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# Solubility and Dissolution Rate Enhancement of Aceclofenac by Solid Dispersion Employing Kneading and Solvent Evaporation Techniques

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**Abstract**

**Background:** Aceclofenac (ACF) is a non-steroidal anti-inflammatory drug with potent anti-inflammatory and analgesic properties. ACF is belongs to BCS class II which has poor solubility in water (practically insoluble) and high permeability that leads to a low dissolution rate and reduced bioavailability.

**Objective:** to enhance the solubility and dissolution rate of ACF using the solid dispersion method (SD) by two common techniques which were solvent evaporation (SE) and kneading (Kn) by using different carriers Mannitol, PVP k30, Soluplus®, and Urea in both techniques at 1:1 and 1:5 wight ratio.

**Methods:** The effects of type of carrier and preparation method on solubility and dissolution rate of SD were studied. Solid dispersions were characterized for their, percentage yield, drug content, drug solubility and *in-vitro* dissolution rate in comparison with pure drug.

**Results:** The best formula is obtained by the Kn formula (F16) which was formulated by the use of ACF: Soluplus®: with a weight ratio of 1:5 which gave a high percentage yield (99.5%), high drug content (99.8± 0.003%) and the best solubility enhancement which was 361 folds compared to pure ACF and faster dissolution rate which was 80% in 10 minutes compared to 20% for pure drug.

**Conclusion:** the solubility and *in-vitro* dissolution rate of ACF was efficiently improved when prepared by SD techniques, utilizing both solvent evaporation and kneading methods. Furthermore, the kneading method was superior to solvent evaporation method due to the greater enhancement of solubility and dissolution rate obtained by all carriers and ratios with higher improvement by 1:5 ratio, and can be considered a successful and efficient strategy for solubility and *in-vitro* dissolution rate improvement of hydrophobic drugs.

# تحسين قابلية الذوبان و معدل التحرر للاسيكلوفيناك عن طريق المنتشر الصلب باستخدام تقنيات العجن و تبخر المذيبات

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**الخلاصة**

ألاسيكلوفيناك هو دواء مضاد للالتهابات غير الستيرويدية له تأثيرات قوية كمضاد للالتهابات ومسكن للالام. وهو ينتمي إلى فئة الثانية في نظام تصنيف المستحضرات الصيدلانية، التي تتميز بقابلية ذوبان ضعيفة في الماء (غير قابلة للذوبان عمليا) مع نفاذية عالية تؤدي إلى معدل ذوبان ضعيف وانخفاض التوافر البيولوجي.الهدف من هذه الدراسة هو تعزيز قابلية الذوبان ومعدل التحرر للاسيكلوفيناك باستخدام طريقة المنتشر الصلب من خلال تقنيتين شائعتين هما طريقة التبخر بالمذيبات وطريقة العجن باستخدام ناقلات مختلفة وهي المانيتول، بولي فينيل بايرولدين k30، الصولبلص، و اليوريا في كلا التقنيتين بنسبة الوزن 1:1 و 1:5.

تمت دراسة تأثير نوع المادة الحاملة وطريقة التحضير على ذوبان ومعدل التحرر. تم تشخيص صيغ المشتتات الصلبة من حيث نسبة إنتاجها ومحتوى الدواء وقابلية ذوبان الدواء ومعدل التحرر في المختبر مقارنة بالدواء النقي.أفضل صيغة تم الحصول عليها هي صيغة رقم 16 المحضرة بطريقة العجن، التي تم صياغتها باستخدام الاسيكلوفيناك: الصولبلص بنسبة وزن 1:5 والتي اظهرت نسبة انتاجية عالية (99.5%)، ومحتوى دوائي عالي (99.8±0.003). % وأفضل تعزيز للذوبان بلغ 361 مرة مقارنة بالاسيكلوفيناك النقي ومعدل تحرر أسرع بلغ 80% في اول 10 دقائق مقارنة بـ 20% للدواء النقي.وأخيرا، يمكن أن نستنتج أن قابلية ذوبان الاسيكلوفيناك تتحسن بكفاءة عندما يتم تحضيرها بكلا الطريقتين. علاوة على ذلك، كانت طريقة العجن متفوقةً على طريقة التبخر بالمذيبات بسبب التعزيز الأفضل الذي حصلت عليه جميع الناقلات مع النسبة المستخدمة ويمكن اعتباره تقنية ناجحة وفعالة لتحسين الذوبانية و معدل التحرر في المختبر للأدوية الكارهة للماء.

**الكلمات المفتاحية:** الاسيكلوفيناك، معدل التحرر بالمختبر، العجن، الصولبلص، المنتشر الصلب، الذوبانية.

## Introduction:

Solid Dispersion (SD) was first studied and proposed as one formulation method used to enhance the solubility and rate of dissolution of compounds with poor solubility. It offered a successful method for enhancing solubility, absorption rate, and bioavailability [(1)]. Several manufacturing techniques were utilized for the preparation of solid dispersion, and the most commonly used methods nowadays are solvent evaporation, fusion (melting), melting-solvent method, and kneading method [(2)].

The oral delivery of drugs poses a significant challenge because more than 40% of new chemical entities are practically insoluble in water. Poor aqueous solubility provides challenges, but also opportunities to scientists working in formulation development [(3)].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed class of medication, with approximately 5–10% of all prescriptions written annually. Aceclofenac (ACF) is a NSAID that was first take the approval in Europe in 1990 as a 100mg tablet to be given twice or thrice daily for inflammatory and painful cases [(4)]. ACF has a strong anti-inflammatory and analgesic action. Its stronger inhibition selectivity on COX 2 than COX 1 explains its safety in comparison to other NSAIDs and COX 2 selective inhibitors, as well as its improved stomach tolerance and fewer side effects [(5)].

ACF is weakly acidic drug with pka about 4.7 and belongs to BCS class II and it's practically insoluble in water (about 0.007 mg/mL) with high permeability and poor dissolution rate that leads to reduced oral bioavailability.

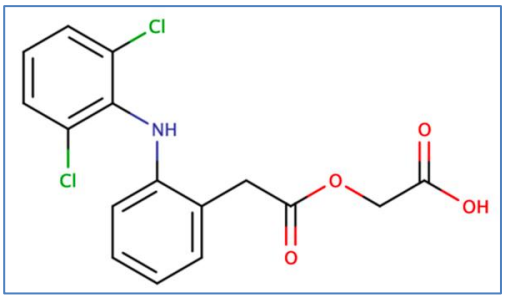


**Figure 1: ACF Chemical Structure**

The poor ACF solubility in gastric region can cause some ulcerogenic effects on gastric mucosa and prolonged onset time that may leads to less efficacy on acute conditions [(6)]. Hence, the enhancing of ACF solubility, dissolution rate, and bioavailability is extremely important for the drug efficacy and patient tolerance.

## Materials and Methods

### Materials

Aceclofenac (Baoji Guokang bio-technology Co., Ltd, China), Mannitol (Avonchem, UK), PVP K30 (Glentham life science, UK), Urea (Thomas baker Pvt. Ltd. India), Soluplus® (BASF pharma, Germany), All other reagents such as ethanol were of analytical grade.

## Methods

### Preparation of ACF-Solid Dispersion

### Preparation of ACF-SD by Solvent Evaporation Method (SE)

The weighed amount of ACF (500 mg) and carriers (Mannitol, PVP K30, Soluplus®, and Urea) in 1:1 and 1:5 drug: carrier ratio as shown in Table (1), was dissolved in a common solvent which was the ethanol. The solution of component was stirred on the hot plat stirrer at around 60 $^{o}$ C (for about 30 minutes) for evaporation of the solvent. The remaining amount was poured in a petri dish and placed in oven at 40 $^{o}$ C for 48 hrs. to completely remove the residual amount of the solvent as shown in Figure (2). The resulted product was crushed using mortar and pestle and sieved through no.60 sieve size and kept in a desiccator to be subjected to further investigations [7].

**Table 1: ACE SD Prepared by Solvent Evaporation at Different Ratios**

| Formula | Carrier | Ratio |
|---|---|---|
| **F1** | Mannitol | 1:1 |
| **F2** | PVP k30 | 1:1 |
| **F3** | Urea | 1:1 |
| **F4** | Soluplus® | 1:1 |
| **F5** | Mannitol | 1:5 |
| **F6** | PVP k30 | 1:5 |
| **F7** | Urea | 1:5 |
| **F8** | Soluplus® | 1:5 |

### Preparation of ACF-SD by Kneading Method (Kn)

Using a mortar, a mixture of the weighed amount ACF (500 mg) and carriers (Mannitol, PVP K30, Soluplus® , and Urea) in 1:1 and 1:5 drug: ratio as shown in Table (2) was wetted with mixture of ethanol and water (1:1) in dropwise and is thoroughly triturated in a pestle and mortar for a specific time (about 20 minutes). This results in the formation of a slurry and the resulted mass was dried in oven at 40 $^{o}$C for 48 hrs. as shown in Figure (2). The dried mass was crushed, pulverized, and sieved through no.60 sieve size to reduce particle size and kept in a desiccator to be subjected to further investigations [8].

**Table 2: ACF SD Prepared by Kneading Method at Different Ratios**

| Formula | Carrier | Ratio |
|---|---|---|
| **F9** | Mannitol | 1:1 |
| **F10** | PVP k30 | 1:1 |
| **F11** | Urea | 1:1 |
| **F12** | Soluplus® | 1:1 |
| **F13** | Mannitol | 1:5 |
| **F14** | PVP k30 | 1:5 |
| **F15** | Urea | 1:5 |
| **F16** | Soluplus® | 1:5 |

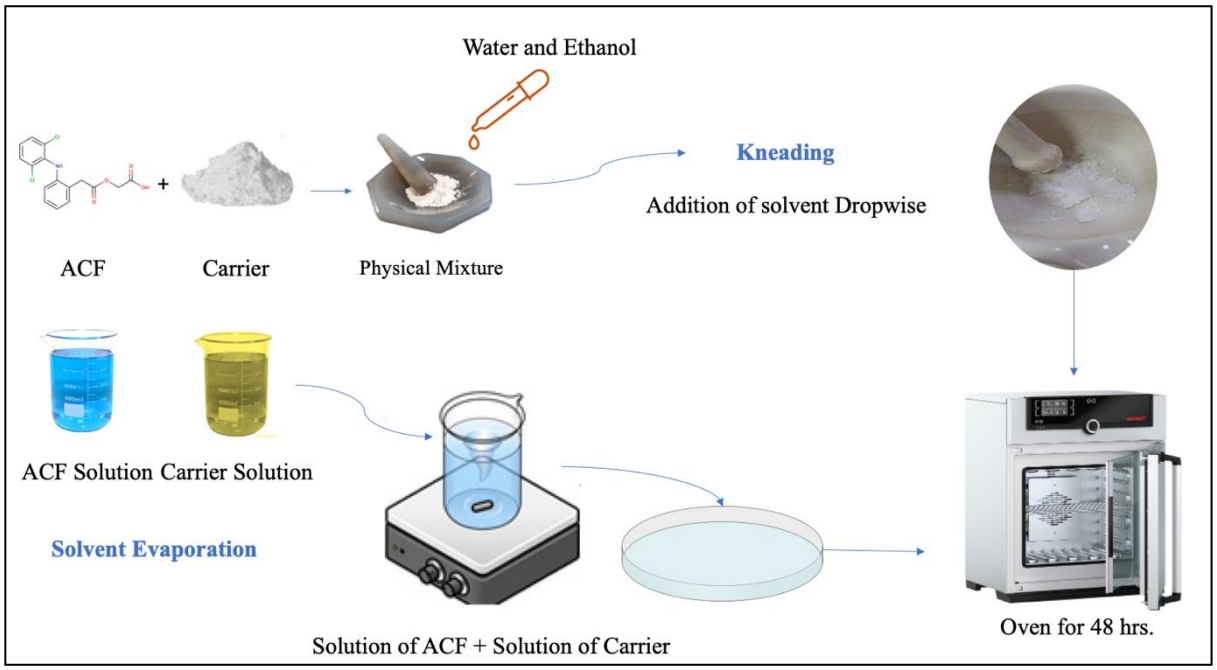


**Figure 2: Preparation steps of ACF-SD by SE and Kn methods.**

**Characterization of ACF-solid dispersion**

**Measuring the percentage yield (PY %) of ACF-SD**

The PY% of the prepared ACF SDs of each formula was determined practically to determine the efficiency of each technique. It was calculated by determination the ratio of the practical mass of the prepared ACE-SD formula to the theoretical mass of ACE-SD which was calculated by the equation below [9].

$$PY\% = \frac{\text{Practical Wieght (SD)}}{\text{Theoretical Wieght (SD)}} \times 100 \qquad \textbf{Equation 1}$$

**Measuring the drug content of the prepared ACF-SD**

An accurately weighed powder of ACF-SD equivalents to 100mg of ACF was dissolved in 50 ml ethanol. Then, the solution was diluted with ethanol; the drug solution was assayed using UV-spectrophotometer at 277nm λmax [10]. The drug content percentage (DC%) was calculated by using the below equation [11].

$$Drug\ Content\%\ (DC\%) = \frac{\text{Actual ACF amount in SD}}{\text{Theoretical ACF amount in SD}} \times 100 \qquad \textbf{Equation 2}$$

**Determination of saturation solubility for pure ACF and SDs formulas**

In a closed tube containing 10ml of (distilled water), an excess amount of pure ACF or SD formula was added. For about 48 hours, the sample was placed in a shaker water bath at 25± 0.5 °C and 50 rpm. The resultant samples were taken out and filtered through filter paper. The concentration of the dissolved ACF was calculated using a UV-spectrophotometer at 275 λmax to estimate the amount of ACF that had been dissolved. The investigation was done in triplicate [12].

***In-vitro* dissolution studies**

The *in-vitro* dissolution of ACF from the prepared SDs of highest solubility, PM, and pure ACF was determined by using USP XXII rotating paddle (apparatus II). ACF-SD equivalent to 100 mg of the pure drug was dispersed in a dissolution medium. An in-vitro dissolution study was conducted in a 900-ml phosphate buffer (pH 6.8); at 37±0.5°C using a thermostatic water bath with a rotating speed at 50 rpm. Five milliliters were withdrawn at different time intervals 10, 20, 30, 40, 50, and 60 minutes. The sink condition was kept by replacing every withdrawn sample with an equal volume of fresh medium. The samples were filtered via a 0.45µm filter membrane and assayed for ACF using UV-spectrophotometer at 275 λ max [13]. This test was performed in triplicate for all samples.

**Selection of the optimum SD formula**

Based on the solid dispersion parameters such as solubility and dissolution study, selection of the best formula for SD to be compared and can be employed for further study and to be formulated as various dosage form in future.

**Results and Discussion**

**Characterization of ACF-SD**

**Percentage yield and drug content of the prepared ACF-SD**

Except for F4 and F8, which resulted in a sticky product with a low yield both the Kn and SE methods generally yielded acceptable PY percentages ranging from 91.8% to 99.5%. These results indicated that both methods are comparable and efficient in producing the solid dispersions.

The DC for all formulas, except F4 and F8, were within the range of 93.5% to 100.1% w/w, aligning with the criteria of the United States Pharmacopeia (90-105%) [14]. The DC of F4 formula, couldn't be determined because of the very low PY, while the relatively low DC of F8, can be attributed to the sticky nature of the product. This stickiness may lead to a non-uniform dispersion of the drug within the mass, affecting the drug content results for this formula. The results of PY and DC for both methods are shown in Table 3.

**Determination of saturation solubility for pure ACF and SDs formulas**

The results of saturated solubility of pure ACF and the prepared ACF-SD in distilled water maintained at 25 °C were illustrated in Table (4 and 5).

**Table 3: The PY% and DC% of ACF-SD Using Different Methods**

| SE Formula name | PY % | Drug content% (W/W) (Mean±SD) (n=3) | Kn Formula name | PY % | Drug content % (W/W) (Mean±SD) (n=3) |
|---|---|---|---|---|---|
| **F1** | 96.2 % | 99.02±0.3 | **F9** | 99.4 % | 99.97±0.1 |
| **F2** | 99.5% | 98.9±0.01 | **F10** | 100.05% | 97.2±0.05 |
| **F3** | 95.7% | 96±0.03 | **F11** | 98.1% | 98.8±0.2 |
| **F4** | Sticky/ Low yield | Not applicable | **F12** | 97.9% | 100.01±0.03 |
| **F5** | 98.5% | 94.2±0.01 | **F13** | 99.1% | 95±0.002 |
| **F6** | 91.8% | 93.5±0.2 | **F14** | 97% | 96±0.01 |
| **F7** | 97% | 98.03±0.001 | **F15** | 96.4% | 100.1±0.4 |
| **F8** | 62% | 75±0.3 | **F16** | 99.5% | 99.8±0.003 |

**Table 4: The Saturation solubility of Pure ACF and ACF SDs Formulas Using Different Drug: Carrier Ratios in SE method in Distilled Water at 25˚C**

| SE Formulas | Carrier (drug: carrier) | Saturation solubility mg/ml Mean ±SD (n=3) |
|---|---|---|
| **Pure ACF** | | 0.067 |
| **F1** | Mannitol (1:1) | 0.16 |
| **F2** | PVP k30 (1:1) | 0.082 |
| **F3** | Urea (1:1) | 0.13 |
| **F4** | Soluplus® (1:1) | **Sticky / No yield** |
| **F5** | Mannitol (1:5) | 0.58 |
| **F6** | PVP k30 (1:5) | 0.92 |
| **F7** | Urea (1:5) | 1.33 |
| **F8** | Soluplus® (1:5) | 3.27 |

**Table 5: The Saturation solubility of Pure ACF and ACF SDs Formulas Using Different Drug: Carrier Ratios in Kn method in Distilled Water at 25˚C**

| Kn Formulas | Carrier (drug: carrier) | Saturation solubility mg/ml Mean ±SD (n=3) |
|---|---|---|
| **Pure ACF** | | 0.067 |
| **F9** | Mannitol (1:1) | 0.29 |
| **F10** | PVP k30 (1:1) | 0.09 |
| **F11** | Urea (1:1) | 0.26 |
| **F12** | Soluplus® (1:1) | 1.28 |
| **F13** | Mannitol (1:5) | 0.82 |
| **F14** | PVP k30 (1:5) | 1.12 |
| **F15** | Urea (1:5) | 2.49 |
| **F16** | Soluplus® (1:5) | 13.01 |

Regarding to statistics that was done using Prism GraphPad, although both ratios provide significant improvement in solubility ($P<0.05$) in comparison to the solubility of the pure drug as shown in Table (4 and 5), which is mainly due to the hydrophilic nature of the carriers that enhanced the solubility of the poorly soluble drug [15], but higher solubility was obtained with higher ratio (1:5), due to higher amount of hydrophilic carrier that may also improves wettability of hydrophobic drug. The solubility of 1:5 ratio ACF SD are showed in Figure 3.

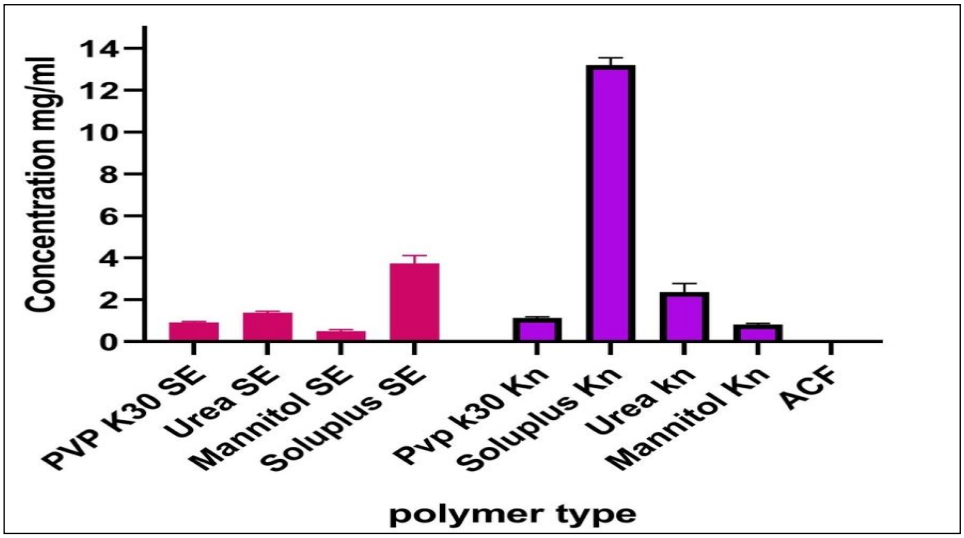


**Figure 3: Solubility of pure ACF and ACF SD prepared by SE and Kn techniques at 1:5 ratio**

Although urea and soluplus® enhanced the solubility of ACF higher than other carriers, however, soluplus® was found as the best carrier polymer in both techniques, but F16 (Kn method) was superior to F8 (SE method) in many folds (361 folds vs 91 folds) as compared to the pure drug as demonstrated in Figure 4 and Table 4.

The explanation for such differences may be due to low PY in F8, which can suggest that a portion of the drug has been lost during the preparation process, which might also affect the uniformity and consistency of the final product, similarly low drug content can indicate that the drug is not uniformly dispersed throughout the carrier matrix, leading to areas where the drug concentration is lower than expected. This non-uniform dispersion can result in variable solubility profiles of ACF as shown in Figure 4. This problem was happened in SE method but not with Kn method may be due to to low *Tg* (about 70 $^{o}$ C) [16].

Solubility of F16 was higher than that of the other formulas may be due to of the formation of an H-bond

between carbonyl oxygen in soluplus® and the -COOH of ACF [13]. The greatest solubility was able to be reached due to soluplus's strong hydration activity in aqueous solutions, large surface area of hydrophilic groups, and good hydrophilic properties [17].

Among all ACF SD formulas, formulas obtained by two methods with highest solubility were subjected for *in-vitro* dissolution study.

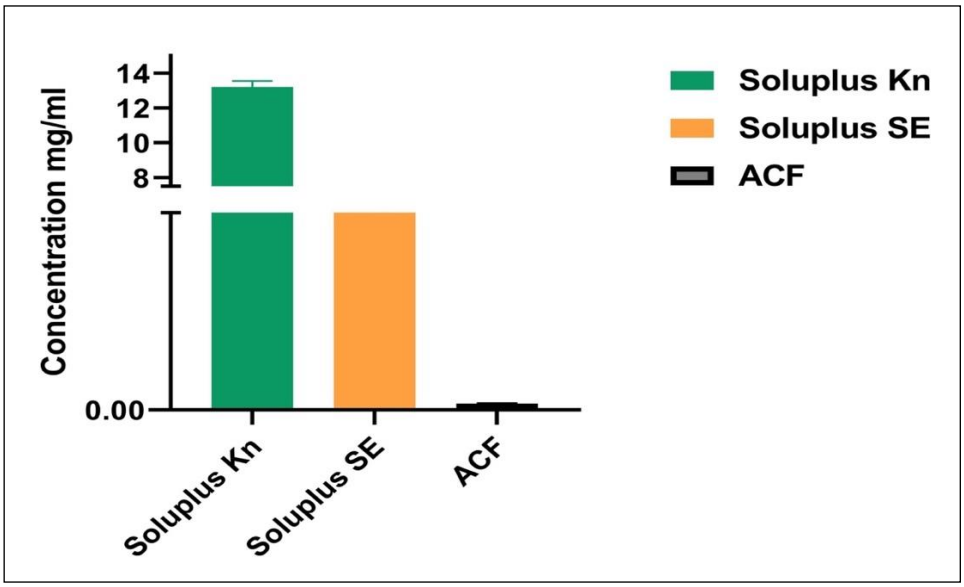


**Figure 4: The solubility of ACF SD using Soluplus® by SE and Kn techniques.**

***In-vitro* Dissolution studies**

In order to assess the effect of polymer type and preparation method on the in-vitro dissolution, soluplus® and urea containing formulas were selected for this test.

Dispersing the drug in a carrier with hydrophilic nature, results in enhanced wettability with expected decrease in particle size during formation of SDs provide an efficient way to overcome the intermolecular forces between drug molecules and promote a faster dissolution [18].

The result reflected that soluplus® gave high release profile that was about 80% in 10 minutes and less than 40% by urea compared to only 20% of the pure ACF by Kn method while in SE method the release of drug was also enhanced for both carriers but less than in Kn method as shown in Figure 5 and 6, which indicate that Kn method was more effective in enhancing the dissolution rate of ACF.

The effect of the type of method can be studied by comparing the release profile of soluplus® formulas (F8 and F16 by SE and Kn method, respectively as shown in Figure (7).

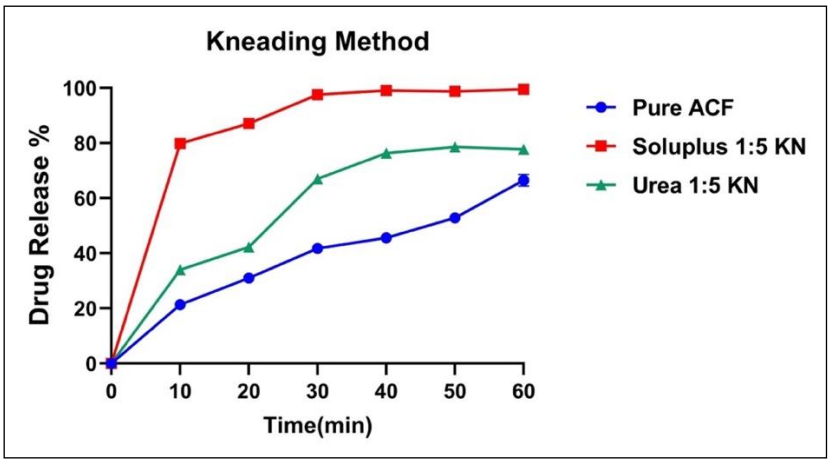


**Figure 5: *In-vitro* dissolution rate of the pure ACF and ACF-SD by soluplus® and urea utilizing Kn method in phosphate buffer pH 6.8 at 37 °C.**

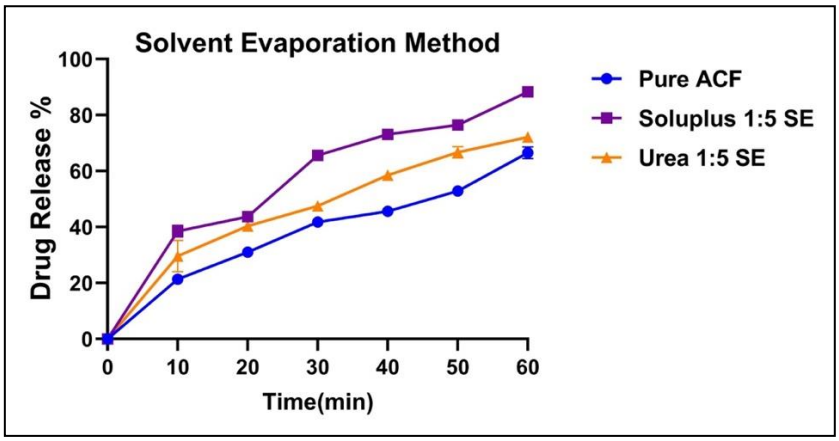


**Figure 6: *In-vitro* dissolution rate of the pure ACF and ACF-SD by soluplus® and urea utilizing SE method in phosphate buffer pH 6.8 at 37 °C.**

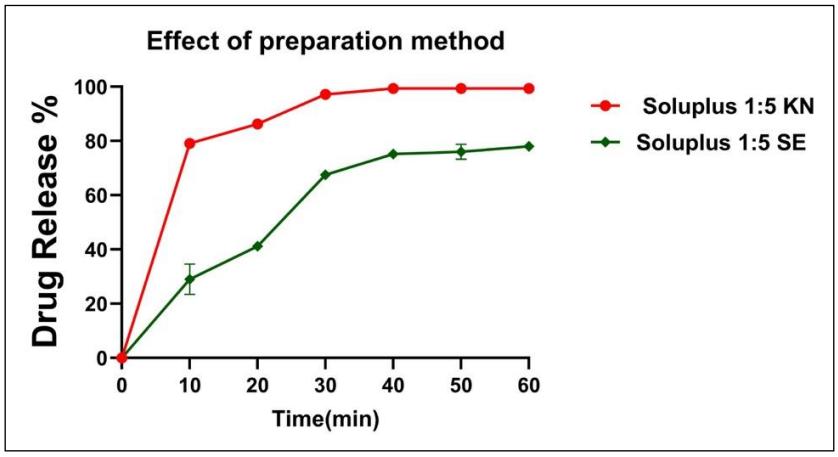


**Figure 7: *In-vitro* dissolution rate of ACF-SD by soluplus® utilizing SE and Kn method in phosphate buffer pH 6.8 at 37 °C.**

## Conclusion

According to the obtained results, the study has proven that ACF was successfully prepared as SD with enhanced solubility and dissolution rate by solvent evaporation method and kneading method using different carriers. Kneading method was superior to solvent evaporation method for solubility improvement by all carriers and all ratios and can be considered a successful and efficient technique for solubility and dissolution rate enhancement of hydrophobic drugs. Among them Soluplus® was the best carrier. The formula (F16) with ACF: Soluplus® (1:5) ratio was considered to be the best formula as it introduced the highest solubility and faster dissolution rate.

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