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Formulation and Evaluation of Kaemferol Containing Solid Dispersion for Oral Delivery

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In order to improve kaempferol's aqueous solubility and, consequently, its bioavailability, nine formulations of kaempferol solid dispersion were made using a solvent evaporation technique with three different carriers (mannitol, polyethylene glycol 6000, and -cyclodextrin) and three different drug carrier ratios (1:1, 1:3, and 1:6). Formulation variables were optimised using a 32-factorial design, and the prepared formulations were assessed for production yield, drug content, micromeritic properties, and in-vitro release. All of the formulations demonstrated high drug content, ranging from 96.98±2.76 to 99.54±2.1%, and high production yields ranging from 96.11±3.13 to 99.65± 3.72%. All of the produced kaempferol formulations demonstrated good flowability, according to the micromeritic characteristics. Compared to the drug's pure form, raising the drug carrier ratio enhanced the solubility of kaempferol, according to the findings of an in vitro release study. It was discovered that KF9 improved kaempferol's solubility and, thus, its bioavailability.

Keywords: Kaempferol, Solid dispersion, oral delivery, antioxidant.

1. Introduction

One kind of flavonoid is kaempferol (KP), also known as kaempferol-3, kaempferide, or kaempferol flavonol. Its chemical name is 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one. KP is a pure golden crystalline powder with a melting point of 276–278°C and a molecular weight of 286.23. [1, 2] It is somewhat soluble in water, ether alkaline, and hot ethanol. KP's diphenylpropane structure gives it hydrophobic qualities. The biosynthesis of KP is as follows: 4-coumaroyl-CoA condensation with tripropionyl-CoA yields naringenin chalcone, which is catalysed by chalcone synthase. Following this, naringenin chalcone is converted to naringenin, a flavanone, which is subsequently hydroxylated by flavanone 3-dioxygenase to provide dihydrokaempferol. [3] Lastly, KP is produced by adding a double bond to the dihydrokaempferol structure at the C2-C3 location. Its many therapeutic benefits, including anti-inflammatory, antioxidant, hepatoprotective, and anticancer properties, have also been documented in traditional medicine. [4, 5] However, due to its restricted membrane permeability and low lipid solubility, kaempferol has a relatively low oral bioavailability. Kaempferol's absorption was found to be low to moderate, resulting in a poor bioavailability of about 2%. It freely dissolves in methanol and has a hydrophobic character [6]. Kaempferol absorption is limited by its solubility and rate of dissolution [6, 7].

In order to overcome these shortcomings, new kaempferol dosage forms that address solubility and bioavailability should be developed. [8, 9] Pharmacokinetic studies have demonstrated that the use of inclusion compounds such cyclodextrins can increase the solubility rate of such medications by reducing crystallinity, reducing particle size to the nanoscale, and creating high energy amorphous form. [10, 11] By delivering kaempferol in prodrugs, nanocrystals, emulsions, liposomes, phospholipid formulations, polymer nanoparticles (PNs), micelles, and solid dispersions, its solubility and, eventually, bioavailability can be enhanced. [12] Solid Dispersion (SD) is one of the many dependable methods for enhancing the solubility of poorly soluble medications that have been documented in the literature. [13, 14] The objective of the present research work was to develop and characterize kaempferol SD- to enhance kaempferol for oral drug delivery.

2. MATERIALS AND METHODS

Materials: Kaempferol was purchased from SRL Chemicals Company (India). The surfactants mannitol, polyethylene glycol and beta-cyclodextrin was purchased from Sigma-Aldrich (India). The solvent evaporation method was employed for preparing the solid dispersions.

The Experimental Design: A (3^2) full factorial design was used to formulate nine formulations of kaempferol solid dispersion (KF1–KF9) using the design expert software program, version 12. The factorial design was employed to study the effect of two independent variables (X_1, and X_2), each with three levels (+1, 0, and −1) on the dependent variable (Y_1). The independent variables were the type of carrier (X_1), drug carrier ration (X_2), while the dependent variable was the percentage of drug released after 1 hr (Y_1). The dependent and independent variables

are represented in Table 1. [15, 16]

Table 1. Dependent and independent formulation variables and their levels according to 3^2 factorial design; PEG: polyethylene glycol

Independent Factors	Low (−1)	Medium (0)	High (1)
X1 = Type of carrier	Mannitol	PEG 6000	β-Cyclodextrin
X2 = Drug: Carrier ratio	1:1	1:3	1:6
Dependent Variables	Goal		
Y1 = The drug release (%)	Maximize		

The Preparation of Solid Dispersion: Three distinct carriers (mannitol, polyethylene glycol (PEG) 6000, and β-cyclodextrin) with three different drug carrier ratios (1:1, 1:3, and 1:6) were used to generate the formulations of kaempferol solid dispersion using the solvent evaporation technique. A 3^2 complete factorial design was used for optimisation. In a round-bottomed flask, 10 mL of methanol was used to dissolve the weighed amounts of kaempferol and the carriers. A Heidolph rotavap (Schwabach, Germany) was used to allow the solvent to evaporate. It was rotated at 100 rpm, 25 ± 1 ◦C, and 600 mmHg of pressure until it was entirely dry. [17] The solid kaempferol dispersion was left on the flask wall when the methanol was evaporated [18]. For additional research, the obtained kaempferol solid dispersions were gathered, dried in an oven at 40 °C for 24 hours, crushed, and stored at room temperature in a desiccator over silica at 60% relative humidity. Table 2 shows the composition of the nine kaempferol solid dispersion formulations. [19, 20]

Table 2. Solid dispersion formulations according to 3^2 factorial designs

Formulation	Variable X^1	Variable X^2
KF1	-1	-1
KF2	-1	0
KF3	-1	1
KF4	0	-1
KF5	0	0
KF6	0	1
KF7	1	-1
KF8	1	0
KF9	1	1

The Percentage Yield of Solid Dispersion: The production yield of all prepared formulations of solid dispersion was estimated by the following equation [21]:
The Percentage Yield was calculated by:

% yield = Weight of the collected solid dispersion/ Total weight of drug and carrier used / 100

Drug Content: The UV technique was used to estimate the drug content. A UV spectrophotometer (UV 1800, Shimadzu) was used to analyse the weighted sample from the produced formulations after it had been dissolved in the solvent and run through a syringe

filter. The following formula was used to determine the drug content. [22].

% Drug content = Actual concentration of drug / Theoretical concentration × 100

The Determination of Micromeritic Properties of Solid Dispersion Powders: In the pharmaceutical sector, solid dispersion flow characteristics are crucial, particularly when mixing powders, compressing tablets, and filling capsules. The created solid dispersion's flow characteristics were measured using a number of measures, including the bulk density, the tapped density, the angle of repose, Carr's index, and Hausner's ratio. [23-25]

The Infrared Spectroscopy Analysis (IR): The Shimadzu 435 U-O4 IR spectrometer (Tokyo, Japan) was used to perform Fourier-Transform Infrared spectra (FT-IR) on the samples in order to determine the infrared spectra of pure kaempferol and its carriers (Mannitol, PEG 6000, and β-cyclodextrin) KF9. To make sure the formulation ingredients utilised to make the kaempferol solid dispersion were compatible, infrared spectroscopy was performed. Potassium bromide was added to each sample before it was mechanically compacted into a disc [26]. Each sample's disc's infrared spectroscopy was measured using a wavelength scanning range of 4000 cm−1 to 400 cm−1. [27, 28].

The In-Vitro Release Study of kaempferol from Solid Dispersion: Using an ERWEKA dissolution tester, apparatus II (Erweka, Heusenstamm, Germany), the dissolution of kaempferol from the formed solid dispersion was investigated. 900 mL of phosphate buffer (pH 6.8) was mixed with a precise weight of kaempferol (2 mg) and each solid dispersion formulation equal to 2 mg of kaempferol [29]. A temperature of 37 ± 1 ◦C and a speed of 100 rpm were maintained for the dissolving media. At various intervals (5, 10, 15, 20, 25, 30, 45, and 60 minutes), the samples were taken out and replaced with an equivalent volume of new medium [30]. A UV spectro-photometer set to 228 nm was used to filter and perform spectrophotometric analysis on the extracted materials [31]. The experiment was done in triplicates, and the mean and the standard deviation were measured [32].

The Selection of Optimized Formulation of Kaempferol Solid Dispersion: The formulation ingredients were optimized to determine the optimum level of X_1 and X_2, which achieve the highest value of Y_1 [33].

The Scanning Electron Microscopy (SEM): A scanning electron microscope (JEOL, Tokyo, Japan) was used to examine the morphology of the kaempferol solid dispersion formulation that was optimised [34, 35]. A thin layer of platinum was applied after a dried sample of the optimised formulation was spread out and stuck to an aluminium stub. SEM captured the image at 30 Kv.

3. RESULTS AND DISCUSSION

Formulation: Using design expert software version 12, 3^2 multilevel factorial designers created nine formulations of kaempferol solid dispersion. The impact of formulation factors on the kaempferol dissolution profile was ascertained using the factorial design.

The Production Yield % (PY%): As indicated in Table 3, nine kaempferol solid dispersion formulations were successfully made using a solvent evaporation approach, with high production yield percentages ranging from 98.4 ± 2.8% to 99.8 ± 2.2%. Sahoo et al. observed

that the production yield percentage of kaempferol solid dispersion was between 96.5 ± 2.1% and 99.4 ± 1.2%. The results were completely consistent with their findings. [22].

The Drug Content %(DC%): The drug content for all kaempferol solid dispersion formulations was determined and found to be between 96.11±3.13 and 99.65±3.72%, as shown in table 3. The high drug content value suggested that the preparation technique and carrier selection were repeatable. These findings were consistent with those of Sahoo et al., who used PEG 6000, PEG 10000, and Gelucire 44/14 to manufacture the kaempferol solid dispersion and discovered that the drug content ranged from 96.98±2.76 to 99.54±2.1%. [22].

Table 3. Characterization of prepared solid dispersion formulations

Formulation	PY%	DC %
KF1	99.17 ± 2.56	98.56 ± 2.23
KF2	96.11 ± 3.13	96.98 ± 2.76
KF3	98.17 ± 2.55	98.56 ± 2.34
KF4	98.45 ± 2.86	97.76 ± 2.43
KF5	98.34 ± 2.27	98.65 ±3.43
KF6	99.25 ± 2.87	97.87 ± 2.98
KF7	99.21 ± 2.18	99.13 ± 2.65
KF8	98.45 ± 2.35	98.37 ± 3.52
KF9	99.65 ± 3.72	99.54 ± 2.17

The Micromeritics Properties of Solid Dispersion

The Bulk and Tapped Density The bulk density and tapped density were measured in order to examine the solid dispersion's flow characteristics. Table 4 displayed the bulk and tapped density data. The bulk and tapped density results were determined to be between 0.39 ± 0.05 and 0.57 ± 0.06 g/cm3 and 0.42 ± 0.01 and 0.62 ± 0.06 g/cm3, respectively.

Hausner's Ratio: The flow characteristics of solid dispersion were found to be indicated by the Hausner's ratio value. Better flowability is indicated by values less than 1.25 than by those greater than 1.25. Table 4 shows that all created solid dispersion formulations had Hausner's ratios between 01.12 ± 0.01 and 1.34 ± 0.02; this range indicated satisfactory flowability.

Carr's Index (the Compressibility%): The flowability of the solid dispersion and the compressibility % are inversely correlated. The flowability dropped as Carr's index rose. Excellent flowability is indicated by values between 5 and 12, good flowability by values between 12 and 16, fair acceptable flowability by values between 18 and 21, bad flowability by values between 23 and 35, and extremely poor flowability by values between 33 and 38. Table 4 shows that all created kaempferol solid dispersion formulations had good flowability, with Carr's index values ranging from 10.43 ± 0.42 to 19.45 ± 0.42%.

Angle of Repose: The angle of repose was discovered to have an impact on the solid dispersion's flowability. When the angle of repose was less than 20◦, excellent flowability was attained. Good flowability is shown by a value between 20 and 30◦, acceptable flowability is shown by a value between 30 and 34◦, and extremely bad flowability is shown by a number more than 34◦. According to Table 4's results, every manufactured solid dispersion showed an

angle of repose between 15.23 and 24.11◦, indicating satisfactory flowability.

Table 4. The bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose

Formulation No.	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Hausenr's Ratio	Carr's Index (%)	Angle of Repose
KF1	0.55 ± 0.05	0.62 ± 0.06	1.18 ± 0.03	11.32 ± 0.46	16.57 ± 0.77
KF2	0.43 ± 0.03	0.51 ± 0.01	1.12 ± 0.01	10.43 ± 0.42	15.23 ± 0.54
KF3	0.48 ± 0.04	0.54 ± 0.01	1.16 ± 0.02	12.96 ± 0.65	17.54 ± 0.75
KF4	0.51 ± 0.01	0.52 ± 0.01	1.12 ± 0.01	10.98 ± 0.52	15.85 ± 0.32
KF5	0.47 ± 0.02	0.49 ± 0.02	1.18 ± 0.01	14.25 ± 0.44	20.65 ± 0.11
KF6	0.39 ± 0.05	0.48 ± 0.02	1.22 ± 0.02	19.45 ± 0.42	24.11 ± 0.34
KF7	0.42 ± 0.03	0.42 ± 0.01	1.34 ± 0.05	17.56 ± 0.55	19.19 ± 0.56
KF8	0.57 ± 0.06	0.43 ± 0.02	1.19 ± 0.03	13.95 ± 0.12	18.67 ± 0.37
KF9	0.42 ± 0.04	0.49 ± 0.01	1.21 ± 0.03	15.23 ± 0.84	21.46 ± 0.33

Values were expressed in mean ±SD (n = 3)

The Infrared Spectroscopy (IR): The infrared spectra of pure kaempferol, mannitol, PEG 6000, β-cyclodextrin, KF9 were illustrated in Figure 1 & 2. The IR spectrum of kaempferol showed characteristic characteristic absorption peaks at ~3427 cm-1 and ~3317 cm-1 (phenolic O-H stretching), ~2954 cm-1 and ~2850 cm-1 (C-H stretching), and at ~1613 cm-1 (C=O stretching). These observations are consistent with those reported earlier for kaempferol. The IR spectrum of KF9 showed all characteristic peaks of kaempferol, which revealed the absence of any physical or chemical interaction between the drug and the used carriers.

The In-Vitro Release Study of Solid Dispersion: According to Figure 3's in-vitro release results, the release for each formulation varied from 66.45 ±2.45 for KF4 to 99.67 ±3.65% for KF9. Additionally, the release from every formulation was noticeably greater than the release of the free drug, suggesting that the solid dispersion approach can speed up the kaempferol's rate of dissolution. This could be explained by the drug changing into a more soluble amorphous state and improving the drug's wettability and dissolution by lowering the interfacial tension between kaempferol and the dissolving media.

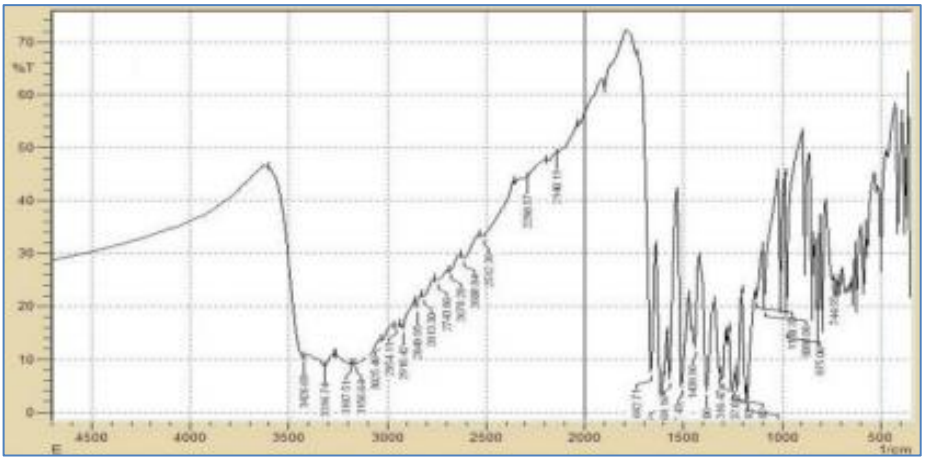

Figure 1: FTIR spectra of Kaempferol

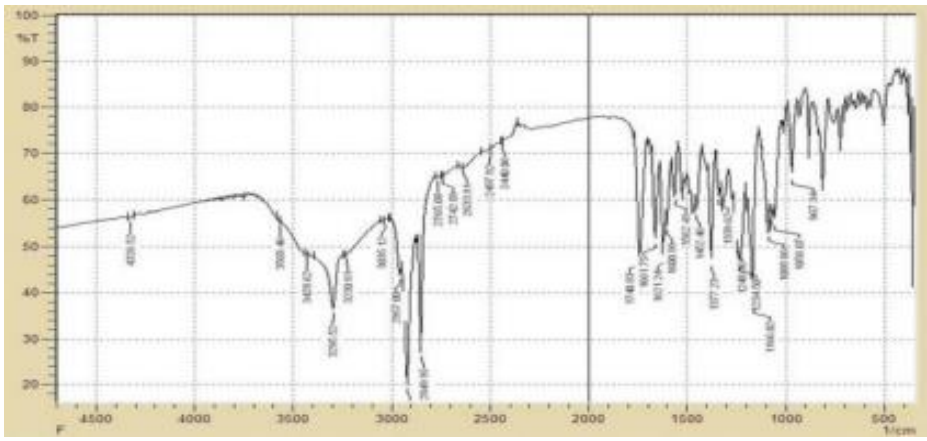

Figure 2: FTIR spectra of Solid dispersion formulation (KF9)

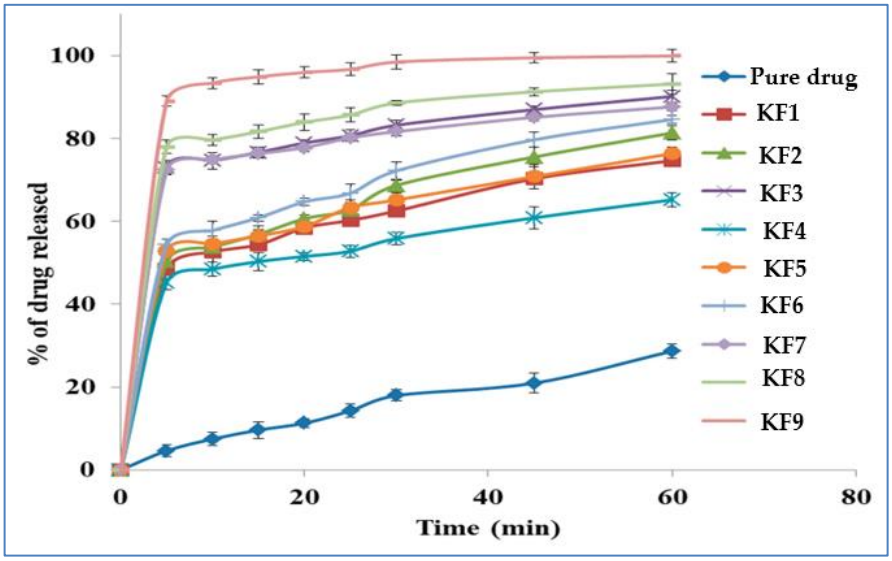

Figure 3. The in-vitro release study of all prepared solid dispersion formulations

The effect of the formulation factors in the in-vitro release (Y_1): Using the Y1 equation, a multiple linear regression analysis was performed to examine the impact of independent formulation factors (X1 and X2) on the in vitro release of produced solid dispersion:

$$Y_1 = +78.56 + 6.78\ X_1 + 7.11\ X_2 - 0.785\ X_1X_2 + 11.56\ X_{21} + 0.0637\ X_{22}$$

It was discovered that the release varied depending on the type of carrier (β-cyclodextrin > Mannitol > PEG 6000), as seen in Figure 4. These outcomes could be explained by variations in the carriers' hydrophilic action. Additionally, by raising the drug-carrier ratio from 1:1 to 1:6, the release increased for each carrier. This may be explained by the increased surface area and wettability as the proportion of water-soluble carriers rose.

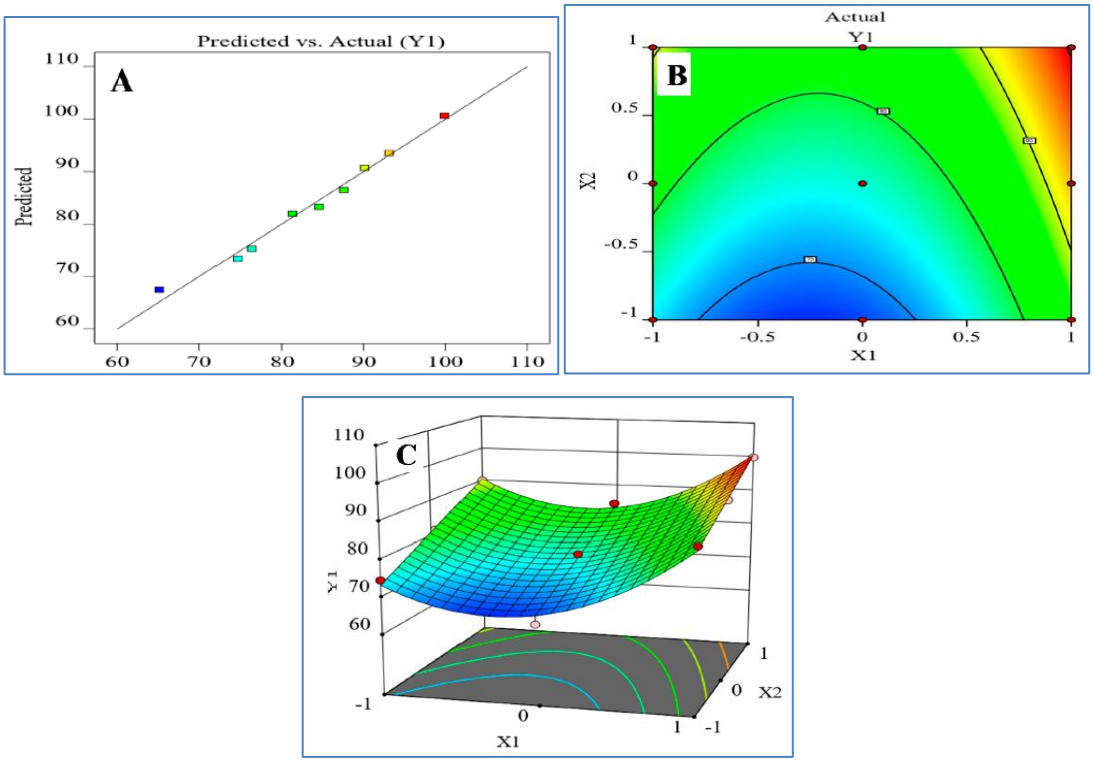

Figure 4. The effect of formulation factors (X1 and X2) in the in vitro drug release (Y_1).

The Selection of Optimized Formulation of Solid Dispersion: To get the optimal formulation, Design Expert software (version 12) was used to optimise the independent variables. Based on which formula produced the maximum drug release (Q1hr), the optimised formula was chosen. KF9 was chosen as the optimal formulation based on the results.

The Scanning Electron Microscopy of the Optimized Formulation (SEM): Figure 5 displayed the optimised solid dispersion's surface morphology. The optimised formulation was discovered to show up as irregular particles, which could indicate that kamepferol was dispersed on the carriers in an amorphous condition.

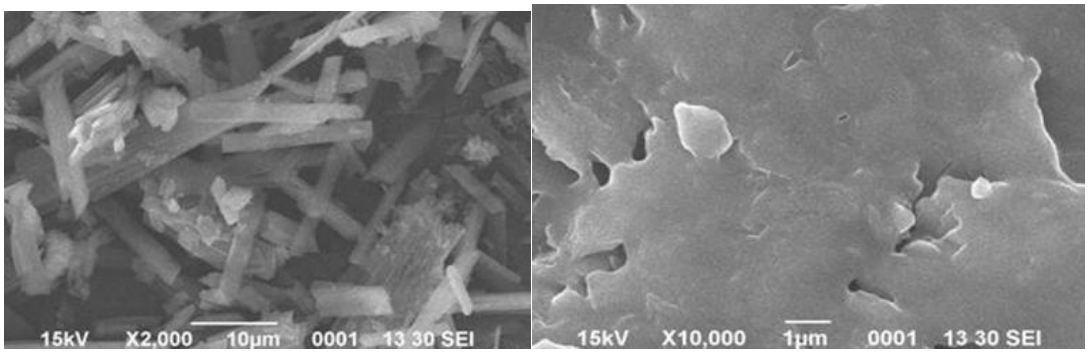

Figure 5: SEM Images of kaempferol And Solid Dispersion

4. CONCLUSION:

Increased interest in kaempferol's many uses as an antioxidant, antiviral, antiplatelet, anti-inflammatory, antineoplastic, and cardio-protective agent has been spurred by its potential as a major therapeutic agent. However, because of their limited solubility, these potential actions cannot be used widely. To tackle this problem, we created solid kaempferol dispersions using a solvent evaporation technique. We discovered that the production of solid dispersions greatly improved the solubility and dissolution of kaempferol. Because of its poor solubility, pure kaempferol had relatively little release. On the other hand, kaempferol released from solid dispersions considerably more quickly.

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