

Paracetamol/ naproxen co-crystals; a simple way for improvement of flowability, tableting and dissolution properties

Amal F.Al-Dulaimi,^{*1} Myasar Al-kotaji,^{**} and Faris T. Abachi^{*}

^{*} College of Pharmacy, University of Mosul, Mosul, Iraq.

^{**} College of Pharmacy, Ninevah University, Mosul, Iraq.

¹Corresponding author E-mail: amal.php1@student.uomosul.edu.iq

Received
08-07-2021

Accepted
16-08-2021

ABSTRACT

Background: The poor solubility of drugs is one of the most important limitations in formulating drugs into suitable dosage forms. In addition, the mechanical properties are the main obstacles in formulating tablet dosage form by direct compression method.

Aim of this research: To investigate the possible improvement in mechanical properties, solubility performance, and tableting properties of drug-drug co-crystals of paracetamol and naproxen.

Methods: The pre-compression parameters (Angle of repose, Carr's index, and Hausner's ratio) of the three paracetamol/naproxen co-crystals were investigated. Moreover, the solubility of the co-crystals was tested as well. In addition, the three paracetamol/naproxen co-crystals were formulated as oral tablets by direct compression method using microcrystalline cellulose and magnesium stearate. The prepared co-crystals were compressed into tablet dosage forms and the dissolution profiles were monitored.

Results: The results showed an enhancement in flowability and compressibility of the prepared co-crystals when compared with paracetamol or naproxen alone. The poor tableting properties of prepared paracetamol tablets were very clear and they are in opposite to the co-crystals prepared tablets, which met all the pharmacopeial requirements. The *in vitro* dissolution study was conducted to compare the dissolution profiles of the prepared co-crystals tablets with marketed paracetamol tablets (Piodol[®]) and marketed naproxen tablets (Napron[®]). The dissolution profile of (1 to 2) co-crystal prepared tablets showed a superior dissolution rate with more than 50 % of the paracetamol drug dissolved within the first 5 minutes of dissolution rate. The dissolution study resulted in a better dissolution of the prepared paracetamol/naproxen tablets due to the co-crystal formation.

Conclusion: It could be concluded that the prepared paracetamol/naproxen co-crystals represent a promising way for improving flowability and compression properties, enabling the formulation of the co-crystals as oral tablets by direct compression method with a clear enhancement in the dissolution rate.

Keywords: Co-crystal, paracetamol, naproxen, Carr's index, dissolution rate.

الخلاصة

الخلفية: يعد ضعف قابلية الأدوية على الذوبان من أهم المعوقات في صياغة الأدوية بأشكال صيدلانية مناسبة. بالإضافة إلى ذلك، فإن الخواص الميكانيكية هي العوائق الرئيسية في صياغة وتحضير الأقراص (أو ما يعرف بالحبوب) بطريقة الضغط المباشر.

الغاية من هذا البحث: التحقق من التحسن المحتمل في الخواص الميكانيكية، والذوبانية وخصائص تكوين الأقراص عن طريق تحضير البلورات الدوائية المشتركة بين الباراسيتامول والنابروكسين.

الطريقة: تم فحص معلمات ما قبل الضغط (زاوية الراحة ، مؤشر كار ونسبة هاوسنر) للبلورات المشتركة الباراسيتامول / نابروكسين الثلاثة. علاوة على ذلك ، تم اختبار قابلية ذوبان البلورات المشتركة أيضاً. بالإضافة إلى ذلك ، تمت صياغة بلورات الباراسيتامول / نابروكسين الثلاثة كأقراص فموية بطريقة الضغط المباشر باستخدام مايكروكريستالين سليولوز وستيرات المغنيسيوم. تم ضغط البلورات المشتركة المحضرة على شكل أقراص وتمت مراقبة الذوبانية.

النتائج: أظهرت النتائج زيادة في قابلية التدفق أو الجريان وانضغاط البلورات المشتركة المحضرة عند مقارنتها مع الباراسيتامول أو نابروكسين بمفرده. كانت الخصائص الضعيفة لأقراص الباراسيتامول المحضرة واضحة جداً وهي عكس الأقراص المحضرة من البلورات المشتركة ، والتي تلمي جميع المتطلبات الدوائية. أجريت دراسة الذوبان في المختبر لمقارنة ملامح الذوبان لأقراص البلورات المشتركة المحضرة مع المستحضرات الموجودة في الاسواق للباراسيتامول (Piodol®) والنابروكسين (Napron®). أظهر ملف الذوبان للأقراص المحضرة من بلورات مشتركة (1 الى 2) معدل ذوبان ممتاز مع أكثر من 50 ٪ من الباراسيتامول المذاب خلال الدقائق الخمس الأولى من معدل الذوبان. أظهرت دراسة الذوبانية إذابة أفضل لأقراص الباراسيتامول/نابروكسين المحضرة بسبب تكوين البلورة المشتركة.

الاستنتاج: يمكن الاستنتاج أن البلورات المشتركة من الباراسيتامول /نابروكسين تمثل طريقة واعدة لتحسين قابلية التدفق وخصائص الانضغاط ، مما يتيح صياغة البلورات المشتركة كأقراص فموية بطريقة الضغط المباشر مع تعزيز واضح في معدل الذوبان.

الكلمات المفتاحية: البلورات المشتركة، باراسيتامول، نابروكسين، مؤشر كار، معدل الذوبان.

Introduction

The oral route represents the most common route for drug administration and oral tablets are considered the most popular dosage forms due to patient preferences, safety, convenience, stability, and low manufacturing costs (1,2). Only a few numbers of active pharmaceutical ingredients (APIs) could be formulated directly as a tablet, the most important properties of APIs to make them suitable candidates to formulate as oral tablets are mechanical properties and solubility.

Mechanical properties of drugs are related mainly to powder flowability and compressibility. In tablets manufacturing, powder flowability and compressibility are two critical characteristics of powder that determine the suitable type of excipients and tableting process (3). Poor flowable and/or poor compressible drugs could not be formulated as oral tablets directly by the direct compression process. The alternative method should be used like dry and wet granulation processes. Otherwise, manipulation of drug powder by using a different solid forms like co-crystal formation or by the addition of a large

amount of free flowable excipients to improve the drug micrometric properties (4).

Paracetamol or acetaminophen is a famous antipyretic and analgesic drug. Paracetamol is found in three different forms: I, II, and III. Form I (monoclinic form) is the most commonly used form in pharmaceutical preparations. It is crystal in nature, thermodynamically stable but known by its poor tableting properties (5). Preparation of paracetamol as tablets by direct compression revealed capping and lamination of tablets due to poor flowability, compressibility, and plastic deformity of paracetamol (6). Various techniques exploited to enhance paracetamol mechanical properties: Some researchers focus on the production of paracetamol in its second form (Orthorhombic) because this form has good solubility and mechanical properties. The obstacles against the use of form II paracetamol are the difficult process of production with the possibility of oxidation, a phase transition to form I and the yield product will be a mixture of both forms (I and II) (5). One of the methods used for the production of form II involves the use of form I paracetamol co-crystal as a template in aqueous solution by cooling

crystallization of paracetamol in water with oxalic acid or maleic acid leading to the formation of co-crystal with lattice structure similar to form II packing pattern (7). Other techniques depend on alteration in crystals shape of form I such as using polymer excipients like chitosan (8) or specific plasticity deforming binder like polyvinyl pyrrolidone (PVP) (6). Using the new process of excipients addition called Co-processing (9) and changes in crystal structure by the production of paracetamol as co-crystal exhibited an improvement in mechanical properties of paracetamol, which allowed its formulation as tablets by direct compression. Paracetamol-caffeine co-crystals were prepared by Latif *et al* using 4 different methods (solvent evaporation, anti-solvent addition, dry and liquid assisted grinding) with distinct solvent mixtures. They illustrated how such co-crystals could improve intrinsic dissolution rate and compression behavior. After that, they formulated paracetamol co-crystals as oral tablets by direct compression and they demonstrated the improved characteristics of co-crystal with enhanced bioavailability in sheep (10).

A non-steroidal anti-inflammatory drug (NSAID), naproxen is known for its poor flowing properties besides the poor water solubility. Vikas G. Rajurkar *et al.* try to resolve these two problems that affected on naproxen formulation as oral tablets by using co-crystallization techniques. They prepared naproxen as co-crystals with two cofomers (Urea and Thiourea) by using the solvent evaporation technique. They approved that these co-crystals could enhance flowability and compressibility of naproxen besides the improvement that occurred in aqueous solubility which was reflected by the higher dissolution rate of co-crystals in comparison with naproxen alone. The angle of repose changed from 46 for naproxen to about 28 and 27 for

naproxen co-crystals with urea and thiourea, respectively. Carr's Index of naproxen was 25% compared with 8% for naproxen/urea co-crystal and about 11% for naproxen/thiourea co-crystal (11).

The co-crystals consist of a stoichiometric ratio of two or more components joined together by hydrogen bonds in most cases. Pharmaceutical co-crystal is formed when one of the co-crystal components at least, is API. The co-crystallization technique approved its unique ability to resolve more than one obstacle faced drug's formulation like poor flowability, compression ability, dissolution, and tableting properties. The good co-crystal properties offer an opportunity to produce a combinational drug dosage form by easy and low-cost process (12).

This research aims to conduct a pre-compression study to measure the flowability and compressibility of previously prepared paracetamol/naproxen co-crystals by solvent-evaporation techniques in three ratios and to formulate these co-crystals as oral tablets by the direct compression process. After that, evaluation of the prepared tablets and conducting *in vitro* dissolution study to compare the dissolution rate of prepared co-crystals tablets with the marketed products such as paracetamol tablet (Piodol®).

Materials and Methods

Materials

Paracetamol and naproxen were obtained as free samples from Pioneer company for pharmaceutical industry in Al-Sulaymaniyah city/Iraq. Microcrystalline cellulose was from JRS pharm, U.S.A while magnesium stearate was from Prachin Chemicals, India. Absolute ethanol, potassium dihydrogen phosphate and sodium hydroxide were purchased from Scharlau, Spain.

Methods

1. Preparation of paracetamol/naproxen co-crystals

Paracetamol/naproxen co-crystals have been prepared in three ratios (1 to 1, 2 to 1, and 1 to 2) successfully by solvent-evaporation process, using absolute ethanol as a solvent. All co-crystals preparation and characterization methods, in addition to solubility study, have been discussed in details in a very recent work (the article is submitted to the Iraqi journal of pharmaceutical sciences).

2. Evaluation of powder pre-compression parameters: flowability and compressibility

Flowability and compressibility study was conducted by measuring of the angle repose, bulk density, tapped density, Carr's Index, and Hausner's ratio of the prepared co-crystals and their pure parent drugs.

a. Angle of repose θ° :

The angle of repose is related to the resistance to flow and the frictional force between the powder particles. It was determined by the fixed funnel method and it was calculated using this equation (13):

$$\tan \theta = \frac{h}{r}$$

Where θ° is angle of repose, h is the height of the powder cone and r is the radius of the powder cone.

b. Bulk density and tapped density:

Bulk density is the ratio of powder weight in gram to the volume of the graduated cylinder occupied by that powder without tapping, as illustrated in the following equation (14).

$$\text{Bulk density} = \frac{\text{weight of powder in g}}{\text{volume of untapped powder in ml}}$$

The tapped density was measured by weighing the sample and pouring it carefully in a clean, dry graduated cylinder. After that, the powder will be tapped for 500 taps at a rate of tapping 300 taps/min by Sotax apparatus (TD1), U.S.A. After the apparatus was stopped, the volume of the sample was recorded and the following equation was applied (15):

$$\text{Tapped density} = \frac{\text{weight of powder in g}}{\text{volume of tapped powder in ml}}$$

c. Carr's Index and Hausner's ratio:

Carr's Index is an index of powder flow rate and it is called compressibility index, while Hausner's ratio is related to inter-particle friction. Both of them are calculated depending on the measurement of bulk and tapped densities using the following equations (13):

$$\text{Carr's Index} = \frac{(\text{tapped} - \text{bulk}) \text{ densities}}{\text{tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

3. The tableting process of co-crystals and pure paracetamol:

Direct compression is the simplest method for tablet production. The prepared co-crystals and pure paracetamol powder were formulated as oral tablets by direct compression technique using manual tablet pressing Manesty Machines LTD, England. The powder of pure paracetamol or either ratio of co-crystal was mixed with 60% microcrystalline cellulose PH102 (avicel) for 5-10 minutes. Then 1%, magnesium stearate was added as a lubricant and mixed for 1-2 minutes (10).

4. Evaluation of prepared tablets:

Evaluation of the prepared tablets was performed by using procedure and limiting range of each test as mentioned in U.S.Pharmacopoeia.

4.1 Weight of tablet and weight variation:

The quantity of powder fills into the die of the tableting machine will determine the weight of that tablet. The weight variation test was run by random selection of twenty tablets and calculate their average weight. After that, each individual tablet's weight was compared with the average weight (16). The requirement of the test was met if no more than two individual tablet weights deviate from the average weight by more than the pharmacopeial percentage and no one individual tablet weight deviates by more than twice the percentage (the maximum allowed difference percent is 10% if the average tablet's weight is ≤ 130 mg, while if the average tablet's weight is between 130 mg and 324mg, the allowed percent will be 7.5%) (14).

4.2 Tablets thickness:

The thickness of the tablet is related to the weight of each tablet and the compression forces applied to the powder by the tableting machine (17). Tablet thickness was measured by Micrometer caliper (Ditron, China) and the result is expressed in millimeters (mm).

4.3 Hardness (tablet Crushing strength):

The hardness of the tablet is the force required to break the tablet in long-axis direction (18). Hardness test was performed by selection of ten tablets randomly and record the power required to break them by using a tablet hardness tester (YD-1, LPMIE, China) (19). The hardness was measured in Newton (N) (Newton =0.102 kg). The accepted hardness for oral tablet is usually between 4-12 Kg (20).

4.4 Friability:

Friability test is measuring the tendency of tablets to resist abrasion and weight loss that occurred during packaging, handling, and transport (20).

Friability test was performed by using a tablet friability tester (CS-3, China) which consists of two drums. Random ten tablets have been weighed and placed in each drum. The friability tester was run for 100 revolutions at a rate of 25 rpm. At the end of the revolutions, the tablets were dedusted and weighed again (21). The friability percentage for most oral tablets was considered to be accepted if it was not more than 1% (22). Friability percentage was calculated using the following equation:

$$\text{Friability \%} = \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \times 100$$

4.5 Disintegration time:

The disintegration is the first change that occurred to the tablet inside the body. Disintegration time could be defined as the time required for the tablet to be disintegrated and converted into small particles. It was measured by a disintegration tester (BJ-2, China). The temperature of the apparatus was set at 37.5°C. A randomly selected tablet was placed in each basket tubes, covered with a disc and the basket will immerse in a 900ml beaker filled with distilled water. The disintegration apparatus will operate and the basket will start moving up and down. The time required for the tablets to break up and disappear from the basket is represented the disintegration time (19). According to British Pharmacopoeia, the conventional uncoated tablet should be disintegrated within 15 minutes (23).

5. Tablet *in vitro* dissolution study:

Dissolution rate is the rate at which the drug being to dissolve in the surrounding liquid before being absorbed and reach systemic circulation. The dissolution rate is considered as the rate-limiting step for the bioavailability of drugs that have low solubility (20).

The dissolution study was performed by using a type II paddle apparatus (Copely apparatus, U.K.) which consists of six vessels, each vessel is filled with 900 ml phosphate buffer (pH= 7.4 ± 1) as dissolution media (24,25). The temperature was set to be 37 ± 0.5°C and the paddle rotating speed was 50 rpm (26). A single tablet was immersed in each vessel and a 5 ml sample was drawn at different time intervals (5, 10, 15, 30 min) for paracetamol. In the case of naproxen, an additional sample was withdrawn after 45 min and each withdrawn sample had been replenished by 5 ml of fresh dissolution media to keep the total volume of media in each vessel equal to 900 ml (27). Each withdrawn sample was filtered by a 0.45 µm membrane filter, suitably diluted, and analyzed by Shimadzu UV-spectrophotometer at 242 nm and 331 nm wavelengths for measuring paracetamol and naproxen, respectively. The dissolution study requirements will be achieved if not less than 80% of the drug was dissolved within 30 minutes for paracetamol and 45 minutes for naproxen (14,23).

The dissolution media consisted of phosphate buffer (pH= 7.4) and it was prepared (26) as follows:

a) 13.608 gram of potassium dihydrogen phosphate was dissolved in distilled water and after complete dissolution, the volume was made up to 1000 ml.

b) 6.804 gram of sodium hydroxide was dissolved in distilled water and after complete dissolution, the volume was made up to 1000 ml.

The two solutions were mixed together vigorously; to ensure the homogenous mixing and the final pH was adjusted by using a sensitive pH meter (Eco Tester pH2®, India).

A dissolution study was conducted to compare the dissolution of prepared co-crystals tablets with the marketed products of the company that supplied the active ingredients (Pioneer company): paracetamol (Piodol® 500 mg) and naproxen (Napron® 250 mg) oral tablets.

In order to evaluate the dissolution profile of prepared co-crystal tablets, Q5 value (which is the percentage of dissolved drugs within the first five minutes of dissolution test) and similarity factors study were conducted to compare the dissolution profile of prepared tablets with the dissolution profile of reference tablets (Piodol® and Napron®). Similarity factor (f_2) was calculated by using the following rule:

$$f_2 = 50 \times \log \left\{ \left[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where f_2 is similarity factor, n is the number of sample points, R^t is the dissolution percent of prepared tablets at time t, and T^t is the dissolution percent of reference tablets at time t.

The dissolution profile of the prepared tablets is considered to be similar to reference tablets if the similarity factor is between 50 and 100 ($f_2 > 50$) (28).

6. Statistical analysis:

In this study, all data are expressed as (mean ± standard deviation). Statistical analysis is performed by using the ANOVA test with Tukey after-test. The difference is considered statistically significant if the P-value is ≤ 0.05 and if the P-value is > 0.05, the difference will be considered statistically non-significant.

Results and Discussion

1. Evaluation of powder pre-compression parameters: flowability and compressibility

The angle of repose is used to measure powder flowability. In poor flowable powder, the particles stick or adhere to each other and resist movement through a fixed-height funnel into a flat surface and this gives a small radius cone and large θ° angle and vice versa (29).

In addition to flowability, powder compressibility could be measured by the calculation of the percentage differences between tapped and bulk densities through Carr's index or by the calculation of the ratio of the tapped to the bulk densities which is called Hausner's ratio.

Paracetamol is known for its poor flowability and poor compressibility. Paracetamol angle of repose is usually more than 40, and this indicates passible powder that may hang up (30). The measured pure paracetamol angle of repose was 44.073 while Carr's index and Hausner's ratio were 25.068% and 1.33, respectively.

Naproxen is also known by its poor

flowability. The high cohesiveness tendency of naproxen powders made them have low inter-particulate friction and it should be agitated through handling (11). The naproxen observed angle of repose was around 47 while Carr's index and Hausner's ratios were 27.058% and 1.373, respectively.

All the prepared co-crystals (N1, N2, and N3), showed excellent flowability as their angle of repose were 29, 24, and 30, respectively, as shown in Table 1.

Compressibility or Carr's index was excellent for N1 and N2, as they were 7.7 and 7.9 %, respectively. N3 co-crystal Carr's index was good, as it was equal to 13.66%. Hausner's ratio is another indicator of flowability and is in parallel to Carr's index. Both co-crystals (N1 and N2) exhibited excellent behavior in comparison to good flowability in the case of N3. However, all the prepared co-crystals demonstrated a clear enhancement and improvement in flowability and compressibility when compared with the paracetamol alone or naproxen alone, which exhibited poor flowability and compressibility.

Table (1): The pre-compression measurements of paracetamol, naproxen and their co-crystals N1, N2 and N3; All values are expressed as mean \pm SD, n = 3.

Formula	Angle of repose θ°	Bulk density g/ml	Taped density g/ml	Carr's index %	Hausner's ratio
Paracetamol	44.073 \pm 0.594 passible	0.324 \pm 0.008	0.433 \pm 0.019	25.068 \pm 1.419 passible	1.33 \pm 0.025 passible
Naproxen	47.192 \pm 0.476 poor	0.306 \pm 0.017	0.421 \pm 0.04	27.058 \pm 3.177 poor	1.373 \pm 0.058 poor
N1 co-crystal	29.421 \pm 0.289 excellent	0.208 \pm 0.007	0.225 \pm 0.006	7.732 \pm 0.704 excellent	1.084 \pm 0.008 excellent
N2 co-crystal	24.284 \pm 0.202 excellent	0.261 \pm 0.006	0.283 \pm 0.004	7.91 \pm 0.033 excellent	1.083 \pm 0.039 excellent
N3 co-crystal	30.324 \pm 0.522 excellent	0.089 \pm 0.009	0.103 \pm 0.01	13.664 \pm 1.032 good	1.157 \pm 0.013 good

The volume of untapped powder gave indication about powder flowability. The good flowable powder tends to occupy the smallest possible volume due to the rapid arrangement of particles with the lowest inter-particulate spaces. This is the opposite to the poor flowable powder that tends to occupy larger apparent volume due to the presence of many spaces between particles (30).

The small difference between tapped and bulk densities indicates the good flowability and compactibility properties of the studied powder making its particles run through the cylinder rapidly, giving compact cake with the lowest inter-particulate spaces before tapping, and this is what occurs in co-crystals (29).

The difference between the tapped and bulk densities in the three co-crystals (N1, N2 and N3) was around 0.018, which indicates excellent flowable co-crystals in comparison with their drugs components; paracetamol and naproxen in which the difference between tapped and bulk densities equal to 0.109, and 0.115, respectively.

The improvement that occurs in poor micrometric properties of the paracetamol and naproxen, when they are formulated as co-crystals, has been attributed to the bonding area that introduces an active flat slip plane with lower interlayer interaction energy which enhances the compression properties by facilitating plastic deformity (31,32). The improvement in flowability characteristics could be attributed to crystal habit of the formed co-crystal which is related to the external crystal shape (33).

2. Tableting process of prepared co-crystal and pure paracetamol:

The manufacturing of tablets through the direct compression method is preferred upon other methods, however, due to paracetamol properties, it is not feasible to produce paracetamol with this method. The

direct compression method was used for the formulation of either the prepared co-crystals or pure paracetamol powder as oral tablets. The excipients added in the formulation are microcrystalline cellulose PH102 (avicel) and magnesium stearate.

Microcrystalline cellulose was chosen because it is the most common direct compression excipient due to its binder activity, self-disintegration effect, and its requirement for a little amount of lubrication as it has a low friction coefficient (34). Magnesium stearate is one of the most common tablet lubricant agents that is used to decrease friction and facilitate tablet ejection. Lubricant agent is used in low percentage (0.05%-0.1%) and mixed for short time to prevent its effect on dissolution rate due to its hydrophobicity (35).

The tablet pressing machine was a single punch machine, operated by hand. The properties of the tablet formed by such tableting machine are depended only on the fed powder properties, because the compression pressure could not be monitored closely, unlike rotatory multiple punch machines in which the tablet weight, thickness, and hardness are closely monitored (36).

The three prepared co-crystals N1, N2, and N3 were successfully manufactured as oral tablets by direct compression method using manual tablet press. In spite of using the same excipients percentage, order of addition, and time of mixing, the manufacturing of tablets of paracetamol powder through direct compression method failed in production of tablets with acceptable properties. The produced tablets suffered from very low formulation performance (hand pressing of the formed tablet leading to break it back into powder). The poor mechanical properties of pure paracetamol render it impossible to be compressed into acceptable tablets by a direct single punch tableting machine

without modification (29).

3. Evaluation of tablets:

All the prepared tablets of the co-crystals ((N1 (1 to 1), N2 (2 to 1), and N3 (1 to 2) paracetamol/naproxen co-crystals)) and the prepared paracetamol tablets were evaluated by different tablet evaluation tests. Pure paracetamol tablets were fragile tablets, and some of the tablet evaluation tests were not applicable to them due to the tablet poor quality.

3.1 Weight of tablet and weight variation:

The weight of the tablet is affected by two main factors: the size of the die and the amount of powder filled in the die which is affected by powder flowability (37).

The same tableting machine, which is a single punch tableting machine, was used in the production of paracetamol and paracetamol: naproxen co-crystal tablets. However, the average weight of the tablets was different.

The average tablet weight of 20 random tablets for paracetamol was (112 ± 3.656 mg) in comparison with (141.65 ± 3.249 mg), (141.15 ± 3.313 mg) and

(140.95 ± 5.385 mg) for N1, N2, and N3 tablets, respectively, as shown in Table 2. The low average weight of the paracetamol tablet, despite the compression by the same tableting machine, might be attributed to the poor compressibility of paracetamol powder and poor flowability, which leads to incomplete die filling and low weight tablets (38). The difference in tablets weight between paracetamol prepared tablets and co-crystals tablets is considered statistically significant (p -value ≤ 0.05).

According to the weight of tablets, the accepted percentage of weight variation was 10% for paracetamol tablets, as the average tablet weight was less than 130 mg, while the three different co-crystals tablet's weight variation percentage was 7.5% according to USP pharmacopeia limits (14).

Although the tablets that have been prepared from poor flowable powder which is known by it is weight variations (38), paracetamol tablets weight were located within the accepted variation percentage due to low tablets average weight that made the variation limits range-wide ($\pm 10\%$).

Table (2): Evaluation tests of paracetamol tablets and co-crystals (N1, N2, and N3) tablets; All values are expressed as mean \pm SD.

Tablets type	Average tablets weight (mg) n=20	Thickness (mm) n=10	Hardness (N) n=10	Friability (%) n=20	Disintegration time (seconds) n=12
Paracetamol	112 ± 3.656	3.743 ± 0.046	8.02 ± 1.641	6.566 ± 1.538	10.605 ± 0.856
N1 co-crystal	141.65 ± 3.249	3.8 ± 0.120	94.61 ± 8.917	0.855 ± 0.001	30.27 ± 1.061
N2 co-crystal	141.15 ± 3.313	4.402 ± 0.039	69.81 ± 5.795	0.568 ± 0.008	31.85 ± 1.626
N3 co-crystal	140.95 ± 5.385	3.907 ± 0.128	93.04 ± 6.660	0.633 ± 0.102	17.785 ± 0.078

3.2 Tablets thickness:

Tablet thickness is the function of the amount of material filled into the die cavity, compression characteristics of this material and the compression forces applied to them (39). The compression forces were fixed for all prepared tablets.

In spite of the differences average weight of paracetamol prepared tablets in relative to the prepared co-crystals tablets N1, there was a non-significant variation in average tablets thickness between paracetamol prepared tablets (3.743 ± 0.046 mm) and N1 co-crystal tablets (3.8 ± 0.120 mm) as the p-value is more than 0.05.

A statistically significant difference in tablets thickness was observed when the paracetamol prepared tablets are compared with N2 and N3 co-crystal tablets. N2 tablets thickness was equal to (4.402 ± 0.039 mm) while N3 co-crystal tablets average thickness was (3.907 ± 0.128 mm) (p-value is ≤ 0.05).

The prepared paracetamol tablets had a lower average weight, despite that their

average thickness was comparable to N1 tablets thickness. This is due to the poor compressibility of paracetamol powder, which made them occupy a larger apparent volume in the die during compression. This leads to decreasing the tablet weight and hardness despite the comparable thickness to the tablets of good compressible powder (40).

3.3 Hardness (tablet Crushing strength):

The hardness of a conventional oral tablet depends on the size of the tablet as the large size tablet usually had a higher hardness than the smaller one. The accepted hardness value ranges from 4 to 12 Kg (39.216-117.647 N) (20).

A paracetamol prepared tablet exhibited a hardness average of (8.02 ± 1.641 N) as demonstrated in Figure 1, which is very low and lower than the USP limits. This means that this prepared paracetamol compact cannot be considered a conventional tablet due to its inability to withstand handling.

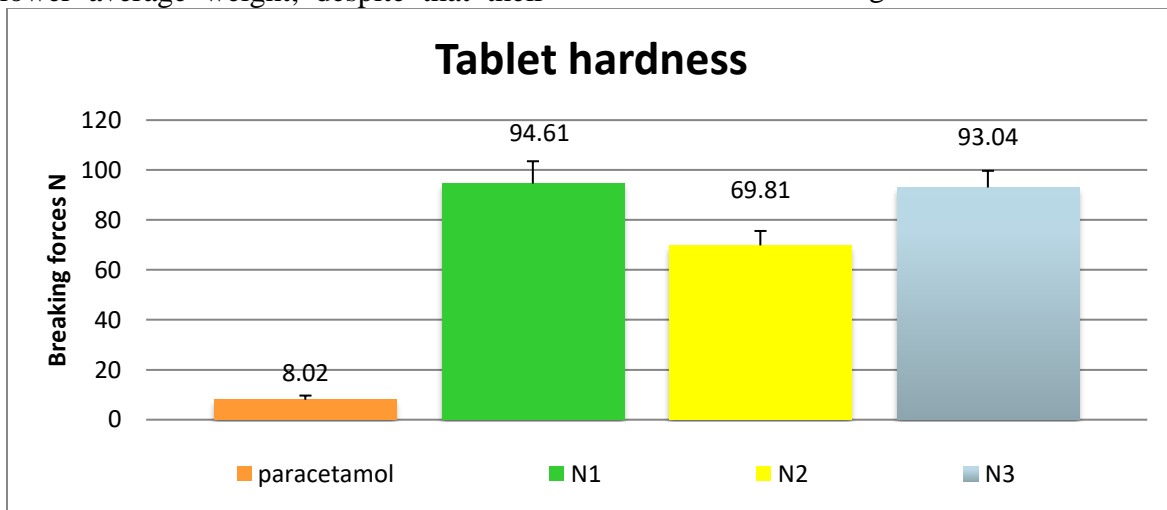


Figure (1): Hardness test of the prepared paracetamol tablets and co-crystals (N1, N2 and N3) tablets.

All of the three prepared co-crystals tablets have hardness strength within the acceptable range, as shown in Table 2 and Figure 1, and they showed statistically

significant differences from paracetamol tablets (p-value ≤ 0.05).

Although the same compression forces and the same type and percentage of

excipient (60% avicel) were used to prepare all tablets in this study, the paracetamol tablets had a lower crushing strength. This might be due to two reasons:

The first reason was poor powder flowability, which leads to incomplete die filling and low tablet weight. As the amount of material filled into the die increases the tablet hardness increase as long as the compression applied forces are constant.

The second reason could be attributed to the low tableting and compression properties of paracetamol, which made the elastic recovery higher than plastic deformity (change in powder structure by applying pressure). So, the tendency of paracetamol particles to return to powder state upon low crushing forces is very high. Elastic recovery is the amount of stored energy upon compression, and this energy tends to release when the compression forces are removed, leading to the formation of a weak tablet with a high

probability of capping and chipping (41).

The three types of the prepared paracetamol/naproxen co-crystals tablets showed a high crushing strength. This is due to the very good tableting properties of the prepared co-crystals which came from the excellent flowability and compression characteristic. The bond formation between paracetamol and naproxen in co-crystals acts like a slip plane. Upon compression, these planes will slip over each other at a lower energy barrier and increase the plasticity of the formed tablet (42).

3.4 Friability:

The three prepared co-crystals tablets (N1, N2, and N3) have an accepted friability percentage and are within the accepted limit (less than 1%). As demonstrated in Figure (2), the average friability percentage for them was (0.855±0.001) % for N1, (0.568±0.008) % for N2, and (0.633±0.102) % for N3.

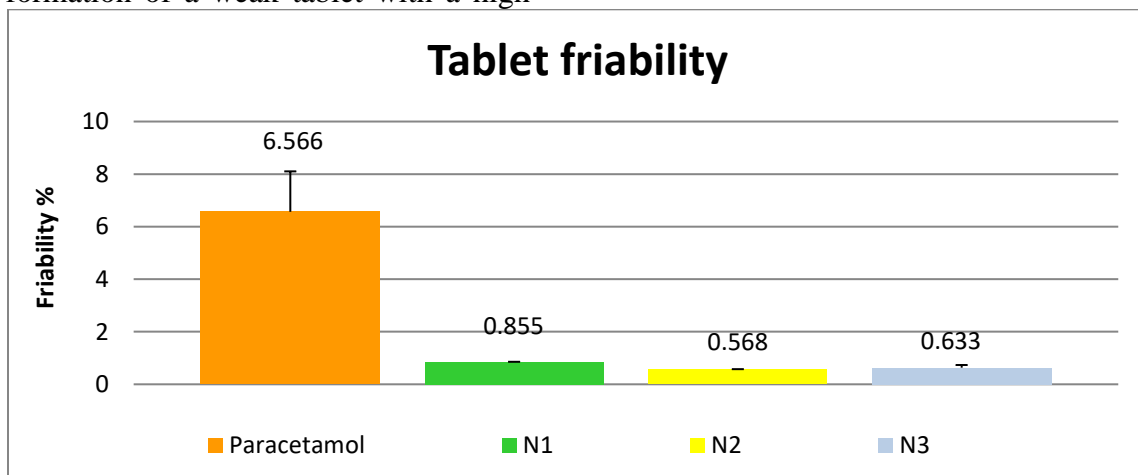


Figure (2): Friability test of the prepared paracetamol tablets and co-crystals (N1, N2 and N3) tablets.

Paracetamol prepared tablets failed in the friability test, not only because of the unaccepted percentage (6.566±1.538) % which was above the limits but also due to breaking and chipping that occurred to the tablets during the friability test and this

indicated the tablets fragility and unsuitability for further processing or customer usage. Paracetamol tablet friability exhibited statistically significant differences from the prepared co-crystals tablets (p-value ≤ 0.05).

3.5 Disintegration time:

The disintegration time is affected by many factors, some of which are related to drug and excipients properties like the type of drug molecule and the binder concentration. Other factors are related to the tableting process like compression force, which has a direct effect on tablet thickness, hardness, and friability. The tablet should be disintegrated into small particles before the dissolution process and for some oral tablets, disintegration is the rate-limiting step for absorption and bioavailability (41). The accepted disintegrated time for conventional oral tablet is less than 15 minutes.

The prepared paracetamol tablets have the lowest disintegration time with an average of (10.605 ± 0.856) seconds as

illustrated in Figure 3. The rapid disintegration rate of paracetamol could be occurred due to the high friability and low hardness of the tablets which indicates the low binding forces between particles and the high porosity degree that made the tablet disintegrate into small particles very rapidly (43). Disintegration time of paracetamol prepared tablet was shown a statistically significant difference from N1, N2 and N3 co-crystals tablets (p -value ≤ 0.05).

N1 and N2 co-crystals tablets had a nearly similar disintegration time with (30.27 ± 1.061) and (31.85 ± 1.626) seconds for N1 and N2 tablets, respectively. Both disintegration times are within the accepted limits, and there is no significant variation between them (p -value > 0.05).

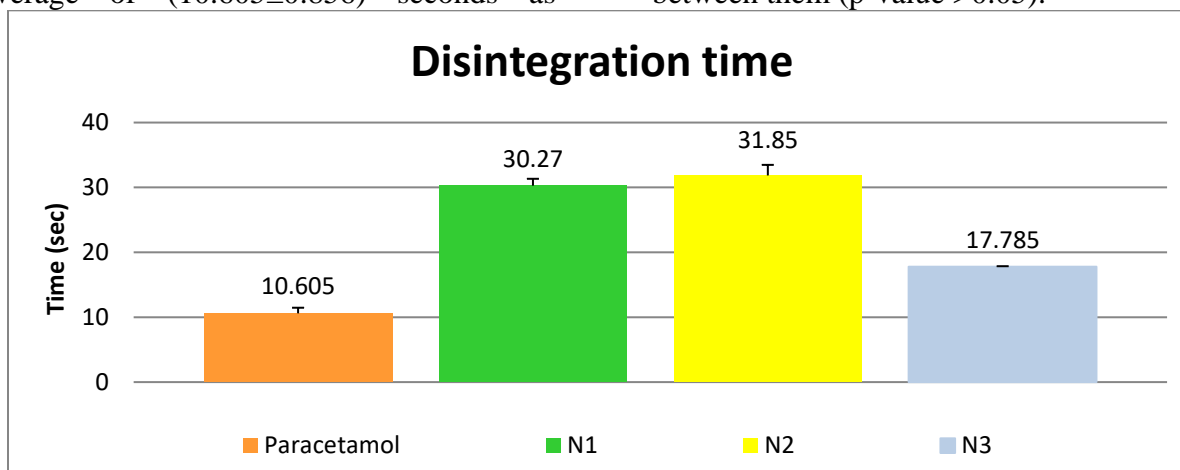


Figure (3): Disintegration time of the prepared paracetamol tablets and co-crystals (N1, N2, and N3) tablets.

N3(1 to 2) paracetamol: naproxen co-crystal tablets had a remarkable rapid disintegration time which was (17.785 ± 0.078) seconds. These rapid disintegration tablets was achieved in spite of a relatively high tablet hardness as recorded in Table 2. It also showed statistically significant differences in disintegration time from paracetamol tablets, N1, and N2 co-crystals tablets (p -value ≤ 0.05).

Rapid disintegration of co-crystal

tablets was reported in many types of research. In accordance with our results, 5-Fluorocytosine co-crystal tablets prepared by Perumalla *et al* that contain avicel, 1% colloidal silica, and magnesium stearate. The disintegration time in this tablet was less than 50 seconds (44). It is worthy to mention that although the huge number of researches on co-crystals, there is no similar work conducted on the preparation of paracetamol/naproxen co-crystal.

4. Tablet *in vitro* dissolution study:

The *in vitro* dissolution test was used to compare the dissolution profile of N1, N2, and N3 co-crystals prepared tablets with the dissolution of paracetamol and naproxen oral tablets (Piodol[®] and Napron[®],

respectively) of an Iraqi drug company called Pioneer. The pharmacopeia dissolution limits state that not less than 80 % of the drug should be dissolved within 30 minutes for paracetamol and within 45 minutes for naproxen (21).

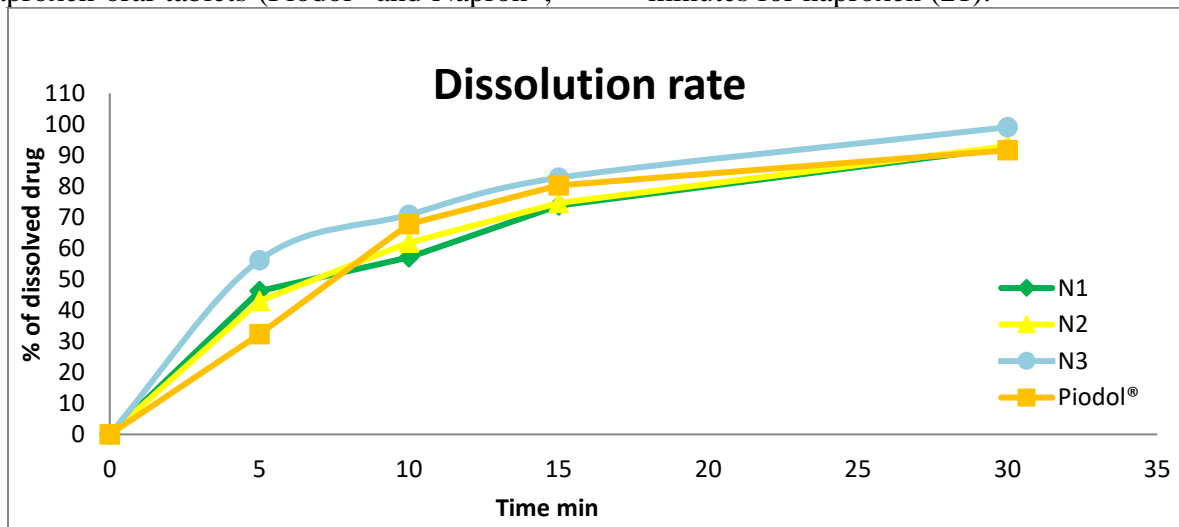


Figure (4): The average percent of dissolved paracetamol drug from N1, N2, N3 and Piodol[®] tablets.

Paracetamol dissolution rates for N1, N2, N3, and Piodol[®] tablets are represented in Figure 4. The difference in dissolution rate between co-crystals prepared tablets and Piodol[®] was clear in the first 5 minutes (Q5) of the dissolution study. The dissolution percentage of paracetamol from N3 tablets was (56.16 % \pm 5.0927) in comparison with (32.26 % \pm 4.938) for Piodol[®]. N1 and N2 co-crystal tablets had a comparable dissolution percent of around 44.5 %. The three co-crystals prepared tablets had a statistically significant increase in drug-dissolution percent from Piodol[®] tablets in the first five minutes (p -value \leq 0.05).

At the end of 30 minutes, the percent of dissolution was more than 90 % for each tablets formula (N1, N2, N3 and Piodol[®] tablets). Although, N3 co-crystal prepared tablets had the highest average of drug dissolution with (99.04% \pm 2.958) of paracetamol drug had been dissolved within

30 minutes, it did not give statistically significant differences from Piodol[®] or other co-crystals prepared tablets (p -value $>$ 0.05).

The results of overall *in vitro* dissolution study of the prepared co-crystals tablets in comparison with Piodol[®] exhibited a comparable rate of dissolution between N1 and N2 co-crystals tablets with Piodol[®] because in both cases, the similarity factors are larger than 50, as demonstrated in Table 3. In fact, although N1 and N2 tablets showed similarity with Piodol[®] tablets, N1 and N2 are better, as they were prepared by direct compression method while Piodol[®] tablets were prepared by wet granulation method. It is known that tablets prepared by wet granulation method have better dissolution than tablets prepared by direct compression method.

N3 co-crystal tablets showed dissimilar dissolution profile from Piodol[®], as the similarity factor value was less than

50. The dissimilarity between N3 and Piodol[®] indicated the better dissolution of N3 tablets (45). The reasons for this rapid releasing rate, especially at the first 5 minutes of dissolution study, could be attributed to the short disintegration time that made the N3 tablet converted rapidly

into small particles which exhibit a large effective surface area to promote a rapid dissolution rate. The other reasons for the high dissolution rate of N3 tablets were due to the co-crystallinity of the prepared tablets that exhibited a high dissolution rate with an increase in solubility at 7.4 pH (46).

Table (3): The similarity factor values between Piodol[®], N1, N2, and N3 tablets.

The compared tablets	Similarity factor (f ₂)
N1 with Piodol [®]	51.228
N2 with Piodol [®]	58.111
N3 with Piodol [®]	44.799
N1 with N2	75.568

Naproxen in general had a lower dissolution rate than paracetamol and had a pH-dependent solubility. The co-crystals prepared tablets (N1, N2, and N3 tablets) had a higher percent of naproxen drug-

dissolution in all co-crystals types in the first 15 minutes in opposite to Napron[®] tablets in which the dissolution of naproxen drug was slow as represented in Figure 5.

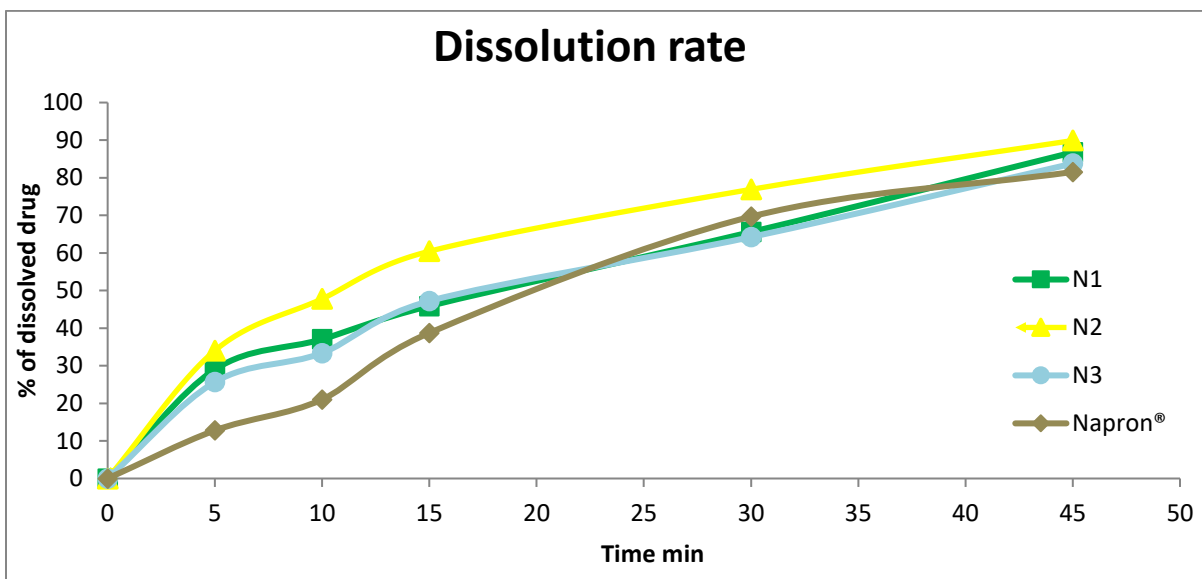


Figure (5): The average percent of dissolved naproxen drug from N1, N2, N3 and Napron[®] tablets.

In the first 5 minutes (Q5), N2 tablets exhibited the highest dissolution rate (34.02 %±3.551) while Napron[®] tablets had the lowest rate with only (12.79 %±3.565). The Q5 of N1 and N3 tablets were

comparable to each other with (28.99 %±4.62) and (25.64 %±1.606), respectively. The three co-crystals prepared tablets showed a statistically significant difference in naproxen dissolution in comparison to

Napron[®] tablets; higher dissolution than Napron[®] tablets in the first five minutes (p -value ≤ 0.05).

The results of the overall *in vitro* dissolution study of the prepared co-crystals

tablets in comparison with Napron[®] demonstrate a comparable rate of dissolution between Napron[®] and N3 prepared co-crystal tablets because the similarity factor is larger than 50, as demonstrated in Table 4.

Table (4): The similarity factor values between Napron[®], N1, N2, and N3 tablets.

The compared tablets	Similarity factor (f_2)
N1 with Napron[®]	47.674
N2 with Napron[®]	36.287
N3 with Napron[®]	51.656
N1 with N3	76.891

The N1 and the N2 co-crystal prepared tablets showed dissimilar dissolution profiles from Napron[®], as their similarity factor values were less than 50. The dissimilarity between N1, N2, and Napron[®] indicated the better dissolution of the prepared co-crystals tablets. The most similar dissolution profile was between N1 and N3, as the similarity factor value was equal to 76.981.

The better dissolution profile of prepared co-crystals could be related to their crystalline nature that indicates lower melting points of the co-crystals in comparison with paracetamol and naproxen.

The Spring-Parachute effect was obvious in the dissolution study of paracetamol from the N3 tablet. The rate of paracetamol dissolution from N3 tablet was very rapid in the first 5 minutes of the dissolution study as demonstrated in Figure 4 and the percentage of the dissolved drugs exceeded 55%, and this represented the Spring effect. After that, the increase in the percentage of drug dissolution did not proceed in the same manner due to the reach of the metastable zone which indicated the presence of the Parachute effect (48).

The variation in dissolution profile among co-crystals tablets in dissolution

study indicates, remarkably, the presence of different co-crystal types that have different particle sizes and shapes, which leads to exhibit different solubility and dissolution profiles (10).

Conclusions

The study of the compressibility and flowability demonstrated excellent improvement in flowability and mechanical properties in N1, N2, and N3 paracetamol: naproxen co-crystals in spite of the poor flowability characteristic of their two components paracetamol and naproxen. This indicates the ability of co-crystal to convert poor flowable drugs into free flowable formulas in a simple way. The direct compression method was used successfully in the manufacturing of N1, N2, and N3 co-crystals as conventional oral tablets. This success, when compared with the inability to convert paracetamol powder into paracetamol tablets by direct compression method, approved the capability of the three prepared co-crystals to enhance the tableting properties of the paracetamol and naproxen. The N3 co-crystals tablets showed a very rapid disintegration time with an accepted hardness and friability. N3 tablets demonstrated high dissolution when

compared with the Piodol[®] tablets. N1 and N2 prepared co-crystals tablets exhibited a higher percentage of dissolution than the marketed naproxen drug (Napron[®]).

To summarize, the new formulation of paracetamol and naproxen as co-crystals could be considered as a feasible alternative to the conventional paracetamol and naproxen oral tablets by virtue of their ability to improve the solubility, flowability, and dissolution of paracetamol and naproxen through their co-crystallinity effects. These co-crystals could be easily formulated into

References

1. Gupta H, Bhandari D, Sharma A. Recent Trends in Oral Drug Delivery: A Review. 2009;(1):162–73.
2. Allen L V., Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. ninth edit. Troy DB, editor. New York: Lippincott Williams and Wilkins; 2011.
3. Mahato RI, Narang AS. Pharmaceutical Dosage Forms and Drug Delivery. Third edit. New York: Taylor & Francis Group; 2017.
4. Chen H, Aburub A, Sun CC. Direct Compression Tablet Containing 99% Active Ingredient—A Tale of Spherical Crystallization. J Pharm Sci [Internet]. 2019;108(4):1396–400. Available from: <https://doi.org/10.1016/j.xphs.2018.11.015>
5. Keshavarz L, Pishnamazi M, Rao Khandavilli UB, Shirazian S, Collins MN, Walker GM, et al. Tailoring crystal size distributions for product performance, compaction of paracetamol. Arab J Chem [Internet]. 2021;14(4):103089. Available from: <https://doi.org/10.1016/j.arabjc.2021.103089>

tablets dosage form by direct compression method.

Acknowledgment

The researchers would like to thanks Pharmacy College/University of Mosul for providing the required facilities. The researchers also would like to express their thanks to Pioneer Drug Company in Al-Sulaymaniyah city/Iraq for providing pure active ingredients.

6. Rose AA, Kaialy W. Improved tableting behavior of paracetamol in the presence of polyvinylpyrrolidone additive: Effect of mixing conditions. Particology [Internet]. 2019;43:9–18. Available from: <https://doi.org/10.1016/j.partic.2018.01.010>
7. Yeh KL, Lee T. Selective formation of form II paracetamol through the assistance of paracetamol co-crystals as templates in a solution. CrystEngComm [Internet]. 2021 Jun 9 [cited 2021 Jun 11];23(22):3940–5. Available from: <https://pubs.rsc.org/en/content/article/html/2021/ce/d1ce00034a>
8. Patil S, Pandit A, Godbole A, Dandekar P, Jain R. Chitosan based co-processed excipient for improved tableting. Carbohydr Polym Technol Appl [Internet]. 2021;2(March):100071. Available from: <https://doi.org/10.1016/j.carpta.2021.100071>
9. Akin-Ajani OD, Odeku OA, Olumakinde-Oni O. Evaluation of the mechanical and release properties of lactose and microcrystalline cellulose and their binary mixtures as directly compressible excipients in paracetamol tablets. J Excipients

- Food Chem. 2020;11(2):42–52.
10. Sumera L, Nasir A, Amjad H, Sohail AM, Irfan BN, Hafsa A, et al. Development of Paracetamol-Caffeine co-crystals to improve compressional, formulation and in-vivo performance. *Drug Dev Ind Pharm* [Internet]. 2018;0(0):000. Available from: <http://dx.doi.org/10.1080/03639045.2018.1435687>
 11. Rajurkar VG, Gite RD, Ghawate VB. Development of Naproxen Co Crystal Formation: An Efficient Approach to Enhance Aqueous Solubility. *Anal Chem Lett*. 2015;5(4):229–38.
 12. Al-Dulaimi AF, Al-kotaji M, Abachi FT. Co-Crystals For Improving Solubility And Bioavailability Of Pharmaceutical Products. *Egypt J Chem* [Internet]. 2021 Jul 5 [cited 2021 Aug 10];0:0–0. Available from: https://ejchem.journals.ekb.eg/article_181944.html
 13. Khan FM, Ahmad M, Batool F. Enhancement of solubility and release profile of simvastatin by co-crystallization with citric acid. *Trop J Pharm Res*. 2019;18(12):2465–72.
 14. United States Pharmacopoeia (USP) 33, NF 28. USA: The United States Pharmacopoeial Convention Inc.; 2010.
 15. Tzankov S, Tzankov B. Process optimization of preparation of pentoxifylline - extended release tablets. *Pharmacia*. 2019;66(2):45–8.
 16. Panzade P, Shendarkar G, Shaikh S, Rathi PB. Pharmaceutical Cocrystal of Piroxicam: Design, formulation and evaluation. *Adv Pharm Bull*. 2017;7(3):399–408.
 17. Shakir R. Formulation and evaluation of orally disintegrating tablets of cinnarizine by direct compression and lupholization methods. Mosul; 2018.
 18. Narang AS, Breckenridge L, Guo H, Wang J, Wolf A (Avi), Desai D, et al. Assessment of Tablet Surface Hardness by Laser Ablation and Its Correlation With the Erosion Tendency of Core Tablets. *J Pharm Sci* [Internet]. 2017;106(1):200–7. Available from: <http://dx.doi.org/10.1016/j.xphs.2016.08.008>
 19. Budiman A, Husni P, Alfauziah TQ. The development of Glibenclamide-Saccharin cocrystal tablet formulations to increase the dissolution rate of the drug. *Int J Appl Pharm*. 2019;11(4).
 20. Chandrasekaran AR. Tablet Assessments Tests in Pharmaceutical Industry. *Anal Chem*. 2011;10(9):581–9.
 21. Alsaifi A, Alyahawi A. Quality assessment of different brands of paracetamol tablets in Yemeni market. *Univers J Pharm Res*. 2018;3(4):39–43.
 22. European Pharmacopoeia. 9th editio. Starsbourg: Council of Europe; 2017.
 23. British Pharmacopoeia. London; 2016.
 24. Chaturvedi H, Garg A, Rathore US. Post-compression evaluation parameters for tablets-an overview. *Eur J Pharm Med Res* [Internet]. 2017;4(11):526–30. Available from: https://www.google.com.np/search?q=pre+and+post+compression+parameters+of+tablet&hl=en&source=lnms&sa=X&ved=0ahUKEwi8_ojZ5ZThAhUKpo8KHZemAosQ_AUICSgA&biw=1396&bih=686&dpr=1.38#
 25. Medina JR, García CA, Hurtado M, Domínguez-Ramírez AM. Simultaneous determination of naproxen sodium and acetaminophen in fixed-dose combination formulations by first-order derivative

- spectroscopy: Application to dissolution studies. *Int J Pharm Pharm Sci.* 2015;7(5):183–8.
26. U.S. Pharmacopeia National Formulary. USP 41 NF. Twinbrook Parkway, Rockville, MD:USA: The United States Pharmacopeial Convention; 2018.
 27. Abebe K, Beressa TB, Yimer BT. In-vitro evaluations of quality control parameters of paracetamol tablets marketed in Gondar City, Northwest Ethiopia. *Drug Healthc Patient Saf.* 2020;12:273–9.
 28. Sheth TS, Acharya F. Optimizing similarity factor of in vitro drug release profile for development of early stage formulation of drug using linear regression model. *J Math Ind [Internet].* 2021;11(1). Available from: <http://dx.doi.org/10.1186/s13362-021-00104-9>
 29. Singh I, Kumar P. Preformulation studies for direct compression suitability of cefuroxime axetil and paracetamol: A graphical representation using SeDeM diagram. *Acta Pol Pharm - Drug Res.* 2012;69(1):87–93.
 30. Šimek M, Grünwaldová V, Kratochvíl B. Comparison of compression and material properties of differently shaped and sized paracetamols. *KONA Powder Part J.* 2017;2017(34):197–206.
 31. Chatteraj S, Sun CC. Crystal and Particle Engineering Strategies for Improving Powder Compression and Flow Properties to Enable Continuous Tablet Manufacturing by Direct Compression. *J Pharm Sci [Internet].* 2018;1–7. Available from: <https://doi.org/10.1016/j.xphs.2017.11.023>
 32. Chen H, Guo Y, Wang C, Dun J, Sun CC. Spherical Cocrystallization □ An Enabling Technology for the Development of High Dose Direct Compression Tablets of Poorly Soluble Drugs. *Cryst Growth Des.* 2019;19:2503–10.
 33. Serrano DR, O'Connell P, Paluch KJ, Walsh D, Healy AM. Cocrystal habit engineering to improve drug dissolution and alter derived powder properties. *J Pharm Pharmacol.* 2016;68(5):665–77.
 34. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment - A review. *Int J Pharm [Internet].* 2014;473(1–2):64–72. Available from: <http://dx.doi.org/10.1016/j.ijpharm.2014.06.055>
 35. Delaney SP, Nethercott MJ, Mays CJ, Winquist NT, Arthur D, Calahan JL, et al. Characterization of Synthesized and Commercial Forms of Magnesium Stearate Using Differential Scanning Calorimetry, Thermogravimetric Analysis, Powder X-Ray Diffraction, and Solid-State NMR Spectroscopy. *J Pharm Sci [Internet].* 2017;106(1):338–47. Available from: <http://dx.doi.org/10.1016/j.xphs.2016.10.004>
 36. Kadis J. Types of Tablet Presses - Federal Equipment Company Blog [Internet]. Federal Equipment Company. 2017 [cited 2021 Jul 4]. Available from: <https://fedequipblog.fedequip.com/types-tablet-presses/>
 37. Siegmann E, Forger T, Toson P, Martinetz MC, Kureck H, Brinz T, et al. Powder flow and mixing in different tablet press feed frames. *Adv Powder Technol [Internet].*

- 2020;31(2):770–81. Available from: <https://doi.org/10.1016/j.apt.2019.11.031>
38. Goh HP, Heng PWS, Liew CV. Understanding die fill variation during mini-tablet production. *Int J Pharm* [Internet]. 2017;534(1–2):279–86. Available from: <http://dx.doi.org/10.1016/j.ijpharm.2017.10.042>
39. Noor S, Salam FBA, Hima HN, Bhuiyan MSI, Chowdhury S. Comparative in-vitro quality evaluation of some brands of metronidazole tablet available in Bangladesh. *Int J Appl Res*. 2017;3(7):753–8.
40. Manley L, Hilden J, Valero P, Kramer T. Tablet Compression Force as a Process Analytical Technology (PAT): 100% Inspection and Control of Tablet Weight Uniformity. *J Pharm Sci* [Internet]. 2019;108(1):485–93. Available from: <https://doi.org/10.1016/j.xphs.2018.07.004>
41. ADELEYE O. Relationship between compression pressure, mechanical strength and release properties of tablets. *Polym Med*. 2019;49(1):27–33.
42. Sun CC, Hou H. Improving Mechanical Properties of Caffeine and Methyl Gallate Crystals by Cocrystallization. *Cryst Growth Des*. 2008;8(5):1575–1579.
43. Markl D, Zeitler & JA, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. *Pharm Res*. 2017;34:890–917.
44. Perumalla SR, Paul S, Sun CC. Enabling the Tablet Product Development of 5-Fluorocytosine by Conjugate Acid Base Cocrystals. *J Pharm Sci* [Internet]. 2016;105(6):1960–6. Available from: <http://dx.doi.org/10.1016/j.xphs.2016.04.006>
45. Zaky MF, Essa EA, Bosela AA, Maghraby GM El. Co-crystallization for enhanced dissolution rate of flutamide. *Eur J Biomed Pharm Sci*. 2018;5(11):12–20.
46. Abbas N, Latif S, Afzal H, Arshad MS, Hussain A, Sadeeqa S, et al. Simultaneously Improving Mechanical, Formulation, and In Vivo Performance of Naproxen by Co-Crystallization. *AAPS PharmSciTech*. 2018;19(7):3249–57.
47. Loiosio-Konstantinidis I, Cristofaletti R, Fotaki N, Turner DB, Dressman J. Establishing virtual bioequivalence and clinically relevant specifications using in vitro biorelevant dissolution testing and physiologically-based population pharmacokinetic modeling. case example: Naproxen. *Eur J Pharm Sci* [Internet]. 2020;143:105170. Available from: <https://doi.org/10.1016/j.ejps.2019.10.5170>
48. Thakuria R, Sarma B. Drug-drug and drug-nutraceutical cocrystal/salt as alternative medicine for combination therapy: A crystal engineering approach. *Crystals*. 2018;8(2).