Formulations Based on Amorphous Solid Disp

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A Comparative Assessment of Capsule Formulations Based on Amorphous Solid Dispersion and Salt Formation of Indomethacin

Khatab Duraid Razooqi [*], Ghaidaa S. Hameed[*], Ali R.M. Albakaa[**], Omar Sarheed[***]
Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
****Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.***
*****School of Pharmacy and biomedical sciences, University of central Lancashire, Preston, United Kingdom***

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Corresponding Author email:
Khattab_duraid@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0009-0002-4863-753X

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Abstract:

Background: Indomethacin (IND) is a nonsteroidal anti-inflammatory drug (NSAID) that belongs to the BCS class II and exhibits poor dissolution in the GIT fluids. Solid dispersion (SD) and salt formation (SF) are two acceptable and widely used approaches for dissolution enhancement.

Objective: The aim of the present study is to formulate and *in vitro* evaluate capsules from IND-Soluplus® SD and IND sodium SF, and compare the dissolution profile of the formulated capsules with pure IND.

Methods: Both IND SD and SF were prepared by the solvent evaporation method and characterized for their production yield, drug content, *in vitro* release, solid state characterization, and stability studies. Capsules were prepared by manual filling into hard gelatin capsules with IND SD and IND SF used as a source for the active ingredient, lactose or mannitol as diluent, and three types of super disintegrants: croscarmellose sodium, crospovidone, and sodium starch glycolate. The prepared capsules were tested for flow properties, weight variation, content uniformity, disintegration time, and *in vitro* dissolution test.

Results: The solvent evaporation method successfully produced IND SD and SF with high production yield and drug content, which were above 95%. Solid state characterization revealed complete amorphization of IND in the SD without any incompatibility, while it was in its crystalline state in SF. Both IND SD and SF were stable during the storage period with minor changes in drug content and drug release. The results showed proper flow properties with acceptable results for the weight variation test (all around 500 mg since it is a size 0 capsule), capsule content uniformity (98-99 %), and disintegration time (4-9 min). The disintegration of hard gelatin capsules is impacted by the type of disintegrant used, with superior performance of crospovidone (4 min) and croscarmellose sodium (5.3 min) compared to sodium starch glycolate (7.1-7.4 min). IND solid dispersion showed an enhanced dissolution (100% within 45 min) compared to the pure IND capsules (less than 50% within 45 min) and IND SF (100% within 45 min). Also, the dissolution of IND SD capsules containing crospovidone was superior to those containing croscarmellose sodium and sodium starch glycolate.

Conclusions: Indomethacin SD proved its efficacy in enhancing the dissolution of IND compared to pure IND capsules and IND SF.

Keywords: Indomethacin, solid dispersion, Indomethacin sodium, hard gelatin capsules, flowability.

تقييم مقارن للكبسولات المحضرة باستخدام طريقتي التشتت الصلب غير المتبلور وتكوين ملح للإندوميتاسين

خطاب دريد رزوقي *، غيداء سليمان حميد*، علي رسول البكاء، عمر سرهيد*****
**فرع الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.*
*** فرع الكيمياء الصيدلانية، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.*
****كلية الصيدلة والعلوم الطبية الحيوية، جامعة سنترال لانكشاير، بريستون، المملكة المتحدة*

الخلاصة:

الخلفية: الإندوميتاسين (IND) دواء مضاد للالتهاب غير ستيرويدي (NSAID) ينتمي إلى الفئة الثانية من نظامBCS ، ويتميز بضعف ذوبانه في سوائل الجهاز الهضمي. يُعدّ التشتت الصلب (SD) وتكوين الأملاح (SF) طريقتين مقبولتين وواسعتي الاستخدام لتعزيز الذوبان.

الهدف: تهدف هذه الدراسة إلى صياغة وتقييم كبسولات من IND-Soluplus® SD و IND sodium SFفي المختبر، ومقارنة خصائص ذوبان الكبسولات المُصاغة مع IND النقي.

الطرق: تم تحضير كلٍّ من IND SD و SFبطريقة تبخير المذيبات، وتمّ وصفهما من حيث إنتاجهما، ومحتواهما الدوائي، وإطلاقهما في المختبر، وتوصيف الحالة الصلبة، ودراسات استقرارهما. تم تحضير الكبسولات يدويًا في كبسولات جيلاتينية صلبة، باستخدام IND SD و IND SFكمصدر للمكون النشط، واللاكتوز أو المانيتول كمخفف، وثلاثة أنواع من المواد المفككة الفائقة: كروسكارميلوز الصوديوم، وكروسبوفيدون، وجليكولات نشا الصوديوم. تم اختبار الكبسولات المحضرة من حيث خصائص التدفق، وتباين الوزن، وتجانس المحتوى، وزمن التفكك، واختبار الذوبان في المختبر.

النتائج: نجحت طريقة تبخير المذيبات في إنتاج IND SD وSF بعائد إنتاج مرتفع ومحتوى دوائي مرتفع، تجاوز 95%. كشف توصيف الحالة الصلبة عن تحول تام لـ IND في SD دون أي تعارض، وهو في حالته البلورية في SF. كان كل من IND SD وSF مستقرًا خلال فترة التخزين مع تغيرات طفيفة في محتوى الدواء وانطلاقه. أظهرت النتائج خصائص تدفق مناسبة مع نتائج مقبولة لاختبار اختلاف الوزن (حوالي 500 ملغ نظرًا لكونها كبسولة مقاس 0)، وتجانس محتوى الكبسولة (98-99%)، وزمن التفكك (4-9 دقائق). يتأثر تفكك كبسولات الجيلاتين الصلبة بنوع المادة المفككة المستخدمة، حيث تفوق أداء كروسبوفيدون (4 دقائق) وكروسكارميلوز الصوديوم (5.3 دقائق) مقارنةً بجليكولات نشا الصوديوم (7.1-7.4 دقائق). أظهر تشتت IND الصلب ذوبانًا مُحسَّنًا (100% خلال 45 دقيقة) مقارنةً بكبسولات IND النقية (أقل من 50% خلال 45 دقيقة) و100% IND SF خلال 45 دقيقة).

الاستنتاجات: أثبت إندوميثاسين SD فعاليته في تعزيز إذابة IND مقارنة بكبسولات IND النقية وIND SF.

الكلمات المفتاحية: الإندوميتاسين، المشتت الصلب، إندوميتاسين الصوديوم، كبسولات جيلاتينية صلبة، قابلية التدفق.

Introduction

One of the oldest medicinal dosage forms is empty capsules (hard-shell capsules), used since Ancient Egypt (1). Because they disguise drug taste and odor, hard-shell capsules are utilized for pharmaceuticals, vitamins, minerals, and nutraceuticals (2). The rigid capsule shell shields the medicine from light, oxygen, contamination, and microbial development (2). Gelatine capsules are the most popular empty capsules which are named for their 30%-45% gelatine content (3).

Indomethacin (IND) is a nonsteroidal anti-inflammatory drug (NSAID) widely used in the pharmaceutical sector for its analgesic, anti-inflammatory, and antipyretic effects (4). The chemical structure of IND is given in Figure 1. IND is considered a weak acidic drug with pKa 3-4.5. Upon oral administration, IND exhibits poor dissolution in the GIT fluids, resulting in limited bioavailability. It belongs to the BCS class II (5).

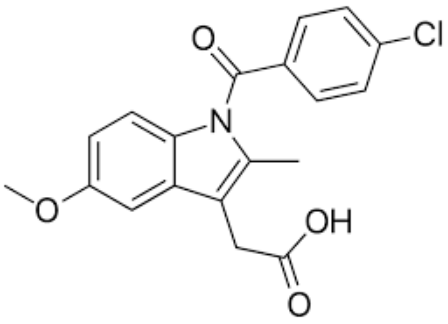

Figure 1: The chemical structure of Indomethacin

In new chemical entity screening and formulation creation, poorly soluble medications are often difficult to solubilize (6). Several ways to increase the solubilization and bioavailability of weakly water-soluble medicines (7). Solid dispersion (SD) is one of the best ways to increase weakly water-soluble medicines' solubility, dissolution, and bioavailability (8, 9). The underlying mechanism behind dissolution enhancement as a result of SD formulations involves several critical components, including the enhancement of wettability, the reduction of particle size, the prevention of aggregation, and the transformation of the drug from a crystalline to an amorphous phase (10-12) On the other hand, salt formation is considered as an effective chemical approach for increasing solubility and dissolution rates of acidic and basic drugs(13). These effects are related to the enhancement of wettability and aqueous solubility(14).

Several approaches have been tried to improve the dissolution of indomethacin (IND) such as solid dispersion techniques utilizing hydrophilic carriers (15) , an inclusion complex with hydroxypropyl-β-cyclodextrin (16) ,co-crystallization(17) and a co-amorphous system (18).

This research aims to prepare and *in vitro* evaluate capsules from IND-Soluplus® SD and IND sodium salt. Furthermore, comparing the dissolution profile of the formulated capsules with pure Indomethacin.

Materials and methods

Materials

Indomethacin was bought from Macklin Pharmaceutical, croscarmellose sodium (CCS), crospovidone (CP), sodium starch glycolate (SSG), and Mannitol were kindly gifted by the pioneer drug industry, Lactose (Alpha Chemika, India), Hydrochloric acid (HCl) (Thomas Baker (Chemicals) Pvt. Ltd, India).

2.Methods

2.1. Preparation of IND- Soluplus® solid dispersion

The solvent evaporation method was employed to produce IND- Soluplus® SD. In a porcelain dish, 25 mg of IND and 50 mg of Soluplus® were weighed and ethanol was utilized as the solvent to dissolve the mixed components producing a solution. The solution was subjected to a process of removal under reduced pressure for 90 minutes at a temperature of 55°C, employing a rotary vacuum evaporator as the extraction apparatus. The resulting solid dispersion was crushed in a mortar sieved and dried in an oven for 2 hours. Thereafter, it was stored in a desiccator with silica gel to reduce moisture for the purpose of further characterization(19).

2.2. Preparation of IND sodium salt

The IND sodium salt was prepared by solvent evaporation using an equimolar ratio of IND with NaOH (400 mg of IND and 44 mg of NaOH). The powder mixture was dissolved in ethanol in a round flask and attached to a rotary evaporator to remove the solvent, leaving behind the

sodium salt of IND. The salt was then thoroughly dried to remove any remaining solvent.

2.3. Determination of drug content and percentage yield (PY %) of prepared SD and SF of IND

The percentage yield for each type of SD and SF was determined by measuring the ratio of the actual weight of the obtained SD or SF to the theoretical weight of SD or SF. The theoretical weight was calculated using the following equation(20).

Yield % = (Actual weight / Theoretical weight) * 100%... eq1

The drug content of SD and SF was determined by precisely weighting IND SDs and SFs equivalent to 5 mg of IND was taken and dissolved in 10 ml phosphate buffer, appropriately diluted, and assayed for drug content using a UV spectrophotometer by determining the absorbance at the specified λmax for IND (9). The percentage of drug content in the SDs and SFs was measured by using the following equation (21).

Drug content %w/w = (Actual IND content / Theoretical IND content) * 100% .. eq2

3.4. Solid state characterization

Differential Scanning Calorimetry (DSC) analysis for IND as received, IND -Na salt, IND- Soluplus® PM, and SD. Crimp-sealed aluminum pans were utilized to contain 3 mg of samples, which had been accurately weighed prior to storage. The measurement was conducted at a rate of 10°C/min, ranging from 35°C to 280°C (22, 23).

Powder X-ray diffraction (PXRD) analysis for IND as received, IND -Na salt, IND-Soluplus® PM, and SD. Operating conditions: The apparatus requires a current of 30 mA, a voltage of 40 kV, a scanning speed of 1/min, and a range of 10–90° (2θ)(24, 25).

2.5. In-vitro dissolution studies

The *in vitro* dissolution studies were conducred for IND as received, IND -Na salt, IND- Soluplus® PM, and SD. An amount of IND equivalent to 25 mg was permitted to dissolve in 900 ml of phosphate buffer (pH 6.8) using a USP type II apparatus (paddle type). The temperature of the dissolution media was 37 ± 0.5℃, with an operating speed of 50 rpm. 5 mL of the dissolution media were withdrawn at regular time intervals and replaced by fresh media. The samples were then filtered and analyzed spectrophotometrically at 319.5 nm. The test was performed in triplicate for all samples.

2.6. Effect of temperature and humidity on the IND -Soluplus® SD and IND- Na SF

A stability experiment was conducted on the selected IND-Soluplus® SD and IND-Na SF samples. The experiment involved maintaining the samples at extreme temperatures and humidity levels for a period of three months. A series of studies were conducted on the stability of the selected IND-Soluplus® SD and IND-Na SF. These studies were conducted within an incubator and desiccator, with the temperature maintained at 40°C and the relative humidity set to 75% (26). The relative humidity level of 75% was attained by employing a desiccator that contained saturated sodium chloride (27). The samples were periodically evaluated for saturated solubility and in vitro dissolution (28).

2.7. Capsule formulation

Capsule formulations from F1-F5 contained IND SD as an active principle while Capsules from F6-F10 contained IND SF as an active principle. Accordingly, a weighted quantity equivalent to 25 mg of IND was taken from the solid dispersion and sodium salt to prepare the capsules. The active ingredients were mixed with super disintegrants (croscarmellose sodium (CCS), sodium starch glycolate (SSG), and

cross povidone (CP)) and diluent (either lactose or mannitol)The resultant powder was manually filled into the hard gelatin capsules with size 0 using an analytical balance (29). Each capsule's formulation components are shown in Table 1.

Table 1: Composition of the prepared capsules

Ingredients (mg)	Formula No.										
	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pure IND	25										
IND Soluplus® SD	-	Equivalent to 25 mg of IND					-	-	-	-	-
IND -Na salt	-	-	-	-	-	-	Equivalent to 25 mg of IND				
SSG	-	-	-	20		-	-	-	20	-	-
CCS	-	-	-	-	20	-	-	-	-	20	-
CP	20	-	-	-	-	20	-	-	-	-	20
Lactose	Q.S.500	Q.S.500	-	Q.S.500	Q.S.500	Q.S.500		Q.S.500	Q.S.500	Q.S.500	Q.S.500
Mannitol	-	-	Q.S.500	-	-	-	Q.S.500	-	-	-	-
Totat weight (mg)	500	500	500	500	500	500	500	500	500	500	500

2.8. Evaluation of the physical properties of the capsule

2.8.1. Capsule pre-formulation tests

In accordance with the European Pharmacopoeia, the angle of repose for the pre-filling powder was determined to assess the type of flow. The fixed funnel method pours powder of each formula onto a bottom plate using a fixed-height funnel. The following equation calculates the angle of repose for each formula (30):

$$\mathbf{Tan\emptyset = h/r} \ldots\ldots \mathbf{eq\ 3}$$

The height of the con is h, the plate radius is r, and the angle of repose tan is Tan Ø. Table 2 shows powder flow versus angle of repose.

On the other hand, the **compressibility Index (Carr's index) and Hausner's ratio were determined by filling** a 10-milliliter graduated cylinder with an initial bulk volume (V0) of each formula powder and tapped using a conventional procedure until Vt was attained. Calculating Hausner's ratio and compressibility index with equations 4 and 5 (31). Interpretation of the obtained values was according to Table 2.

$$\mathbf{Hausner's\ ratio} = V_o / V_t \ldots\ldots \mathbf{eq\ 4}$$

$$\mathbf{Compressibility\ Index} = (V_0 - V_t)/V_0 \times 100 \ldots\ldots \mathbf{eq\ 5}$$

Table (2) The relationship between Angle of Repose, Carr's index, and Hausner ratio with the flow type (31).

Angle of repose	Carr's index	Hausner 's ratio	Powder flow
< 25	5–10	1.05–1.11	Excellent
25-30	11–15	1.12–1.18	Very good
31-35	16–20	1.19–1.25	Good
36-40	21–25	1.27–1.33	Fair
41-45	26–31	1.35–1.45	Passable
46-55	32–37	1.47–1.59	Poor
> 56	38–45	1.16–1.82	Very poor

2.8.2. Capsule post-formulation tests

1. Weight Variation

Twenty capsules were chosen. Each capsule was weighed on an analytical balance, carefully emptied, and the shells reweighed. The weight of the content was obtained by subtracting the total capsule weight from the weight of the shell. The test is passed if not more than 2 capsules of the individual masses deviate from the average mass by more than 7.5 % and none deviates by more than 15% (32).

2. Capsule content uniformity

The drug content was determined individually for ten capsules. The IND content was moved into a 100-milliliter volumetric flask containing 10 mL of ethanol and the volume was completed to 100 mL with phosphate buffer (pH 6.8). The solution was filtered, diluted, and measured using spectrophotometry at 319.5 nm employing the same solvent as the blank and using the standard calibration curve equation ($y=0.0179x-0.0178$, $R^2=0.9983$). According to the British Pharmacopeia, capsules will pass the test if not more than one capsule's content is outside 85 to 115 % of the average value and none is outside the limits of 75 to 125 % (32).

3. Disintegration test

Using a disintegration tester manufactured by ERWEKA in the United States, six capsules were disintegrated in 900 mL of 0.1 N hydrochloric acid with a pH of 1.2. The disintegration process was carried out in a cylindrical container at a temperature of 37 ± 0.5 °C. It should be half full of fluid in the jar. Place six capsules in the tubes of the basket rack in a random order. The machine should be started with a plastic disc placed on each capsule. Discs should gently rub capsules. It was determined that disintegration had taken place when the monitor did not reveal any capsule fragments or soft residue. From the results of three different formula tests (n=3), the average disintegration time was calculated (33, 34).

4. *In-vitro* dissolution study for all formulas of IND capsules

The USP dissolution apparatus II (Paddle type) was used for all dissolution studies at 37 ± 0.5 °C. The prepared capsule formulas were agitated at 50 rpm in 900 ml of phosphate buffer (pH 6.8). Samples of 5 ml were withdrawn after 15, 30, 45, 60, and 120 min and replaced with a warmed (37 °C) medium to maintain volume. Samples were filtered using a 0.45 mm filter syringe and analyzed at 319.5 nm with a UV-Vis spectrophotometer (35).

Statistical analysis

Statistical analysis was performed using Graph Pad Prism version 9. Results were expressed as mean ± SD for all data. Analytical statistics were thus implemented to probe the significance of relationships between the groups through an analysis of variance (ANOVA) test and a post hoc Tukey's multiple-comparisons test. Statistical significance corresponds to having the value of $P < 0.05$.

Results

The percentage yield and drug content for the prepared IND-Soluplus® SD and IND-Na salt formulas are illustrated in Table 3 below

Table 3: The percentage yield and drug content for the prepared IND-Soluplus® SD and IND-Na salt formulas

Formula code	Percentage yield (PY %)	Drug content (%)
IND-Soluplus® SD	99.1±0.01	98.5±0.05
IND- Na SF	98.78±0.16	99.15±0.03
Data are presented as mean ± standard deviation, n=3		

DSC analysis showed that IND as received has a single sharp endothermic peak at 167.74 °C representing its melting point. While both IND-Soluplus® PM and SD did not show the endotherm for melting of IND (Figure 2). However, the sodium salt of IND kept its crystallinity with sharp melting points at 156.52°C. On the other hand, PXRD analysis showed that the diffractogram of IND (Figure 3) has many peaks at 2θ angles in the Braggs peaks. Binary mixtures of IND with Soluplus® show Braggs' peaks with small intensity changes while IND-Soluplus® SD showed amorphous halo peaks and no sharp peaks. The PXRD pattern of IND-Na salt revealed the diffraction peaks of IND were still, but their position was shifted.

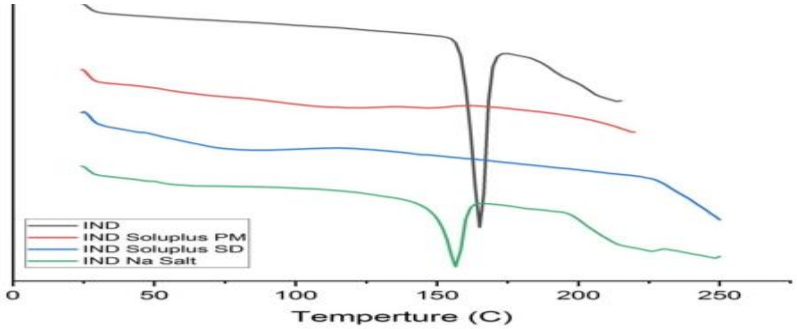

Figure 2: DSC analysis of IND as received, IND-Na salt, and IND-Soluplus® PM and SD

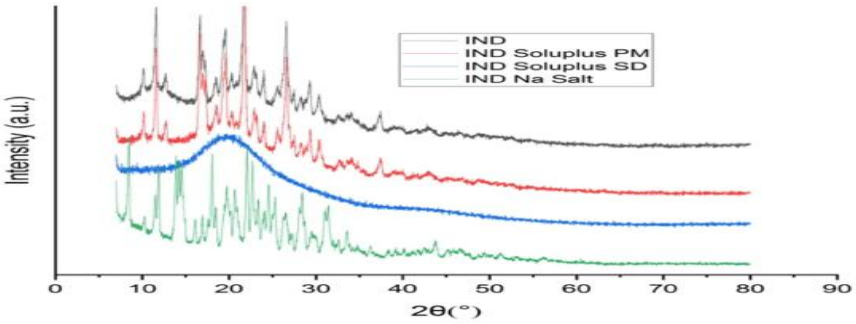

Figure 3: PXRD analysis of IND as received, IND-Na salt, and IND-Soluplus® PM and SD

The in vitro release of IND as received, IND-Na salt and IND-Soluplus® PM, and SD is illustrated in Figure 4 below. IND-Soluplus® SD showed significantly higher (P <0.05) Q0.5h and Q_{2h} over IND as received, IND-Soluplus® PM and IND-Na salt. Additionally, IND-Na salt showed significantly higher (P <0.05) Q0.5h and Q2h values over IND as received and IND-Soluplus® PM.

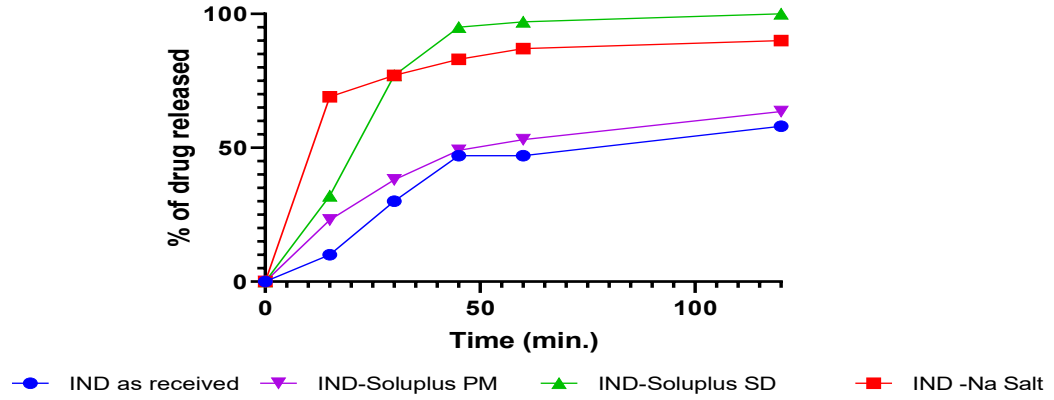

Figure 4: The *in vitro* release of IND as received, IND-Na salt, and IND-Soluplus® PM and SD in phosphate buffer (pH 6.8) at 37 ± 0.5 °C (mean ± SD; n = 3).

Regarding the stability analysis of **IND-Na salt, and IND-Soluplus®SD, the** *in vitro* drug release and drug content for IND Soluplus® SD and IND-Na SF at 0, 30, 60, and 90 days of storage at 40±2°C and 75±5% RH, as illustrated in Table 4 below. According to the results obtained, it can be concluded that both formulas are stable and hold their original properties with minor variations.

Table 4: Stability studies IND -Soluplus® SD and IND- Na SF at 40±2°C/75±5% RH

Formula code	Re-test time (days)	% Drug content	*In vitro* drug release (%) after 2 hours
IND-Soluplus® SD	0	98.5±0.05	100±0.1
	30	98.12 ±0.7	99.8±0.14
	60	97.15±0.19	99.1±0.17
	90	96.03±0.12	97.12±0.14
IND- Na SF	0	99.15±0.03	86.16±0.06
	30	98.03±0.12	85.11±0.02
	60	97.01±0.19	84.02±0.76
	90	96.06±0.54	83.08±0.12

One important consideration in the formulation of tablets and capsules is the flow properties of the drug powders and granules. The measured flowability indicators for the pre-filling powder for F1-F10 are reported in Table 5. It could be seen that the angle of repose for the pre-filling powder was between 29±1.15 and 33±1.65, indicating good flow behavior. Similarly, the compressibility (Carr's) index values were between 1.132±0.14 to1.163±0.17, and for the Hausner ratio the values were between 12.23%±1.1 to 13.6%±1.18 which further confirms good flow properties.

Table 5: Flow properties of the pre-compression powder for formulas F1-F10

F-code	Angle of repose	Hausner 's index	Carr's ratio
F1	29.2±1.2	1.132±0.14	13%±0.16
F2	31±1.5	1.156±0.13	12.7%±1
F3	32±1.1	1.149±0.01	12.23%±1.1
F4	31±1.34	1.137±0.14	13.3%±1.2
F5	30±1.47	1.163±0.17	13.6%±1.18
F6	31±1.23	1.145±0.16	12.7%±0.09
F7	29±1.15	1.143±0.15	13.14%±0.18
F8	30.6±2.01	1.152±0.12	12.4%±0.45
F9	32±1.91	1.134±0.03	13.1%±0.19
F10	33±1.65	1.157±0.08	13.58%±0.06

The capsules' weight, content, disintegration time, and dissolution test were used to evaluate their quality. Table 3 shows the result of the weight variation test for the prepared formulas. No capsule from F1-F10 deviated from the average weights, and all formulas passed the test. Also, the results of the content uniformity test of the prepared capsules were between 95.18 ± 1.04 and 100.42 ± 1.24. Since the results of the weight variation test and the content uniformity test for all the prepared capsule formulas are by the Pharmacopoeia standards, these tests are passed, and the next stage of the study is to perform capsule disintegration and dissolution tests.

Time of disintegration is a key capsule quality parameter. Once the capsule breaks, the medication is released. All prepared capsule formulas from F1–F10 disintegrated in less than 10 minutes as indicated by Table 5. The prepared capsules' disintegration time was longer in capsule formulas that did not contain disintegrants (F1, F2, F6, and F7). Formulas containing SSG as super disintegrant showed significantly longer disintegration time than those containing CP and CCS because the super disintegrants can absorb moisture quickly sweal and disintegrate so enhance the dissolution process (31). It was also found that there was an insignificant difference in disintegration time between formulas containing CP and CCS.

Table 5: Physical characterization of the prepared capsules

F-code	Uniformity of weight		Content uniformity (%)	Disintegration time (min.)
	no. of capsule deviating by ±7.5 %	no. of capsule deviating by ±15 %		
F1	Nil	Nil	99.17 ± 0.18	9.03± 0.13
F2	Nil	Nil	98.15 ± 1.73	9.15± 0.11
F3	Nil	Nil	98.56 ± 1.45	7.43± 0.13
F4	Nil	Nil	97.15 ± 0.16	5.27± 0.31
F5	Nil	Nil	95.18 ± 1.04	4.30± 0.11
F6	Nil	Nil	100.42 ± 1.24	9.16± 0.01
F7	Nil	Nil	98.47 ± 1.55	9.20± 0.18
F8	Nil	Nil	101.42 ± 1.54	7.16± 0.13
F9	Nil	Nil	97.16 ± 1.23	5.36± 0.10
F10	Nil	Nil	98.15 ± 1.15	4.24 ± 0.12

The dissolution test is a key capsule quality test as it measures the time it takes a dosage form to release a defined amount of medication into a solution. The dissolution of the IND capsules (SD and salt form) was impacted by the type of super disintegrates used, with CP showing the superior effect **Figure 5. A and B** and this is consistent with the findings of Karim S.et al who used super disintegrants with clonazepam to improve the dissolution of the slightly soluble drug (31). Both IND SD and salt form showed enhanced dissolution over pure IND when the capsule's dissolution was compared. However, the salt form showed a low dissolution of IND compared to the SD since the physical form of IND in its salt **Figure 5. C.**

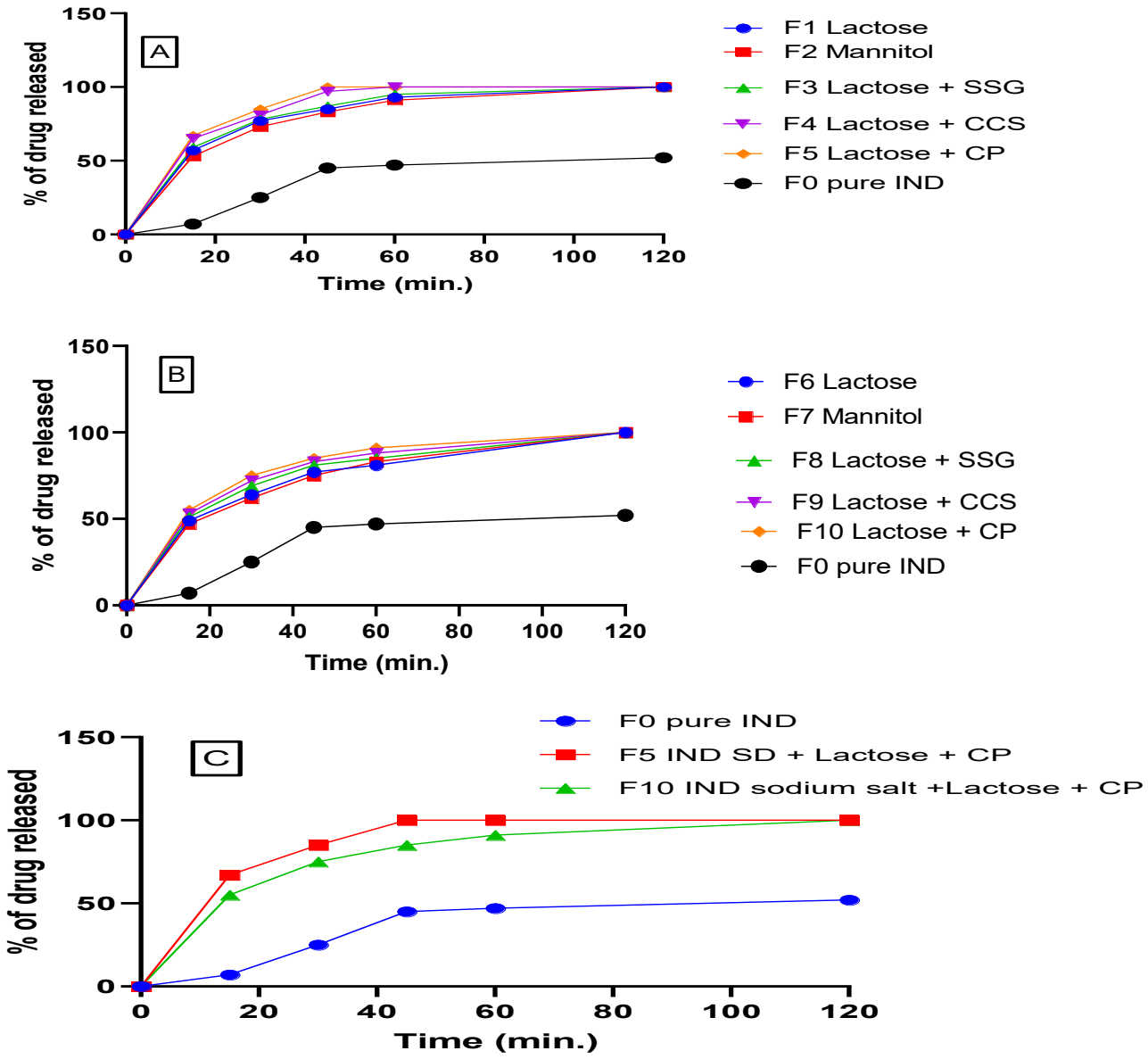

Figure 5: In *vitro* dissolution of IND capsules formulas. (A) In *vitro* release of IND capsules based on its SD form compared to its pure form (B) In *vitro* release of IND capsules based on its sodium salt compared to its pure form (C) Comparative *in vitro* dissolution of IND capsules based on its SD, sodium salt and its pure form. Dissolution was carried out in 900 mL of phosphate buffer (pH 6.8) at 37 ± 0.5 °C (mean ± SD; n = 3).

Discussion

The results of the. production yield and the content uniformity tests indicates that the solvent evaporation method was successful in producing **IND -Soluplus® SD and IND- Na SF** with a high drug content and percentage yield.

Furthermore ,the results of the DSC analysis revealed that the obtained Tm value is close to that reported in the literature for the most thermodynamically stable crystalline form of IND (163°C)(36). Additionally, the physical mixture of IND with Soluplus® did not show the endotherm for melting of IND indicating that IND crystals dissolved in polymer during thermal analysis. The IND melting endotherm is absent in IND-Soluplus® SD thermograms (Figure 2) as Soluplus® disseminated IND without crystallinity (37). However, the sodium salt of IND kept its crystallinity with sharp melting points at 156.52°C. The difference in melting point between IND and its salt form is related to a different molecular arrangement and cohesive forces among salt molecules than IND powder molecules(14). On the other hand, PXRD analysis showed that the diffractogram of IND (Figure 3) confirmed its crystalline form, with many peaks at 2θ angles in the Braggs peaks, as previously described (38). Binary mixes of IND with Soluplus® show Braggs' peaks with small intensity changes, indicating crystalline composition. Excipients may dilute PM drug peaks, changing intensity (39).However , the binary SD of IND with Soluplus® showed amorphous halo peaks and no sharp peaks, demonstrating a thorough transition from crystalline to amorphous SD. In case of IND sodium salt form, the crystalline states of IND were maintained as the diffraction peaks of IND were still, but their position was shifted in both salts. The shifting in the position of the peaks indicates different arrangements of the salt's crystalline state than the pure IND. Similar outcomes were documented by another research on mefenamic acid salt with Na in which different crystal shape was detected with the salt form as compared to the pure drug and reflected as different positions in the diffraction peaks demonstrated by the PXRD study(40). These findings are consistent with those previously mentioned DSC results.

In case of the in vitro dissolution studies, the superior release of Soluplus® based solid dispersion is attributed to particle size reduction and the consequent increase in the surface area results in improved dissolution(41). Moreover, drug solubility and wettability may be increased by surrounding hydrophilic (42). Several types of research documented the benefit of Soluplus® in enhancing the dissolution of poorly soluble drugs when used as a carrier in SD (43). Soluplus® is an innovative co-polymer that is amorphous in nature , having amphiphilic characteristics and made of of polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol (44). Through the creation of micelles and as a polymer matrix in SDs, the bifunctional property Soluplus® has the ability to increase the dissolution rate of medications that are not very soluble formation of micelles and as a polymer matrix in SDs(45). Also, several research articles proved drug amorphizations and crystallization inhibitory effect of Soluplus® , which promotes dissolution enhancement(46) . Regarding the results of the stability analysis, it can be concluded that both formulas are stable and hold their original properties with minor variations in drug content and drug release.

The preformulated powder for F1-F10 was tested for flow qualities to avoid uneven flow and flow obstruction during encapsulation. Proper flow suggests weight and content homogeneity from the outcomes. They also flow without vibration, agitation, or mechanical help during manufacturing.

The results of the content uniformity and weight variation test were acceptable according to the requirement of the

European pharmacopeia. Good flow properties resulted in acceptable content uniformity and weight variation results. Therefore, the chosen excipients and the dosages of those excipients ensured that the encapsulated combination was administered in the correct capsule dosage (47).

The European Pharmacopoeia requires non-modified capsules to disintegrate within 30 minutes, so capsules F1–F10 meet this requirement (47).The dissolution enhancement effect of IND from its solid dispersion as compared to the pure IND capsules is attributed to many factors such as amorphization, increased wettability, particle size reduction, and increased porosity accomplished by dispersing the drug within the polymeric matrix (48, 49). The amorphous form of a drug is known to promote the solubility of a drug due to the depletion of the crystal lattice barrier (50). In contrast, IND-Na salt dissolved better than pure IND capsules. Due to salt form dissolution's self-buffering. Dissolution is limited by drug distribution through the unstirred water layer on every dissolving particle in the media. The production of salt changes the pH of the proximal microenvironment in the unstirred water layer around the dissolving solid, increasing medication ionization and solubility (51). Salt formation's self-buffering properties allow faster dissolution than free acid or base and improve dissolution(52) .

However, the salt form showed a low dissolution of IND (Figure **2 C**)compared to the SD since the physical form of IND in its salt retained its crystalline state compared to the amorphous state of the SD, which lakes the crystal barrier and dissolves rapidly (51).

This superior effect of CP compared to the CCS and SSG may be due to the disintegration mechanism of CP which works through a combination of wicking and swelling processes(53). Firstly, drawing water into the tablet through capillary action caused by its porous particle shape then causes secondary swelling that leads to the breaking of inter particulate connections, leading to tablet disintegration(54).On the other hand, the disintegration mechanism of SSG, which functions by swelling when it comes into contact with aqueous medium, was associated with a much longer disintegration time and lower dissolution of capsules that included SSG. Gelling occurs concurrently with the swelling of SSG, which contributes to the prevention of further water penetration into the formulation, which in turn slows down the release of the medication(55).

Conclusion

Indomethacin solid dispersion proved its efficacy in enhancing the dissolution of IND compared to pure IND capsules and IND-sodium salt. Also, the dissolution of IND solid dispersion capsules containing crospovidone was superior to those containing croscarmellose sodium and sodium starch glycolate.

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