymer ingredient is a common method used in drug release (25-28). Hydrophilic polymers and polymer combinations are attractive for controlled-release studies, and these combinations have been used to formulate dosage forms for many years due to their unique features for efficient and specific drug delivery. Different types of polymers are used in release dosage forms. Mucoadhesive polymers are extensively selected in

tablet formulations due to their ability to adhere to the required sites for a prolonged period of time in the prepared formulation. Carbomers, commonly referred to as Carbopols, are weakly cross-linked polymers of acrylic acid with effective mucoadhesive properties, making them attractive for use in release systems. Additionally, Carbopol is a hydrophilic, cross-linked polyacrylic acid polymer with a high molecular weight. Additionally, drug dissolution and diffusion through the polymer are significant phenomena that influence the controlled release properties of the drug formulation. PAA and PAANa are among the materials preferred in many industries due to their properties, including hydrophilicity, non-toxicity, dispersion, and binding capacity (29-31).

Gelatin is a type of natural hydrophilic polymer and non-toxic material derived from the acid or alkaline hydrolysis of collagen, which has a variety of effective advantages, including good biocompatibility, solubility, easy acquisition, and biodegradability (32).

Paracetamol (acetaminophen) is probably the most common, widely available, and important analgesic and antipyretic active pharmaceutical ingredient, commonly used to relieve pain such as headaches, toothaches, and sprains. Furthermore, paracetamol is available in various dosage forms, including tablets, intravenous solutions, suspensions, capsules, and suppositories (29). The direct compression method for the oral solid form of paracetamol is mostly selected (24).

The current work aims at creating a release system through the preparation and characterization of prepared tablets. The effects of gelatine and paracetamol types on *in vitro* release of drugs have also been studied. As a result, different particle sizes, types of APIs, and kinetic models were significant determiners for drug delivery studies. Characterization and microbial analyses were evaluated, and all results were promising for the effective delivery of paracetamol.

2. EXPERIMENTAL SECTION

2.1. Materials

J.T. Baker provided sodium hydroxide (99.0%) and monobasic potassium phosphate. Sodium chloride (≥99.5%) and hydrochloric acid (37.0%) were supplied by Merck. Atabay Pharmaceutical Company kindly provided paracetamol APIs (assay: 100.5-100.7%). Gelatine (microbial grade) was purchased from Carlo Erba. Poly (acrylic acid sodium salt) with an average Molecular Weight of ~2,100 (for R&D usage) was supplied by Sigma Aldrich. Sabouraud 4% Dextrose Digest Agar (SDA) and Tryptic Soy Agar were provided by Merck. All chemical materials used were of analytical grade.

Table 1: API's sieve properties.

	Specification	**Results**	**Method**
Micronized API	325 Mesh (45 µm) =0	0	
Superfine API	80 Mesh (180 µm) = Max. 2	1	
	140 Mesh (106 µm) = Max. 5	3	Air jet sieving
Purified API	80 Mesh (180 µm) = Max 2	1	
	140 Mesh (106 µm) = Max. 5	4	

2.2. Preparation of Matrix Types of Tablets

Gelatine and poly(acrylic acid sodium salt) were prepared using a clean and dry mortar. All the ingredients were weighed accurately, as shown in Table 1, and then mixed thoroughly. API and excipient were completely blended in a mortar. A total of nine formulations were prepared using gelatin and various paracetamol APIs. A direct compression method was employed to prepare paracetamol-loaded tablets. The method used is simple and lacks critical manufacturing and formulation levels, making it easy to standardize for industrial-scale production. A 0.5±0.02 g mixture was manually added to the pellet (tablet) pressing device. A pressure of 160 kPa was applied for 5 minutes to produce tablets. A desiccator was used for storing the prepared tablets until further studies.

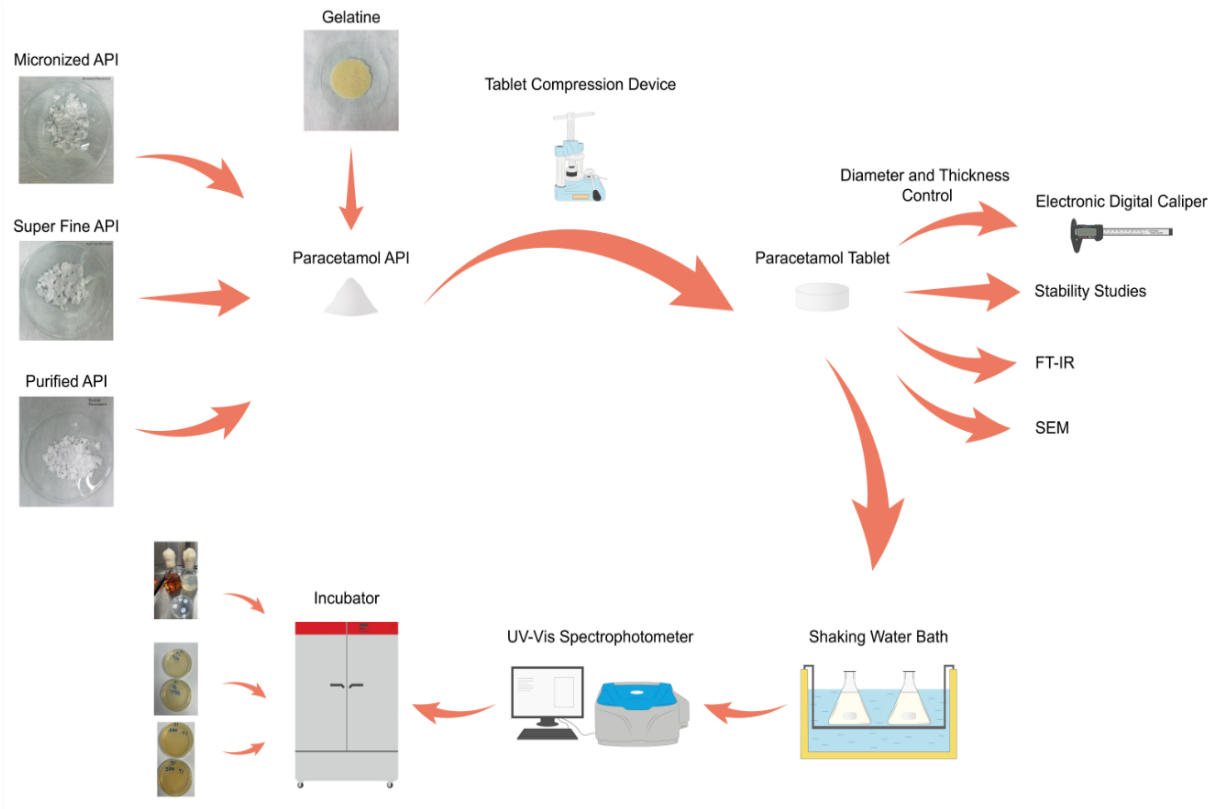

Figure 1: Experimental setup.

2.3. Characterization of The Tablets

A digital caliper was used to measure the diameter and thickness of the tablets (Carbon Fiber Composites Digital Caliper). Fourier Transform Infrared Spectroscopy (FT-IR, PerkinElmer Spectrum 100) was used for the characterization of chemical groups present in the tablets. A spectrum is obtained using the ATR technique with a diamond internal reflection element mounted on a holder, at a resolution of 4 cm-1, in the range of 4000-650 cm-1, with a total of 16 scans for each tablet. SEM photographs were taken with a JEOL JSM 6335F.

2.4. *In vitro* Drug Release of The Tablets

pH 1.2 and pH 6.8 buffer solutions were prepared for *in vitro* drug release tests at 37 ± 0.5 °C and 50 rpm. 50 mL of dissolution medium was used, and 2 mL of the same medium was taken for analysis. The quantity of paracetamol released over time was obtained by withdrawing samples at predetermined time intervals for 4-6 hours. The withdrawn volume was replaced with the same amount of additional buffer. The measurements were performed three times at 270 nm by using a UV-Vis spectrophotometer (Analytik Jena Specord 200/Plus). The reproducibility of this approach is 1 to 3%. A pH 1.2 buffer is prepared according to USP 29. The drug concentrations in the sample were validated using a standard calibration curve. The complete experimental procedures, including details of the buffer solution, were reported previously (3).

2.5. Kinetic Evaluation

First-order, Zero-order, Hixson-Crowell, and Korsmeyer-Peppas kinetic models were studied to examine the kinetic mechanism. The data from the *in vitro* studies were analysed using Korsmeyer-Peppas models to determine the release profile. Korsmeyer and Peppas's empirical equation was used to understand the dissolution mechanisms from the matrix-type tablets (31,33,34).

The equation represents the release of the drug,

$$\text{Korsmeyer – Peppas model: } M / Mt = K_{KP}t \qquad (1)$$

In the equation, M/Mt is the fraction of the drug released at time t, K_{KP} is the drug release rate constant, and n is the diffusional exponent (31,32).

2.6. Stability Studies

Tablets were subjected to stability studies by storing them at 25 ± 2 °C and 65 ± 5% relative humidity for a period of 3 months. At the end of the analysis, the formulation was evaluated for *in vitro* release profile. It was determined from the stability analyses that there were no significant differences in the drug quantity of the tablets. The physical appearance also showed no difference in tablet formulation.

3. RESULTS AND DISCUSSION

3.1. Characterization of the tablets

The produced tablets were characterized with the digital microscope, Fourier Transform Infrared spectroscopy (FT-IR), and Scanning Electron Microscopy (SEM). Figure 2 shows the images of tablets taken with the digital microscope. The diameter and thickness were 2.40 ± 0.05 and 0.20 ± 0.03 cm, respectively.

Table 2: Type of the prepared tablets.

	Content, w/w %				
	Poly(acrylic acid sodium salt)	**Micronized Paracetamol API**	**Superfine Paracetamol API**	**Purified Paracetamol API**	**Gelatine**
Tablet 1 (T1)	90	10	-	-	-
Tablet 2 (T2)	90	-	10	-	-
Tablet 3 (T3)	90	-	-	10	-
Tablet 4 (T4)	85	10	-	-	5
Tablet 5 (T5)	80	10	-	-	10
Tablet 6 (T6)	85	-	10	-	5
Tablet 7 (T7)	80	-	10	-	10
Tablet 8 (T8)	85	-	-	10	5
Tablet 9 (T9)	80	-	-	10	10

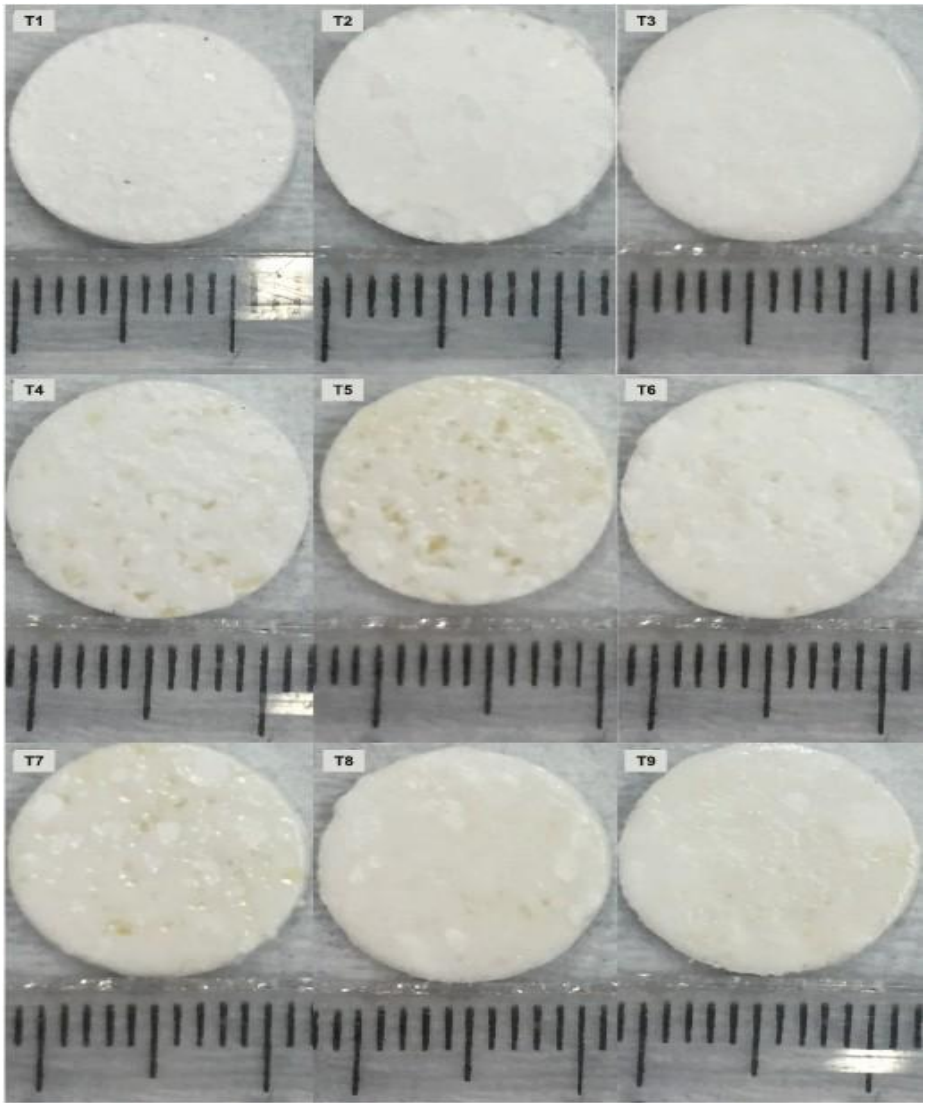

Figure 2: Image of tablets.

FT-IR was applied to determine the intact functional groups of samples. The position of the band in the FT-IR spectra of paracetamol APIs was compared with that in the FT-IR spectra of different types of paracetamol APIs with gelatin. The characteristic peaks of paracetamol were intact in the FT-IR spectrum of different kinds of paracetamol APIs with gelatin used in the formulations. The data showed no changes in the characteristic peaks of the tablet formulations compared to the APIs. When the FT-IR spectrum of PAANa is examined, the peaks related to the asymmetric and symmetric stretching vibrations of the carboxylate group occur at wavenumbers of 1543 cm^{-1} and 1400 cm^{-1} (35). The characteristic

bands around 2940 cm^{-1} and 1107 cm^{-1} can be assigned to the -CH_2 stretching and C-H bending of PaaNa (36). Vibrational peaks for O-H and -CH_3 stretching appeared at 3318 cm^{-1} and 3161 cm^{-1}, respectively. Vibrational peaks at 1649 and 1609 cm^{-1} were assigned to C=O and C=C stretching, respectively, for the paracetamol spectrum (37). The amide II peak was observed at 1547 cm^{-1} in the spectrum of gelatin (38). The N-H amide II bonding, asymmetrical C-H band, and C-C stretching peak appeared at 1562 cm^{-1}, 1503 cm^{-1}, and 1416 cm^{-1} in the spectrum of Paracetamol, respectively (37). The absorption peaks at 1369-1321 cm^{-1} and 1258-1223 cm^{-1} were examined for symmetrical banding C-H and C-N (aryl) stretching. Additionally, absorption peaks at 1171 cm^{-1} and 966 cm^{-1} were assigned to C-O stretching and C-N (amide) stretching, respectively. Vibrational peaks for the para-disubstituted aromatic ring and out-of-plane ring deformation of the phenyl ring were observed at 835 and 671 cm^{-1}, respectively (37).

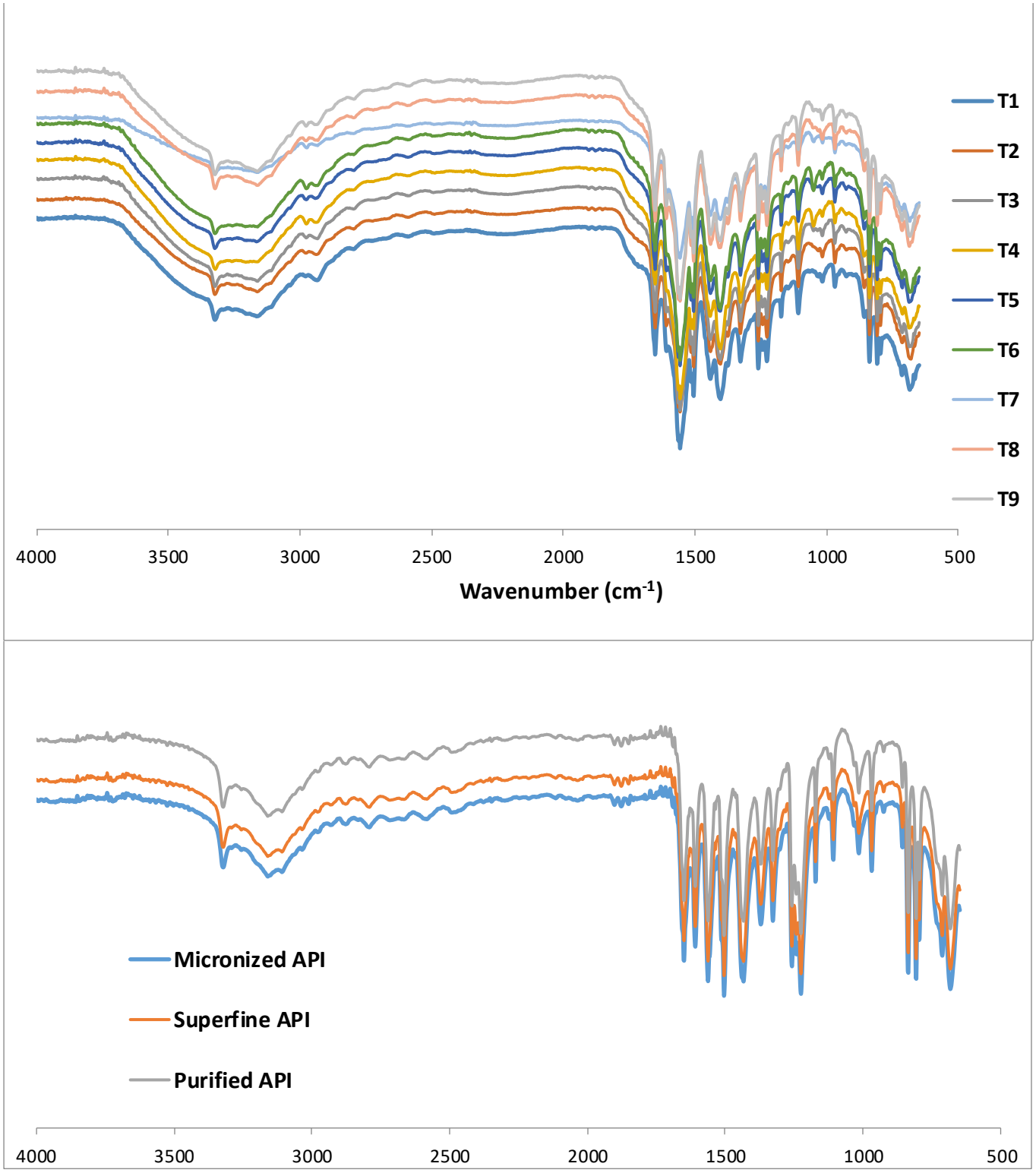

Figure 3: FT-IR analyses of matrix types of tablets and Paracetamol's APIs.

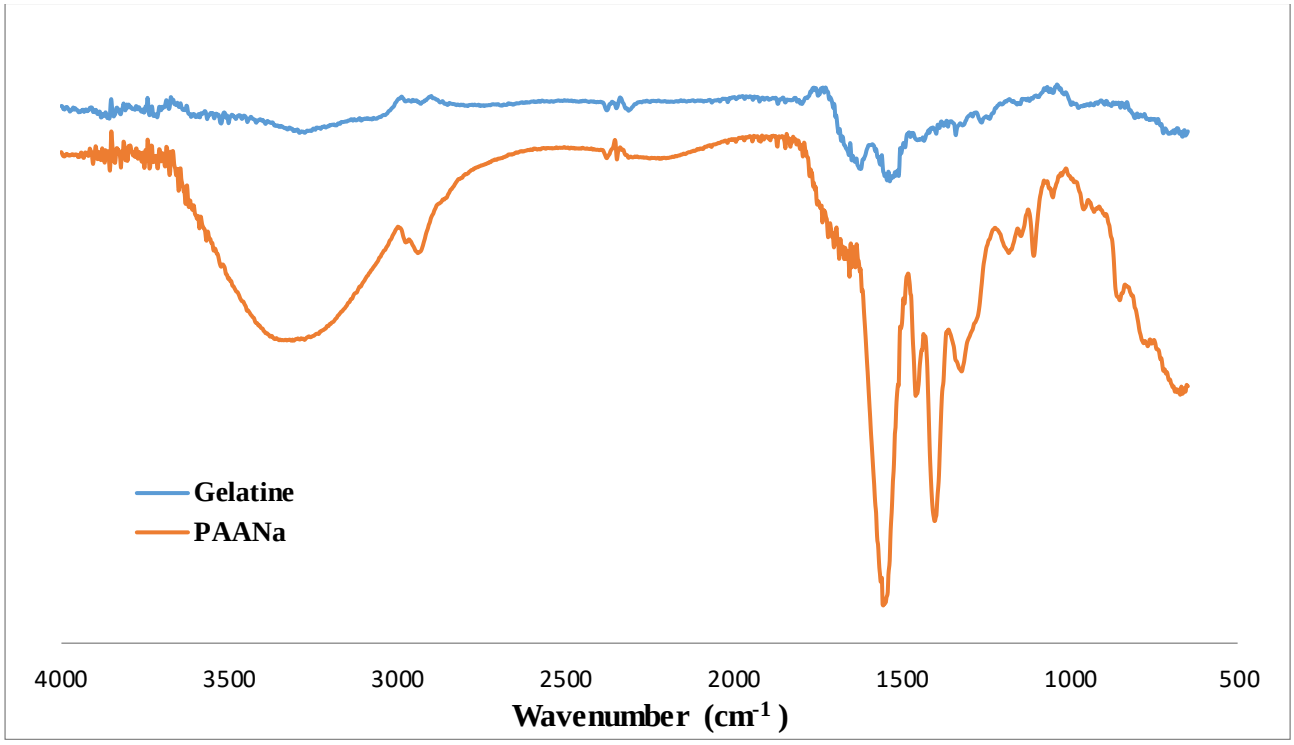

Figure 4: FT-IR analyses of gelatine and PAANa.

3.2. SEM Analysis

A Scanning Electron Microscope (SEM) was used to determine the morphology of the samples. SEM photographs of tablets are given in Fig. 4. T1 (a) and T5 (c) SEM images are powder forms of the tablet before pressing the tablet. T1 (b) and T5 (d) are tablet forms after pressing. T1 tablet has a large, channel-like, and open structure. The presence of gelatine in the T5 tablet exhibits a less porous structure. SEM images demonstrated that the tablet surface became nearer with the addition of gelatine (T5).

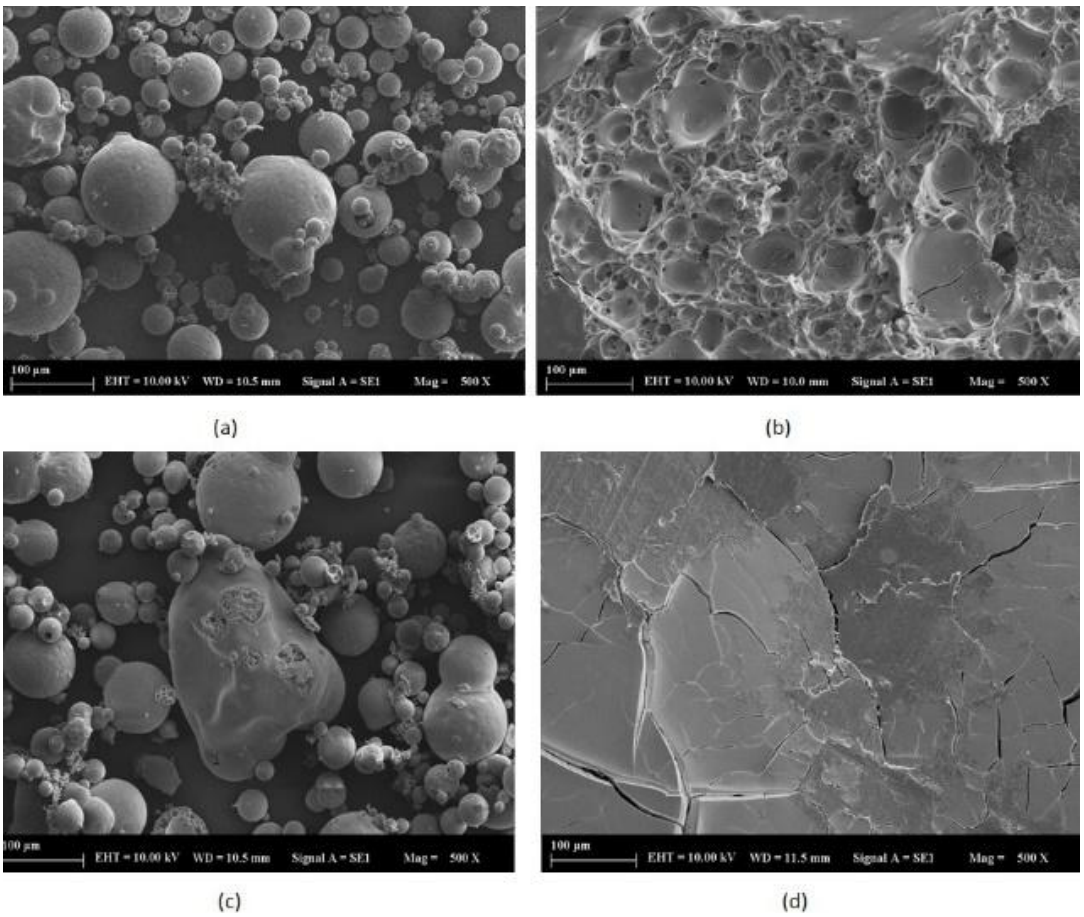

Figure 5: SEM images of tablets (a) T1 powder form before pressing, (b) T1 tablet form, (c) T5 powder form before pressing, (d) T5 tablet form.

3.3. In vitro Drug Release Studies

3.3.1. In pH 1.2 media (simulated gastric fluid)

Figure 6 shows the percent cumulative release of paracetamol at a pH 1.2 medium. Micronized API exhibited a significant effect on release enhancement. Additionally, the T2 tablet with superfine API exhibited high paracetamol release, reaching 94.02%. The *in vitro* drug release data for formulations T1 and T5, containing micronized API, showed a maximum percent cumulative release of paracetamol of 96.72% and 93.39% after 4 hours, respectively (39-41). The addition of gelatine in tablet formulation resulted in a decrease in the amount of drug released. The percentage of paracetamol release of T8 reached 58.78% within 4 h at pH 1.2.

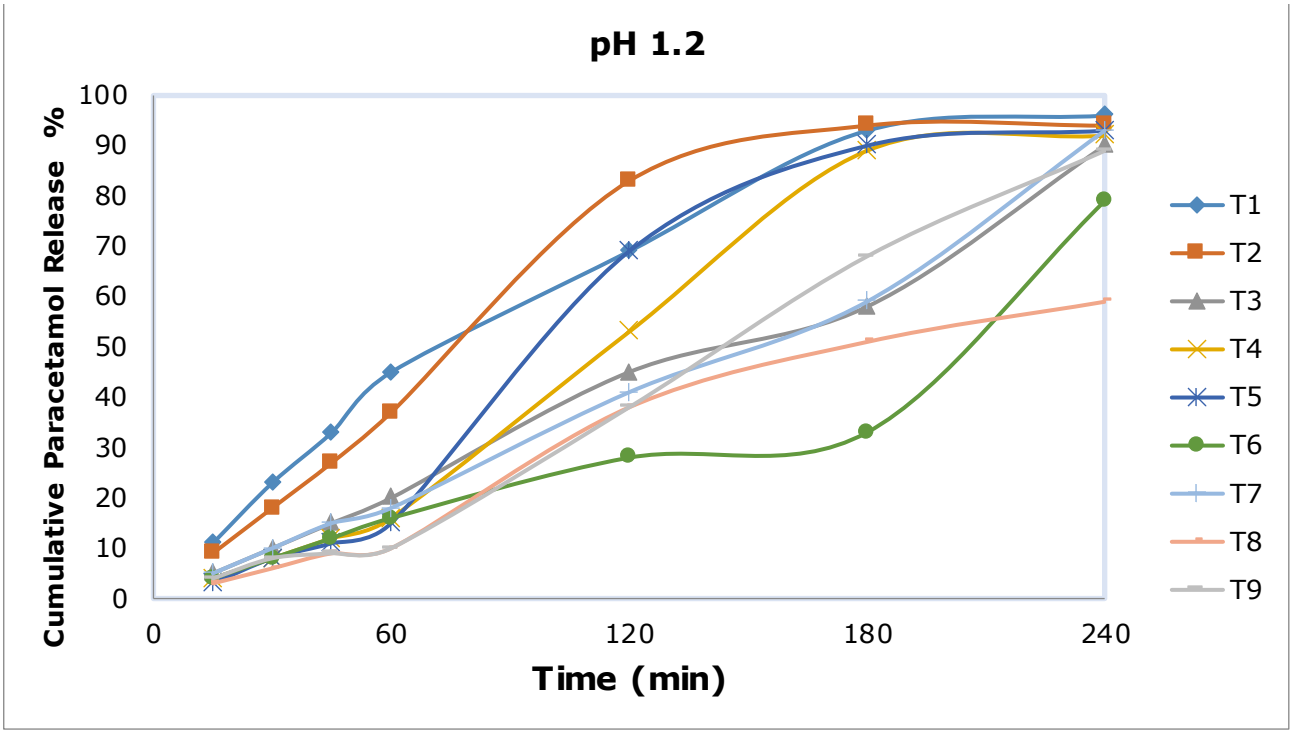

Figure 6: Paracetamol release profiles of matrix tablets at pH 1.2.

3.3.2. In pH 6.8 media (simulated intestinal fluid)
The release of paracetamol from matrix-type tablets was studied for 6 hours in simulated intestinal fluid. The T1 tablet (micronized API) showed 97.03% paracetamol release at the end of 6 hours. T5 and T4 tablets with micronized API showed good performance with 96.40% and 91.54% paracetamol release, respectively. Additionally, the T2 tablet with superfine API showed a percent cumulative release of paracetamol of 91.58%.

T8 exhibited the minimum percent cumulative release of paracetamol with 81.19% in 6 h. The release rate of tablets with gelatine was slower at both pH 1.2 and pH 6.8. Also, as shown in Figs. Results 7 and 8 indicate that the presence of gelatin in tablets causes a lower drug release ability. In general, matrix-type tablets exhibit higher cumulative paracetamol release in a pH 6.8 medium (39,42).

T1 is a tablet containing micronized API, and T4 and T5 are versions of this tablet with added gelatin. T2 is a tablet containing superfine API, while T6 and T7 are tablets with added gelatin. T3 is a tablet containing purified API, and T8 and T9 are tablets with added gelatin. Figure 8 shows the highest release rates of the tablets at pH 1.2 and pH 6.8. In Figure 8, it is observed that tablets with added gelatin have a lower release rate than those without gelatin.

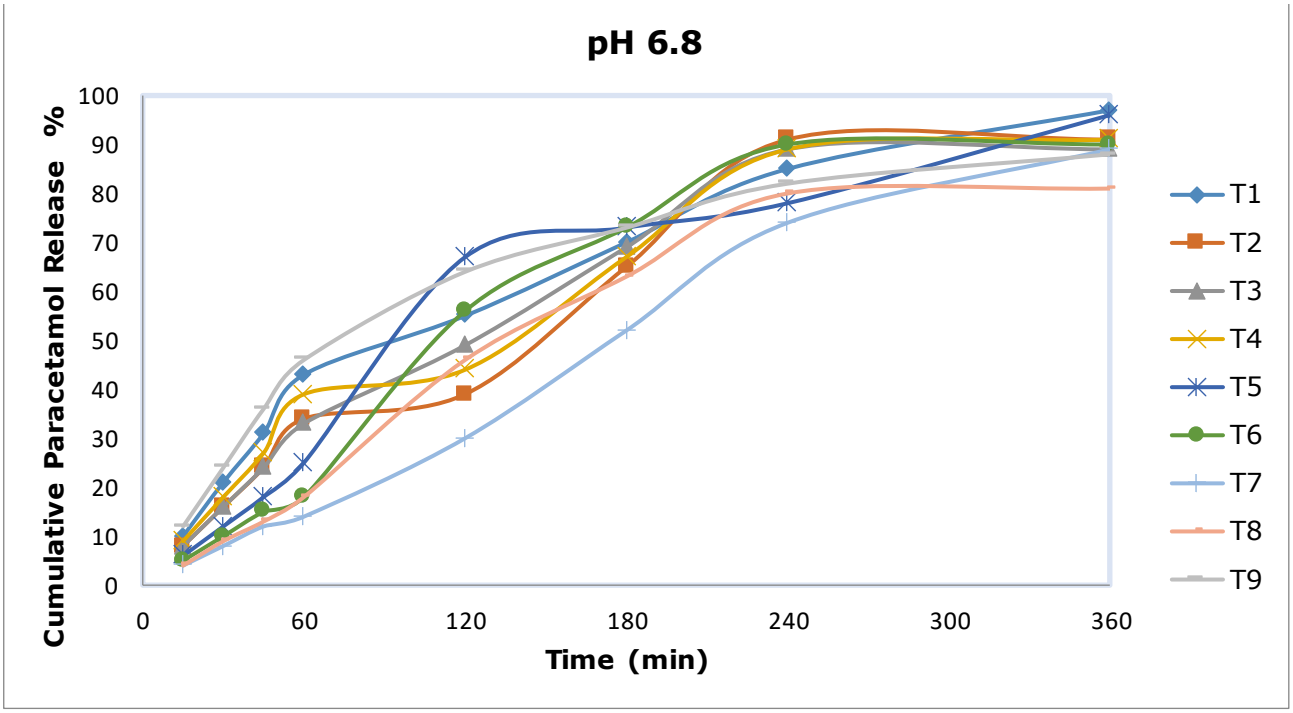

Figure 7: Paracetamol release profiles of matrix tablets at pH 6.8.

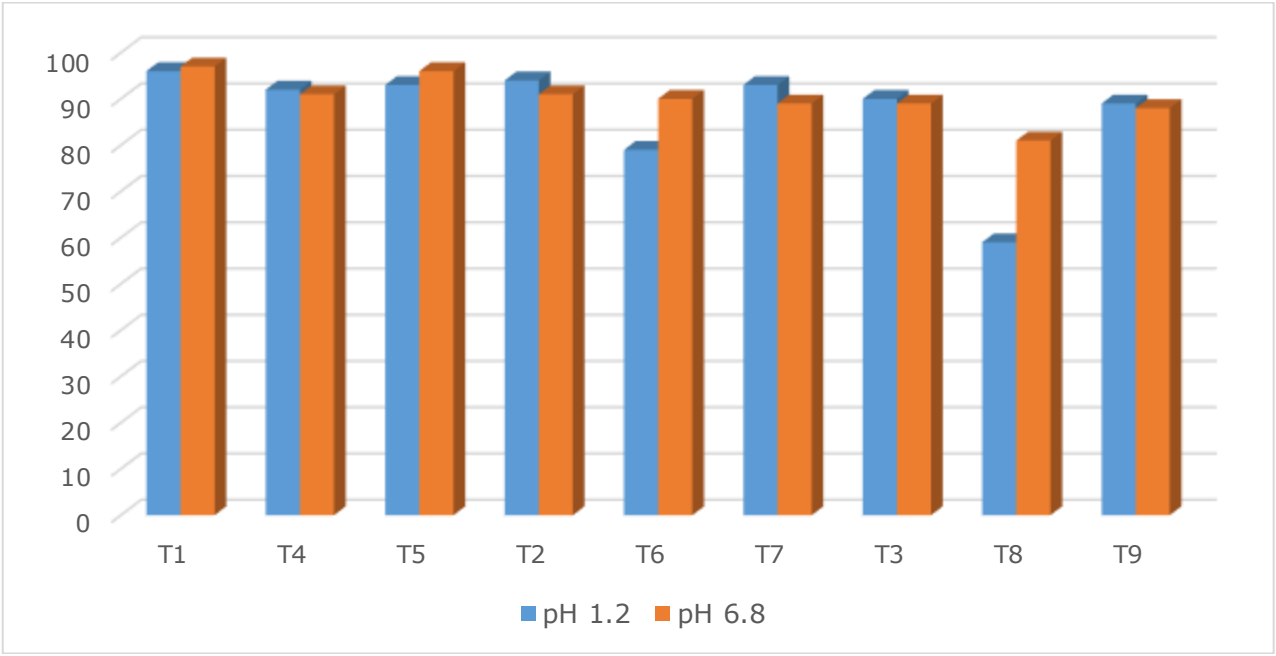

Figure 8: Paracetamol maximum release profiles at pH 1.2 and pH 6.8.

3.4. Microbial Analyses

In this section, microbial analyses were conducted to assess the compatibility of the produced tablets with their health properties. The pour-plate method was used according to the European Pharmacopoeia (EP) 2.6.12 and the United States Pharmacopoeia (USP) 61-62 (43, 44). Microbial analysis procedures consisted of the following steps: 10.0 g of product was weighed, and 100 mL (1/10) of N/Peptone was added. 10 mL of this dilution was taken, and 100 mL (1/100) was completed. 1 mL was poured into two pieces of Tryptic Soy Agar-Sabouraud 4% Dextrose Agar (TSA-SDA) medium. They were incubated at 30 – 35°C for 3-5 days for total aerobic bacteria and incubated at 20-25°C for 5-7 days for molds and yeasts.

For specific microorganism analysis, 10 mL of a 1:10 dilution was added to 90 mL of Tryptic Soy Broth (TSB) medium in a beaker. They were incubated for 18-24 hours at 30-35 °C.

Microbiological contamination limits follow as:
Total aerobic microbial count: Not more than 1,000 colony-forming units (CFU) per gram.
-Total molds and yeast counts: Not more than 100 CFU per gram.
-Pathogens: No *Escherichia coli (E. coli)* per gram.

Table 3 represents the acceptance criteria for the microbiological quality of tablets. The total aerobic microbial count, total mold, and yeast count were found to be less than 100 colony-forming units (CFU). *E. coli* must be absent in oral drugs, and E. coli was not found in the tablets. According to the specifications presented in Table 3, the formulations comply with the required microbiological standards for pharmaceutical preparations. These findings provide strong evidence supporting the quality and safety of the T1–T9 formulations.

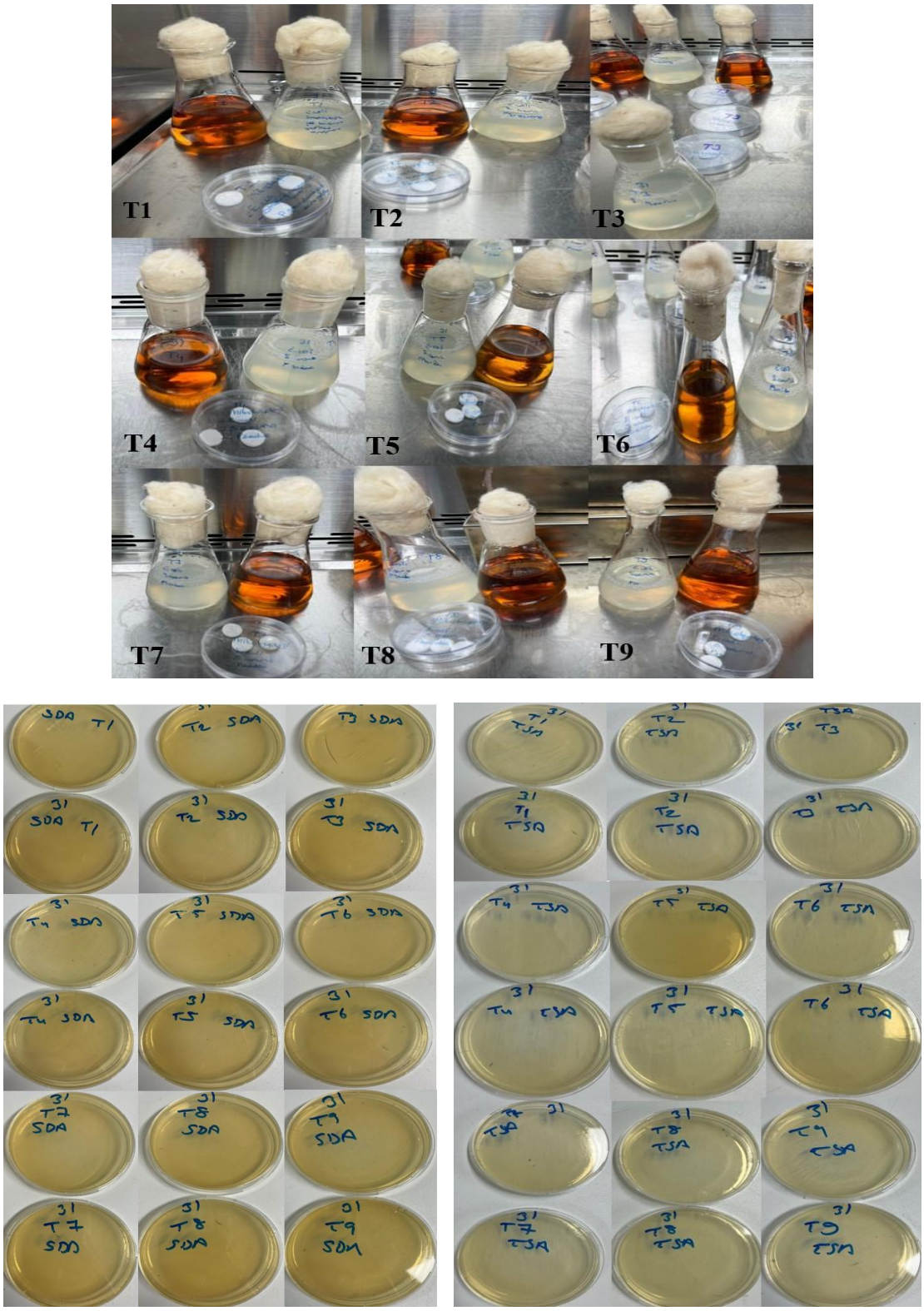

Figure 9: Images of microbial analyses.

Table 3: Microbial limit test results.

	T1-T9
Method	Pour Plate Method
Media	Sabouraud Casein Digest Agar Medium
Incubator temperature and time	32.5 ± 2.5 °C, 5 days
Number of samples	3
Total Aerobic Microbial Count	<1000 CFU / g
	T1-T9
Method	Pour Plate Method
Media	Sabouraud Dextrose Digest Agar Medium
Incubator temperature and time	22.5 ± 2.5 °C, 7 days
Number of samples	3
Total Aerobic Microbial Count	<100 CFU / g
Escherichia coli (*E. coli*)	0 CFU / g

3.5. Paracetamol Release Kinetic Tests

The release data were fitted into the Korsmeyer-Peppas kinetic model to understand the release mechanism. The model with the higher R-squared value is considered optimal for the release data. The kinetic values obtained for different formulations are indicated in Table 4. The release data were investigated using the Korsmeyer-Peppas equation; the n values for the prepared tablet formulations ranged from 0.9470 to 0.9901 in pH 1.2 and pH 6.8 media. It was observed that the drug release data for all formulations fit well to the Korsmeyer-Peppas kinetic model (R^2 values ranged from 0.9470 to 0.9901). Most tablet formulations exhibit a non-Fickian mechanism, as indicated by their n-release exponent values within the range of 0.45 < n <, as shown in Table 4. These values support the notion that the drug release mechanism may be related to polymer relaxation and drug diffusion. Drug release, erosion, and swelling processes can affect the non-Fickian release mechanism. Moreover, non-Fickian release kinetics can facilitate the development of controlled-release formulations that modulate the drug release rate over an extended period. The development of the formulation can also increase patient compliance and treatment efficacy (45-47).

Table 4: Release kinetic studies of tablets.

	pH	**Zero order**		**First order**		**Hixson-Crowell**		**Peppas**		**Best Fit Model**
		R^2	K_0 [mg / h] $*10^{-4}$	R^2	K_1 [h^{-1}]	R^2	K_s	R^2	n	
T1	1.2	0.8061	7.720	0.6583	1.4583	0.7222	0.0138	**0.9667**	0.6228	Korsmeyer-Peppas
	6.8	0.9219	7.345	0.7098	1.5815	0.7978	0.0137	**0.9669**	0.6073	
T2	1.2	0.6950	7.995	0.6241	1.6187	0.6615	0.0151	**0.9652**	0.7683	
	6.8	0.9110	7.695	0.7644	1.8652	0.8383	0.0152	**0.9698**	0.6768	
T3	1.2	0.9232	8.270	0.7891	2.3233	0.8589	0.018	**0.9901**	0.8523	
	6.8	0.9007	7.540	0.2914	1.7789	0.8135	0.015	**0.9851**	0.6882	
T4	1.2	0.8376	9.135	0.7463	2.4958	0.7939	0.0201	**0.9753**	0.9886	
	6.8	0.9071	7.370	0.7360	1.7268	0.8144	0.0143	**0.9685**	0.6374	
T5	1.2	0.7974	9.275	0.7024	2.5732	0.7511	0.0207	**0.9629**	1.0642	
	6.8	0.8787	8.160	0.7230	2.075	0.7884	0.0170	**0.9798**	0.8140	
T6	1.2	0.9045	7.114	0.8388	2.6196	0.8982	0.0173	**0.9632**	0.8331	
	6.8	0.8765	8.49	0.753	2.3011	0.8096	0.0184	**0.9779**	0.8846	
T7	1.2	0.9283	8.635	0.8118	2.3638	0.8771	0.0185	**0.9789**	0.8618	
	6.8	0.9768	7.955	0.8491	2.6292	0.9195	0.0187	**0.9789**	0.8864	
T8	1.2	0.8554	5.690	0.7476	2.8178	0.7965	0.0166	**0.9663**	0.9268	
	6.8	0.8994	7.580	0.2782	2.3366	0.8219	0.0178	**0.9880**	0.8974	
T9	1.2	0.9047	8.790	0.8173	2.7221	0.8608	0.0204	**0.9470**	0.9692	
	6.8	0.8382	6.320	0.6476	1.4076	0.7211	0.0118	**0.9513**	0.5411	

4. CONCLUSION

A direct compression method was successfully applied to prepare the matrix-type tablet. According to experimental data, a greater quantity of the drug was released from the tablet as the environmental pH increased. The results of *the in vitro drug release study revealed that the type of gelatin and APIs,*

especially micronized active pharmaceutical ingredients, played a crucial role in enhancing drug release. Gelatine decreased the release ratio of paracetamol in both media. It was indicated that the release of paracetamol was slower in formulation T8, which contained gelatin with purified paracetamol. Additionally, the T1 tablet exhibited the maximum percent cumulative release of paracetamol in both pH 1.2 and pH 6.8 media. The present study demonstrated that matrix-type tablets with added gelatin can be formulated for the controlled delivery of paracetamol, achieving the desired release profile *in vitro*. Microbial analyses showed that produced tablets were suitable for health. From this perspective, the current study and its results were promising for paracetamol drug delivery. However, it should be taken into consideration that in vivo studies are required to determine whether the prepared and chosen formulation(s) will be accurate.

5. CONFLICT OF INTEREST

The author of the manuscript declares no conflicts of interest.

6. ACKNOWLEDGMENTS

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