

Development a taste-masked acetaminophen solid dispersions using Eudragit® E100 polymer by solvent evaporation technique

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Received: 12 December 2022 / Revised: 10 April 2023 / Accepted: 11 April 2023

ABSTRACT: The bitter taste of acetaminophen greatly reduced its formulation in oral dosage forms, so masking the taste was tested using the solid dispersion technique by Eudragit E100 and the solvent evaporation method. The obtained solid dispersions were characterized by FT-IR and DSC. Then, production yield, and drug loading have been determined, and the efficiency of this technique in taste masking by in vitro-in vivo evaluation were investigated by measuring the amount of drug released at pH=6.8 similar to saliva and pH=1.2 similar to stomach. FT-IR demonstrated that absence of interactions between drug and polymer and DSC results showed the complete formation of solid dispersion for F2 and partial formation with F1 and F3. Production yield was more than 96% for all formulations, and drug loading ranged between 99-103% and this increased with special dishes, while in vitro drug release results at pH=1.2 after 15min reached 84.95±0.55, 100.89±0.70, and 95.78±0.71 (µg/ml) for F1, F2, and F3 respectively. In another hand, taste-masking evaluation at pH=6.8 showed drug release amount after 2min less than the determination bitterness threshold (900µg/ml) there were 114.98, 75.97, and 10.26 µg/ml for F1, F2, and F3 respectively. Therefore, this technique is considered efficient in masking the taste with obtaining a good production yield.

KEYWORDS: Acetaminophen; taste-masking; solid dispersion; Eudragit E100; solvent evaporation; threshold bitterness.

1. INTRODUCTION

Oral dosage forms are the best route for drug delivery for different age segments, and specialists because of facility manufacturing and compliance which is noted with patients. It contains solid dosage forms such as tablets, capsules, and liquid forms like solution, syrup, emulsion, suspension, etc. Solid dosage forms have an important place because of the low cost of manufacture, packaging, and shipment. Acetaminophen is an analgesic and antipyretic, due to its safety using it is very common for children and infants has a bitter taste which makes formulating it at oral dosage forms (for example syrup, chewable, and oro-dispersible tablet) difficult [1,2,3]. But the most important consideration for the formulation of these tablets is palatability especially pleasant taste and after-taste when chewing, disintegration, and swallowing [4,5]. So many taste masking techniques are developed to solve the problem of unpleasant taste for many drugs such as bitter blockers and taste modifiers, sweeteners and flavors, modification of API solubility, applying a physical 'barrier' on the API or the dosage form by polymer-film coating or lipidic barrier system, complexation by ion-exchange resins or cyclodextrins, microencapsulation, multiple emulsion, and solid dispersions technique [6,7]. Solid dispersion term is used when active ingredients are dispersed in inactive carriers at a solid state and this is usually done by fusion, solvent, and fusion-solvent methods [8,9]. Solvent evaporation techniques include centrifugal spinning, electrostatic spinning, supercritical fluid, supercritical anti-solvent, spray drying, freeze drying, and fluid bed coating [10]. Several carriers have been used however, the most effective one at suppressing bitterness without effect on drug release is the pH-dependent polymer Eudragit E100 which is not dissolved at Salvia pH but is dissolved at pH<5, therefore it is utilized to taste masked sildenafil citrate, prednisolone, potassium chloride, ornidazole, etc. by using different techniques like spray drying, fluid bed coating, solid dispersion, microencapsulation [11,12,13,14].

How to cite this article: Shahoud S, Abdelwahed W, Hammad T. Development a taste-masked acetaminophen solid dispersions using Eudragit® E100 polymer by solvent evaporation technique. J Res Pharm. 2023; 27(5): 1998-2006.

The study aimed to taste masked acetaminophen so that it can be formulated into palatable oral dosage forms for pediatrics and all age stages who suffer from dysphagia by employing sophisticated technologies such as solid dispersion technique using Eud E100 polymer by solvent evaporation method at room temperature. Three different ratios of drug to polymer were optimized using the solvent evaporation method at room temperature. Acetaminophen solid dispersions were characterized by FTIR (Fourier-transform infrared spectroscopy) and DSC (Differential Scanning Calorimetry) and were evaluated by determining production yield and drug loading, then the efficiency of this technique in taste masking was investigated by in vitro evaluation through measurement the amount of drug released at pH=6.8 similar to saliva and pH=1.2 similar to stomach.

2. RESULTS

2.1. Characterized of acetaminophen solid dispersions

2.1.1. Fourier-transform infrared (FTIR) spectroscopy

Figure 1 shows the IR spectrum for acetaminophen and Eudragit E100, in which the special absorption bands were detected as follows: 3325 cm^{-1} (N-H Stretching), 3035-3162 cm^{-1} (O-H Stretching), 1654 cm^{-1} (C=O stretching in amide functional group) for acetaminophen, and 2955-2823 cm^{-1} (C-H stretching symmetric/asymmetric), 1730 cm^{-1} (C=O stretching), 1272 cm^{-1} (C-O stretching), 1242-1017 cm^{-1} (C-N stretching) for Eudragit E100. This Test is used also for determining the drug-excipient compatibility, where no difference was detected among physical mixture and solid dispersion in Figure 1, where a superposition spectrum of acetaminophen and Eudragit E100 was obtained without any shift, the disappearance of the existing peaks or emergence of new peaks. These indicated the absence of any interaction between the drug and excipients.

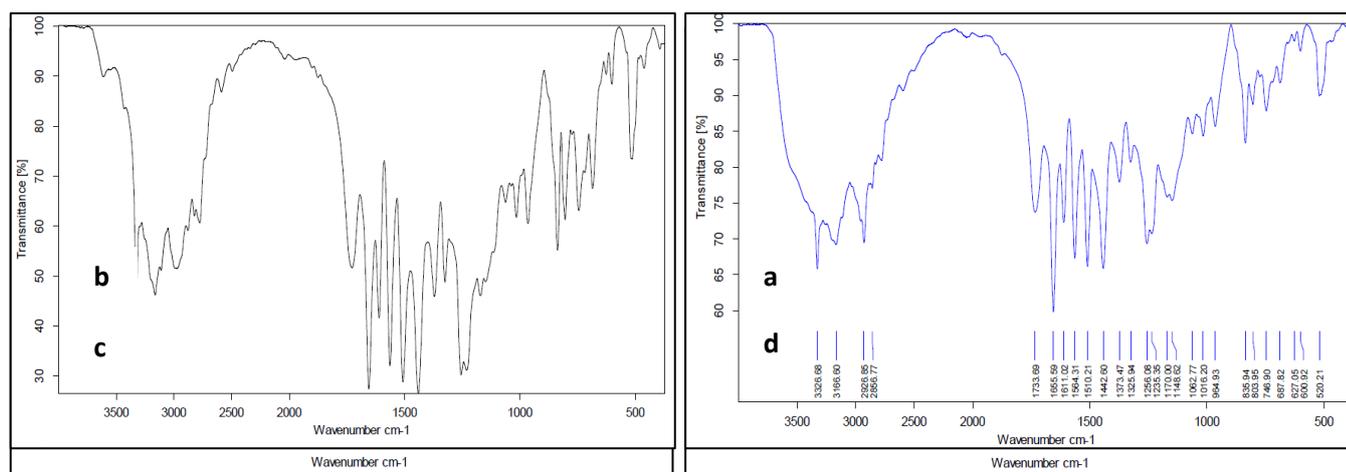


Figure 1. (a) FTIR spectra of pure acetaminophen, (b) FTIR spectra of Eudragit E100, (c) FTIR spectra of the physical mixture, and (d) FTIR spectra of prepared solid dispersion

2.1.2. Differential scanning calorimetry (DSC) analysis

Figure 2 shows the thermograms of acetaminophen, Eud E100, physical mixture, F1, F2, and F3. The thermogram of acetaminophen shows a melting point onset at 171.1°C, while Eud E100 exhibits a glass transition at approximately 62°C. The physical mixture did not show a noticeable difference at Tg of Eud E100 but there was a shift at the acetaminophen onset melting peak from 171.1°C to 159.9°C and the form of this peak become broader. F1 and F3 show a small shift at Eud E100 Tg to 55.52°C, but there was a significant shift of acetaminophen onset melting point to 144.141°C respectively with become smaller and border this indicates present a crystalline form. As for F2, the melting peak of the drug has completely disappeared indicating the absence of crystalline form which means the complete formulation of solid dispersion.

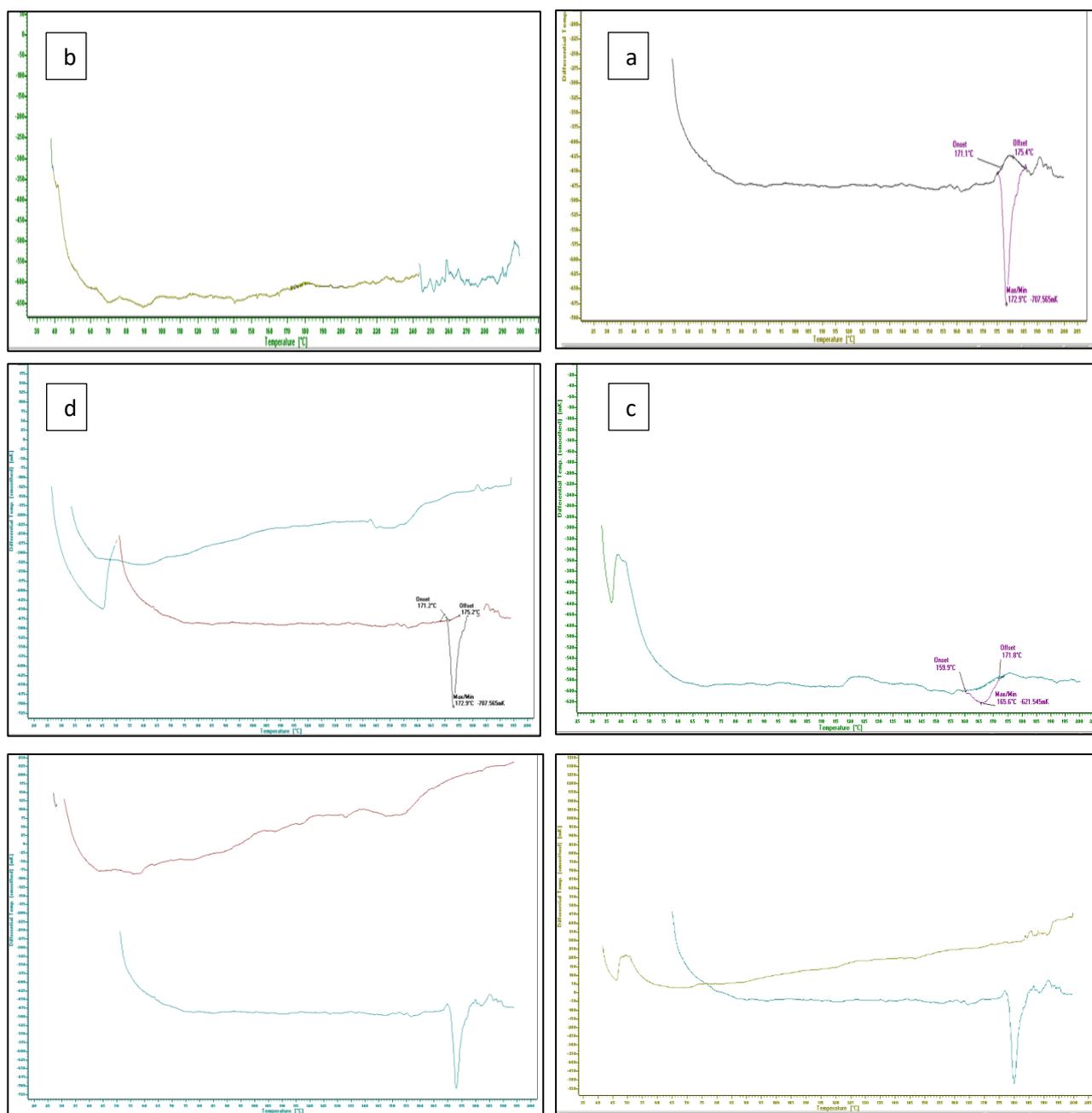


Figure 2. DSC curves of (a) acetaminophen, (b) Eudragit E100, (c) physical mixture, (d) F1 comparison of acetaminophen, (e) F2 comparison of acetaminophen, (f) F3 comparison of acetaminophen

2.1.3. Determination of production yield and drug loading

As shown in Table 1 the production yield ranged between 96-97% for the solvent evaporation method used, which makes this method highly productive. Table 1 shows that the acetaminophen loading% of F1, F2, and F3 is 97.3%, 96.5%, and 97.38%, respectively. Ehsaneh Jafari has demonstrated using Eud E100 for solubility enhancement of diclofenac sodium using solvent evaporation and attaining 98.43-99.74% loading [15]. Basher Alkasmí et al. have reported using Eud E100 for taste masking paracetamol using a modified coacervation method and achieving 6.57-40.65% for formulation containing Eud E100 with SLS and 17.35% for these were prepared by addition PEG [16]. Drug loading of solid dispersion valsartan which was prepared by solvent evaporation for improved dissolution rate and bioavailability was 96.15-104.26% [17]. Another study by Gaurav Sharma et al. has shown a drug loading ranged between 78.41 to 106.06% for promethazine solid

dispersion prepared using Eud E100 by solvent evaporation method [18]. Thus, the solvent evaporation technique can be considered a suitable method to obtain a good drug loading.

Table 1. Production yield and drug loading of prepared solid dispersions (mean ± SD, n=3)

Formula code	Production Yield%	Drug loading%
F1	97.300±0.028	99.77±1.56
F2	96.546±0.065	103.7±3.34
F3	97.383±0.035	101.34±1.29

2.2. In-vitro taste masking study

2.2.1. Determination threshold bitterness

As shown in Table 2 the threshold bitterness of acetaminophen was determined at a concentration of 900µg/ml, it was the lowest concentration where more than half of the volunteers felt a bitter taste [19]. This value is close to what was specified by Albertini et al, which was 1080µg/ml [20]. The value of this threshold varied from 35µg/ml by Shiino et al to 350µg/ml by Sharma et al [19,21], which may be due to the dissolution medium used.

Table 2. Results of determination of bitterness threshold

Concentration (µg/ml)	1	2	3	4	5	6
200	-	-	-	-	-	-
300	-	-	-	-	-	-
400	-	-	-	-	-	-
500	-	-	+	-	-	-
600	+	+	+	-	-	-
700	+	+	+	+	+	+
800	++	+	++	-	+	+
900	-	++	++	++	++	+
1000	++	++	++	++	++	++

2.2.2. Taste masking evaluation (pH=6.8)

The amount of acetaminophen released from solid dispersion in a simulated saliva medium Table 3 was compared with the threshold bitterness which determined, to select the best one. The results showed a released amount after 2 min less than the bitterness threshold for all prepared formulations. Indicating the success of taste masking bitterness of acetaminophen.

Table 3. Taste masking evaluation [amount of drug release after 2 min at pH=6.8 (mean ± SD, n=3)]

Formula Code	Amount released(µg/ml)
F1	114.98
F2	75.97
F3	10.26

2.3. In vitro drug release study

Table 4 shows the cumulative percentage of drug release for F1, F2, and F3 formulations, and Figure 3 displays the dissolution profile for it. F2 administrated the maximum release rate in comparison with the other formulations, and all these have a good drug release ratio. These results are attributed to increasing the specific surface area due to the formation of solid dispersions in addition to the transformation of a large part of acetaminophen from crystalline form to amorphous (according to DSC results) which is the most dissolution form. And these results are simulated with the study reported by Mohamad Mamdouh et al., which aimed to enhancement solubility of acetaminophen using a solid dispersion technique, different carrier including Eud E100 which administrated the most affinity of enhancement solubility, where the release amount of acetaminophen increased from 18.5% for standard acetaminophen to 84% for acetaminophen solid dispersion after 2 min (%Q_{2min}) [22]. Furthermore, these results are very close to that reported by Basheer Alkasmī et al,

where the formulation prepared by 1:1 ratio (Eud E100: acetaminophen) showed a cumulative amount reaches 83.97% after 20 min (%Q_{20 min}) [16].

Table 4. In vitro drug release at pH=1.2 (mean ± SD, n=3)

Time (min)	F1	F2	F3
0	0	0	0
2	81.81±2.62	92.77±2.36	93.41±1.38
5	83.81±0.74	96.82±0.54	94.89±0.66
10	84.36±0.94	100.08±0.82	95.65±1.17
15	84.95±0.55	100.89±0.70	95.78±0.71
20	86.26±0.34	101.79±0.49	95.88±0.80
30	87.47±0.71	102.34±1.57	96.35±0.48
45	87.72±0.50	103.59±0.72	96.41±0.10
60	88.31±0.42	104.68±1.05	98.21±0.63

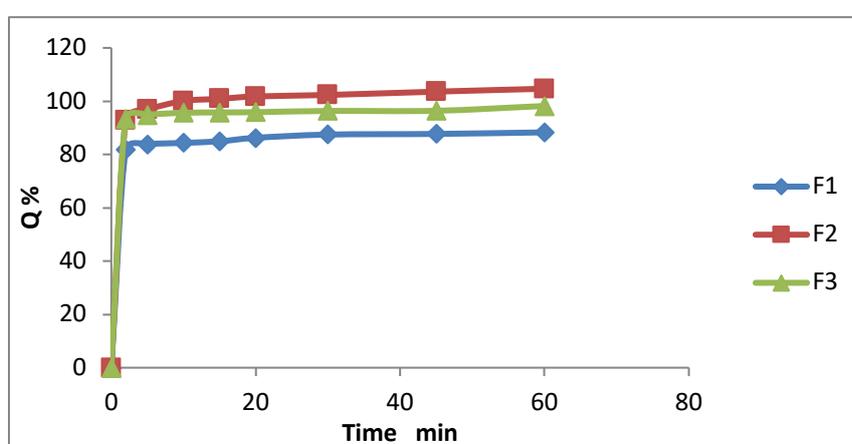


Figure 3. In vitro cumulative drug release curve at pH=1.2

3. DISCUSSION

The solvent evaporation method has a good production yield, especially when using polypropylene dishes, as these dishes facilitated the extraction of the resulting solid dispersions, which reached 97% approximately. Selecting the pH-dependent polymer was the correct choice, as it was able to reduce the amount of drug released to less than of threshold bitterness that indicated a successful *in-vitro* taste masking, as the lowest value of the released amount appeared with F3. Furthermore, this process did not affect the drug released at pH=1.2, this indicates that the drug has reached the site of maximum absorption in the required amount.

4. CONCLUSION

Acetaminophen has been considered a widely used pain reliever and antipyretic for a long time due to its safety for different age groups especially children, but the spread of the problem of difficulty swallowing among a group of people made it important to formulate easy-to-swallow dosage forms, but this requires an acceptable taste, which prompted the formulation of acetaminophen taste-masking solid dispersions using Eud E100 polymer, where it was a successful choice as taste masking agent without effect on the rate of drug release, that allowing to use this prepared solid dispersions in the future to formulate oral dosage forms such as chewable tablets, orally dispersed tablets, etc.

5. MATERIALS AND METHODS

5.1. Materials

Acetaminophen was gifted by Proline Pharmaceutical Co.Ltd (Tartous, Syria). Eudragit E100 polymer was obtained from Human Pharmaceutical Co.Ltd (Tartous, Syria). Ethanol was purchased from SARI Co (Syria). All other reagents and chemicals were analytical grades and were used as received.

5.2. Preparation of solid dispersions

Solid dispersions of acetaminophen were prepared by using the solvent evaporation method. The drug: polymer ratios are given in Table 5. The components of each formula were mixed well, then ethanol 75% (note: ethanol 96% was used first, but for reducing the amount of solvent used ethanol 75% was used) was added to the mixture in the least amount to dissolve it and stirred until the formulation of a homogenous thick gel. Molding has been tried in various dishes of porcelain, glass, and stainless steel, but there was difficulty in extracting the solid dispersion formed due to the formation of a very hard layer, may be due to formulation a band between eudragit and these materials, which lead to experimenting with polypropylene dishes, with made a very thin layer to insure rapid evaporation and left it at room temperature 25°C for 48 hours, then it was crushed by using mortar and pestle then sieved.

Table 5. Composition of prepared formulations

Formula Code	Ratio Drug: Polymer	Method
F1	1:1	Solid dispersion (solvent evaporation)
F2	1:2	Solid dispersion (solvent evaporation)
F3	1:3	Solid dispersion (solvent evaporation)

5.3. Characterization of solid dispersions

5.3.1. Fourier transform infrared FT-IR spectroscopy

FTIR spectrum of acetaminophen, Eudragit E100, Physical mixture, and solid dispersions were obtained using an FTIR spectrophotometer (Bruker FTIR Alpha, Germany) in the scanning range 4000-500 cm⁻¹. Samples were mixed well with potassium bromide (KBr) to formulate discs and a disc of potassium bromide was used as a blank. These spectra are used to determine any interaction between polymer and drug.

5.3.2. Differential scanning calorimetry (DSC)

Thermograms were recorded for acetaminophen, Eudragit E100, physical mixture, and solid dispersions to confirm the formulation of amorphous solid dispersions which indicated that taste-masked acetaminophen was formulated. Samples (2-5mg) were prepared in closed aluminum pans and heated at a scanning rate of 5 °C/min in a temperature range between 50-200 °C by using LINSEIS DSC calorimeter (LINSEIS DSC-PT10, Thailand).

5.3.3. Determination of production yield

Samples were obtained and then weighted to determine whether the method used had a good yield by applying the following formula: [11]

$$\text{Production yield(\%)} = \frac{\text{The total mass of recovered solid dispersions}}{\text{The total mass of (polymer+drug)}} * 100$$

5.3.4. Determination of drug loading

Acetaminophen content at each formula was determined at maximum absorption wavelength (λ_{max} = 243nm) by using UV spectrophotometry (Specord 50 plus: Analytik Jena, Germany). The solution of each formula which contains an amount equivalent to 120mg of acetaminophen was prepared by dissolved solid dispersion at 100 ml HCl (0.1N) and sonicated for 10 min until formulated a clear solution then filtered and measured the absorption with the presence of the blank of Eudragit E100 in HCl. The drug loading was calculated by the following equation: [23]

$$\text{Drug Loading(\%)} = \frac{\text{weight of acetaminophen in solid dispersions}}{\text{weight of theoretical acetaminophen amount}} * 100$$

5.4. Structural evaluation of a taste masking process

In this section, the FTIR and DSC tests also were used to determine structurally the efficiency of the used method to taste-mask.

5.5. In vitro taste masking study

5.5.1. Determination threshold bitterness

A series of acetaminophen aqueous solutions were prepared in concentrations between (200-1100) µg/ml, then requested 6 volunteers (3 male, and 3 female) aged around 18-25 years were to give their opinion after tasting 5 ml of each solution by putting it on the middle of the tongue and kept it for 30 sec then spitting it and waiting for 1 min before testing the next solution to ensure the absence of after taste, then were asked to gargle by distilled water and wait 10 min before tasted next solution. They were asked to remark on taste and register their note as follows:

(-) If no difference between the solution and distilled water

(+) If remarkable different taste but it is not bitter

(++) Exist an obvious bitter taste

The lowest concentration in which more than half of the volunteers felt a bitter taste was determined as the bitterness threshold for acetaminophen [20].

5.5.2. Taste-masking evaluation (pH=6.8)

A solution of phosphate buffer was prepared to simulate saliva medium, whereby it should have a minimized solubility in the oral cavity less than of threshold bitterness of acetaminophen to say that a taste masking formula has been done successfully. This test had been done according to explained by Shagufta Khan et al.,2007. Solid dispersions, equivalent to 120 mg of acetaminophen were placed in 10 ml of SSF and shaken for 60 seconds. The amount of drug released was analyzed at 243 nm [24].

5.6. In vitro drug release study

Despite the importance of the FT-IR and DSC tests to confirm formulation solid dispersion, subsequent success tastes masked. However, it is very important to ensure that this technique and materials do not affect the rate and space of drug release, subsequently achieving a desirable therapeutic effect [25]. So this test was done using USP apparatus 2 (paddle), 900 ml HCl (0.1 N) dissolution medium, setting the speed at 100rpm, the temperature at 37±0.5 C°, and 5ml samples were withdrawn after specified intervals [22]. Then the amount of drug dissolved was determined after filtering by microfilter (0.45µm) and measured absorption at 243 nm using a UV spectrophotometer (Specord 50 plus: Analytik Jena, Germany). Each sample was triplicated and the results were reported as mean ± SD.

Acknowledgements: The authors are thankful to the management of collage of pharmacy at Aleppo university for providing us with the facility for carrying out the research work. Also, thankful to Proline and Human company for pharmaceutical industries for providing us with the necessary raw materials.

Author contributions: Concept – S.S., T.H.; Design – S.S., T.H.; Supervision – T.H.; Resources – S.S., T.H.; Materials – T.H.; Data Collection and/or Processing – S.S., W.A., T.H.; Analysis and/or Interpretation – S.S., W.A., T.H.; Literature Search – S.S.; Writing – S.S.; Critical Reviews – S.S., W.A., T.H.

Conflict of interest statement “The authors declared no conflict of interest”.

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