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Concurrent Enhancement of Curcumin's Stability and Dissolution by the Preparation of its Eutectic Mixtures

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Abstract

Rhizomes of Curcuma longa is the source of the chemical curcumin. It possesses several pharmacological characteristics, including anti-inflammatory, anti-hyperlipidemic antioxidant properties. But it also has several drawbacks, that limit its application as a medication. Curcumin's drawbacks that impede its application as a therapy include its poor chemical instability, solubility, bioavailability, and quick systemic clearance because of its rapid metabolism under physiological conditions. Its weak internal physicochemical properties make it less effective. These characteristics include photoinstability, limited bioavailability due to hydrolysis, and water insolubility. For the purpose of this investigation, a eutectic combination of 15% and 85% curcumin and nicotinamide was made. DSC, FTIR, and XRD analyses were used to assess the product's dissolving rate and photostability. The eutectic combination dissolved ten times faster after forty minutes than the parent medication. Following the 7th s day of accelerated photostability testing, curcumin-nicotinamide eutectic combinations shown 36% degradation, which was 34% less than pure curcumin. The photostability nvestigations were carried out in accordance with ICH Q1B recommendations. According to current research, cucumin may be a viable contender for pharmaceuticals in the future.

Keywords: Curcumin, DSC, Eutectics, Nicotinamide, Stability.

Introduction

It is commonly recognized that a number of medications that emerge from drug development pipelines exhibit issues such as low stability, limted aqueous solubility, etc. Numerous methods have been investigated to modify the medications' medicinal qualities. Making solid dispersions, which include dispersing a therapeutic component in a hydrophilic inactive material, is the most used method (1). Solid dispersions come in two varieties: amorphous and crystalline, depending on the drug's condition. Drugs dispersed in semi-crystalline polymers or polymers (amorphous form) can produce solid dispersion. There is instability in these systems. When crystalline form of drug and polymer are used, they form a thermodynamically stable system which is crystalline in nature. Pharmaceutical experts are drawn to crystalline solid dispersion because of the system's straightforward formulations (2). Eutectic mixes are made up of two components that are entirely miscible in liquid state but immiscible in solid state when included in crystalline solid dispersion. A particular kind of crystalline solid dispersion is the eutectic mixture. These systems are referred to as intricately mixed physical mixes in thermodynamics. The melting points of eutectic mixtures are lower than those of their constituent parts. Eutectic mixes have been utilized in metallurgical procedures to create different metal blends ever since their discovery in the year.

However, until 1961, when Sekiguchi created the first eutectic combination of sulphathiazole and urea, their utility in medicine was unknown. Since then, eutectic mixes have caught the interest of medical researchers because of their ability to produce spontaneously, easily scale up, and show promise for improving water solubility and stability. Eutectic mixtures were once thought upon negatively by the pharmaceutical industry, however for the following reasons, interest in their use in

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pharmaceutical formulations is growing (i) Eutectics don't need clinical studies because they're not unique chemical entities or new crystal formations, and (ii) the preparation and scale up of eutectic mixture is very easy; (iii) Unlike amorphous materials, both components are present in eutectic systems in their extremely stable crystalline form (3).

Curcumin is a significant chemical in pharmacy since it has demonstrated a variety of pharmacological effects, including anti-inflammatory properties, antibacterial, antioxidant, and antinociceptive qualities. It has been employed as a food dye because of its coloring qualities, and dietary supplements because of its medicinal qualities (4). In 1995, the United States of America filed patents on the antibacterial, surgical wound healing, and healing characteristics of turmeric. India challenged these patents, citing the fact that turmeric was already a part of Indian traditional medicine and that the patents lacked originality.

Turmeric is the primary ingredient in many Ayurvedic formulations; yet, because to its poor water solubility and degradation, its application in contemporary medicine is restricted. As a result, patents were revoked and India was granted geographical designation for turmeric (5). The Zingiberaceae family includes curcumin**.** This vivid yellow chemical is turmeric's primary ingredient. This polyphenol comes from the Curcuma longa species.

Curcumin is categorized as class II in the Biopharmaceutics Classification System , meaning it is extremely permeable and weakly water soluble (6, 7). This substance photodegrades rather quickly. These issues— low dissolution profile, poor water solubility, and photodegradability cause the molecule to respond poorly in clinical trials or to fail as a treatment. Enhancing these limiting characteristics is therefore a major formulation development task. Innovations that alter solubility, dissolution profile, and stability—such as the micronization, solid dispersions, complexation, etc. have been the subject of relatively few research (8, 9).

One kind of vitamin B3, known as pyridine carboxamide or nicotinamide, is an easily soluble water vitamin. Nicotinamide's structure is made up of a pyridine ring with a main amide group bonded to it in the meta position. It is an amide of nicotinic acid with the chemical formula $C_6H_6N_2O$ (10). It has been applied in the past to improve the rate of dissolution and solubility of drugs. This amino acid has previously been utilized to create metal complexes of curcumin and nicotinamide that have antibacterial qualities and increase medication solubility. To improve these qualities, solid curcumin and nicotinamide dispersions were also made. Because of its charge separation in the current situation, this molecule can be regarded as a good contender for the potential production of a eutectic blend with curcumin (11).

Methodology

Nicotinamide was procured from Nice Chemicals (P) Ltd. (Kerala) while curcumin was bought from CDH Ltd. New Delhi). Additionally, methanol and ethanol that were of HPLC quality were utilized. The remaining substances are all reagent-grade (12).

Estimation of the compound's eutectic behavior:

• Curcumin-notinamide was synthesized as a binary combination at various percentages. The Van't Hoff equation was used to compute the percentage (2).

$$Ic = (Tf_d\text{-}Tf_p)\,\Delta Hf_d/R(Tf_d)^2 \text{ ……..[1]}$$

$$\text{and T mix} = Tf_d\text{-}w_p[R(Tf_d)^2]/\Delta Hf_d, \text{ ……..[2]}$$

(where Tf_d is the main component's melting point, Wp is its weight fraction, R is the molar gas constant, ΔHf_d is the major component's molar heat of fusion, and T mix is the temperature along the liquidus line). Based on the aforementioned equation, Law *et al*. (4) proposed an index for determining the conformer and medicine composition at the eutectic point. The Ic value index is shown in Table 1.

• Table 2 displays the computed Ic values for curcumin and nicotinamide, which are 1.92. Therefore, several ratios of curcumin and nicotinamide were utilized to generate binary combinations, such as 35% and 65% of curcumin and nicotinamide respectively, 34% curcumin and 66% nicotinamide, 36% curcumin and 64% nicotinamide, and 40% curcumin and 60% nicotinamide.

Table 1: Prepared by Law *et. al* (4)

I_C value	Percent (w/w) drug in carrier
0.0<I_c<0.5	App. 35
0.5< I_C<1.5	App. 25
1.5< I_c<2.5	App.15
2.5<more	Monotectic

Development of curcumin-nicotinamide (CN) mixtures

Solvent evaporation was used to produce binary mixtures. Curcumin was weighed and added to the mortar after nicotinamide had been precisely weighed. To properly combine these powders, a pestle was employed after a spatula was used to stir them together. Ethanol was used to dissolve the powdered powder. Room temperature, or 25±20C, and 40±5% relative humidity (RH) was used for this experiment. To allow the solvent to evaporate, the solutions were stored in a desiccator. The binary combinations were obtained for additional research after drying (13).

Table 2: I_C value calculated for drug and other components

S. No	Drug+ other component	I_c value
1	Glycine+ Curcumin	0.49
2	Curcumin +nicotinamide	1.92
3	Curcumin + tartaric acid	4.08(monotectic)
4	Curcumin + salicylic acid	0.876

Characterization

Differential scanning calorimetry (DSC)

DSC2-00347 was subjected to differential scanning calorimetry (192.168.10.2). For studies, samples were put into crimped and vented metal pans. Sample size is 3 mg. The heating of samples were done 5˛C/min and urged in stream of dry nitrogen. The scan temperature range was 30–300˚C (14). However, this technology has several shortcomings, including its destructive character, its incapacity to disclose structural details, and its incapacity to investigate molecular interactions.

Fourier-Transform Infrared (FTIR) Spectroscopy

Using the KBr disc method, spectroscopy was carried out on the FT-IR Bruker (1206 0280, Germany) apparatus. 4000-400 nm was the scan range (13).

Hot-stage Microscopy

LINKAM (DSE600) was used to conduct hot-stage microscopy. Samples went into the pan. Range of temperatures was 1 to 2000C. This method is used for microscopy and thermal analysis. DSC investigations were supported by it (15).

Constructing a Calibration Curve

Using ethanol as a solvent, curcumin was dissolved to yield a solution with a 100µg/ml concentration. The stock solution was subsequently diluted to provide final concentrations (2, 4, 6, 8, and 10 µg/ml). Calculating the absorbance at 425 nm was necessary in order to plot the calibration curve(16). Table 4 contains the data for the calibration curve.

Dissolution Studies

Dissolution investigations, using the ELECTROLAB dissolution test apparatus, the paddle technique described in the USP (United States Pharmacopoeia) was used to test the binary mixture (CN) for dissolution. 500mL of a 40% ethanol-water combination was used as the dissolving medium for each test. Empty capsule shells were filled with binary mixes prior to the dissolving test. A dissolving medium was used to dissolve the 500 mg of each of the following: physical mixture, pure drug, binary mixes, and marketed formulation. The temperature was set to 37±0.5° C and the stirring speed of the solution was set at 150 rpm. To maintain a steady level, 5 mL of aliquots were removed every 20 minutes and replaced with a new medium. After ten

repetitions of sample dilution, a membrane filter (0.45µm) was used to filter the material. Vibration spectroscopy was used to analyze the samples further (13).

Research on Photostability

One extremely photounstable chemical is curcumin. When exposed to light, it breaks down into ferulic acid and vanillin. In accordance with ICH Q1B recommendations for photostability testing, the photostability of curcumin and CN eutectic combinations alone was assessed in a photostability chamber (Thermolab ES2000UV) equipped with a near fluorescent lamp and a cool fluorescent lamp. The total light level was set at 1.2 million lux h-1 using irradiance power. We kept the temperature at 25 0C and the relative humidity at 40%. The samples (2.5 mg) were distributed on glass Petri plates with a 6 cm diameter. Following a seven-day stay in the stability chamber, samples of the eutectic mixture and pure curcumin were obtained at predetermined intervals and subjected to HPLC analysis (17).

In vitro anti-inflammatory activity

Inflammation is primarily caused by denaturation of proteins. Consequently, a paradigm for investigating anti-inflammatory efficacy in vitro may be employed, namely protein denaturation. The reaction mixture consists of a bovine albumin (1%) solution and a curcumin-nicotinamide eutectic blend at different concentrations. 1N HCl was used to alter the pH. After incubating at 37° C for 20 minutes, samples were heated to 57° C for 20 minutes. After cooling, samples were analyzed spectroscopically at 660 nm. The experiment was carried out three times (22, 23). The formula used to compute percentage inhibition was:

percentage inhibition = (Abs control-Abs sample)/abs control * 100.

Table 3: Various groups with different treatments.

S No.	Group	Treatment	Dose	Route of administration
1	Group 1	carageenan	.05ml sol of 1% sol	The planter side of left hind paw (injection method)
2	Group 2	Curcumin	100mg/kg	Oral Route (suspension in 0.5% solution of CMC)
3	Group 3	Curcumin + nicotinamide (eutectic mixture)	100mg/kg	Oral route (suspension in 0.5% solution of CMC)
4	Group 4	Curcumin + nicotinamide (eutectic mixture)	50mg/kg	Oral route (suspension in 0.5% solution of CMC)

In Vivo anti-inflammatory activity Paw edema caused by carrageenan

in vivo investigations were carried out under approved circumstances in accordance with IAEC criteria, with clearance from the IAEC committee (MDU, Rohtak). Curcumin (pure medication) was used as the reference drug for in vivo research, with the half dosage (50 mg/kg) and equivalent dose (100 mg/kg) of eutectic mixes used to investigate anti-inflammatory efficacy.

Because the eutectic mixture preparation improved the drug's solubility profile, half the dosage of eutectic mixes was employed. Rats were starved for a whole night. Four groups of rats were created (24, 25). Which group receiving which treatment is displayed in Table 3.

Result and Discussion

Differential scanning colorimetry

The most useful approach is DSC since it is the only one that can provide information on the eutectic phase. DSC examination revealed that the product made using the solvent evaporation process at a heating rate of 5° C/min. The mixture of curcumin and nicotinamide was created in five different

proportions, which were then subjected to DSC analysis. These proportions were 13%, 87%, 14%, 16%, and 18% curcumin and 82% nicotinamide, respectively. See the thermograms in Figure 1. The melting points of 15% curcumin and 85% nicotinamide are lower than those of the starting materials (Curcumin 181.4° C and 129° C, respectively) (CUR–NICO 72.09° C). Because there was little to no decline in the melting points, the remaining preparations were abandoned.

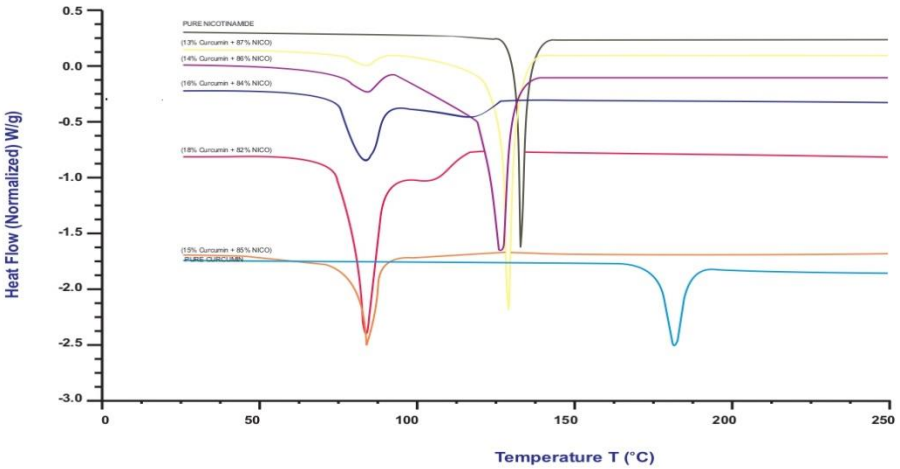


Figure 1: Overlay of DSC thermograms i.e., purple shows thermogram of 14% curcumin and 86% nicotinamide, Red shows thermogram of 18% curcumin and 82% nicotinamide, orange shows 15% curcumin and 85% nicotinamide, and blue shows 16% curcumin and 84% nicotinamide, yellow shows 13% curcumin and 87% nicotinamide, blue shows pure curcumin and black shows pure nicotinamide.

FTIR Spectroscopy

The stretching vibrations at 3200–3500 cm^{-1} attributed to the phenolic hydroxyl groups, the stretching vibration at 1490 cm^{-1} linked to the aromatic C=C bond, and the bending vibration at 1246 cm^{-1} resulting from the phenolic C–O group were all seen in the FT–IR spectra of pure curcumin.

Hot stage microscopy

A multicomponent system's melting of any component may be seen with the aid of HSM when the sample's temperature is gradually raised. Figures 4a and 4b of this study show that the mixture of curcumin and nicotinamide melted at 75° C, confirming the formation of a eutectic mixture and supporting the DSC investigation. Curcumin melts at 183° C, while nicotinamide melts at 129° C, both of which are higher than the eutectic mixture's melting temperature.

Curcumin Standard Curve: Curcumin was administered at various doses in a combination of ethanol and water. The absorbance at 425 nm was measured. In Table 4, data is displayed. Based on the calibration curve, the R-value was determined to be 0.969, as seen in Figure 5 (26).

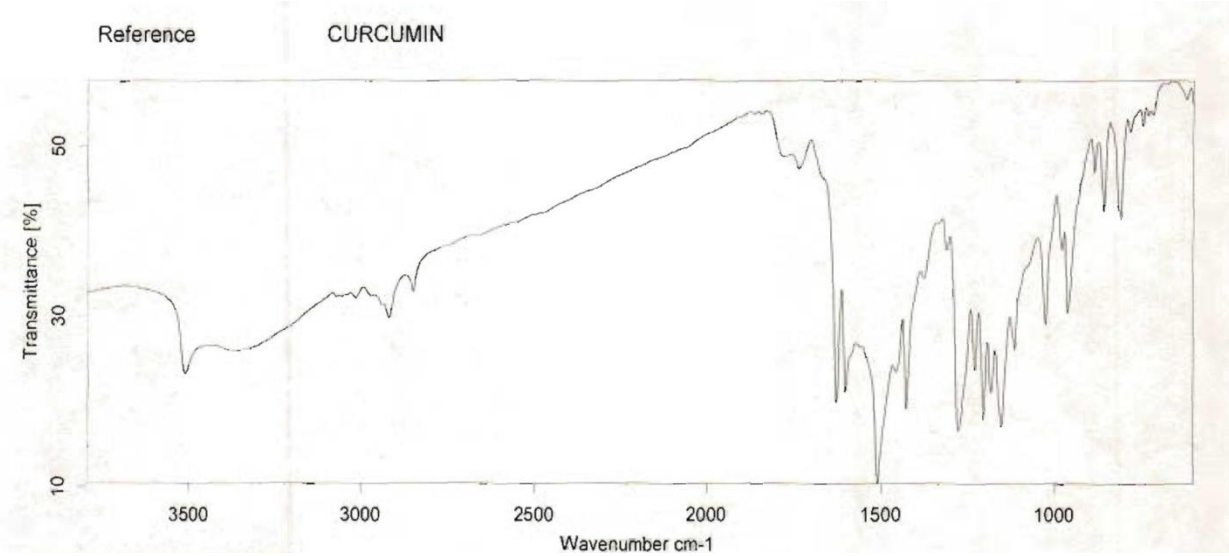


Figure 2: Pure curcumin (FTIR)

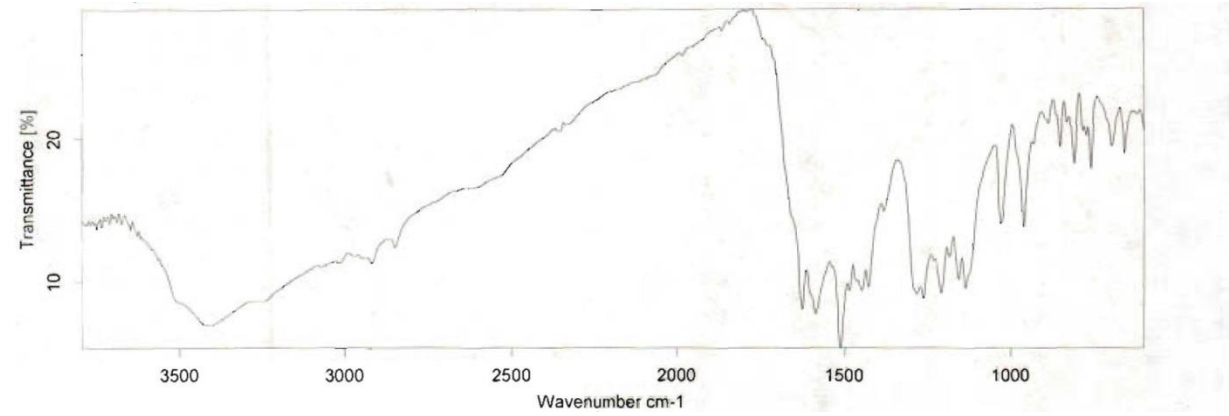


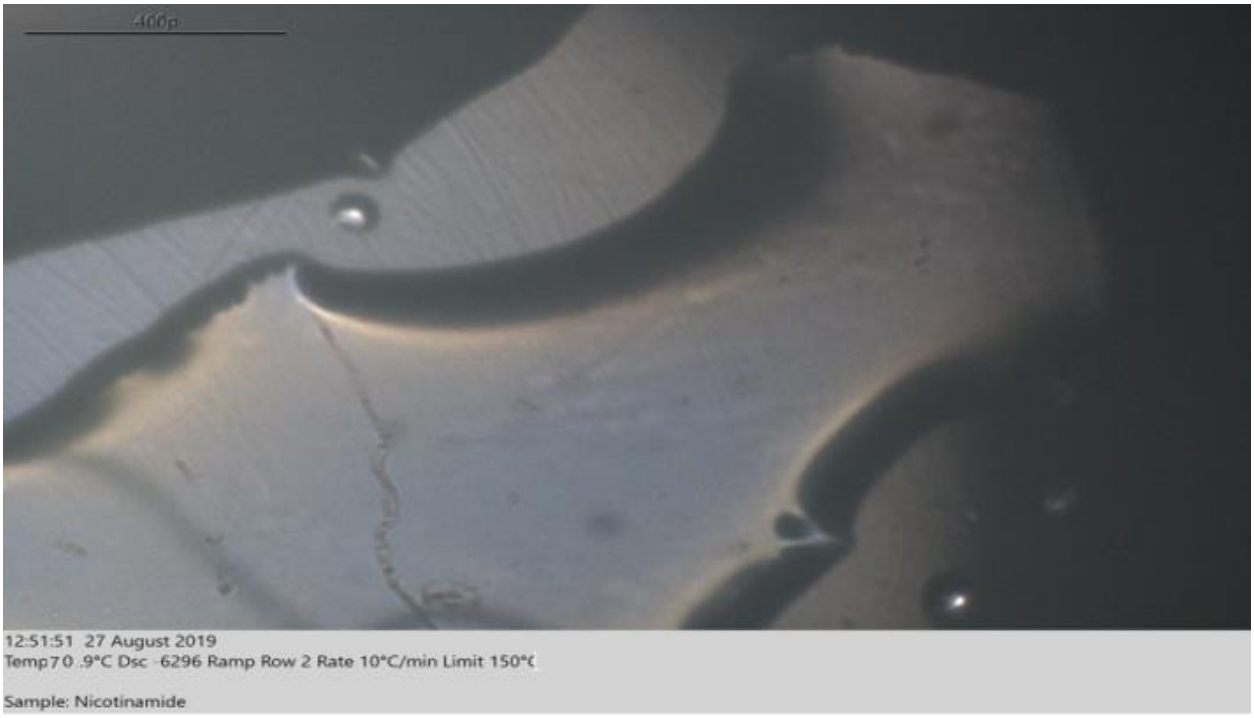
Figure 3: Curcumin-Nicotinamide (EM) FTIR

FT-IR studies of the curcumin-nicotinamide eutectic blends: The C-H Stretch, O-H (H Bonded), C=O Stretch, and =C-H Stretch peaks were found at 2816–3088,3310–3457, 1615–1911, and 848–1065, respectively, according to the FT-IR spectra of the curcumin-nicotinamide eutectic combination (Figure 2 and 3). One possible explanation for the shifting of some peaks in the eutectic mixture's spectrum is the interaction between the medication and the nicotinamide. The eutectic mixture spectrum's absence characteristic at peaks 2617–2810 differs from the conformer and drug spectra. This verified that a eutectic mixture had formed.

Dissolution studies

The in vitro dissolution profiles of pure curcumin, eutectic and physical mixes of curcumin and nicotinamide, and commercial formulations (Dr. Morepen curcumin veg capsule) are displayed in the accompanying Figure 6. Drug release from curcumin was around 13%, but drug release from the physical mixture, eutectic mixture, and commercial formulation was roughly 16%, 19%, and 18%, respectively. Due to the eutectic mixture's high solubility, there was a burst effect in the dissolution profile of curcumin-nicotinamide combinations at 60 minutes. The results of this in vitro drug release investigation showed that the curcin-nicotinamide eutectic mixture's solubility profile was improved over that of the drug's pure form and commercial formulation. The outcomes demonstrate that the eutectic combination outperforms the pure medication, physical mixture, and commercial formulation in terms of dissolving qualities. The readings were taken in triplicates.

(a)



(b)

Figure 4: Micrograph of the curcumin-nicotinamide eutectic mixture at 50° C and 72° C (a and b). Hot-stage microscopy was used to generate both micrographs, which unequivocally demonstrate absence of interaction at 50° C and that both compounds melt at 72° C. This demonstrates that eutectic combinations of nicotinamide and curcumin have formed.

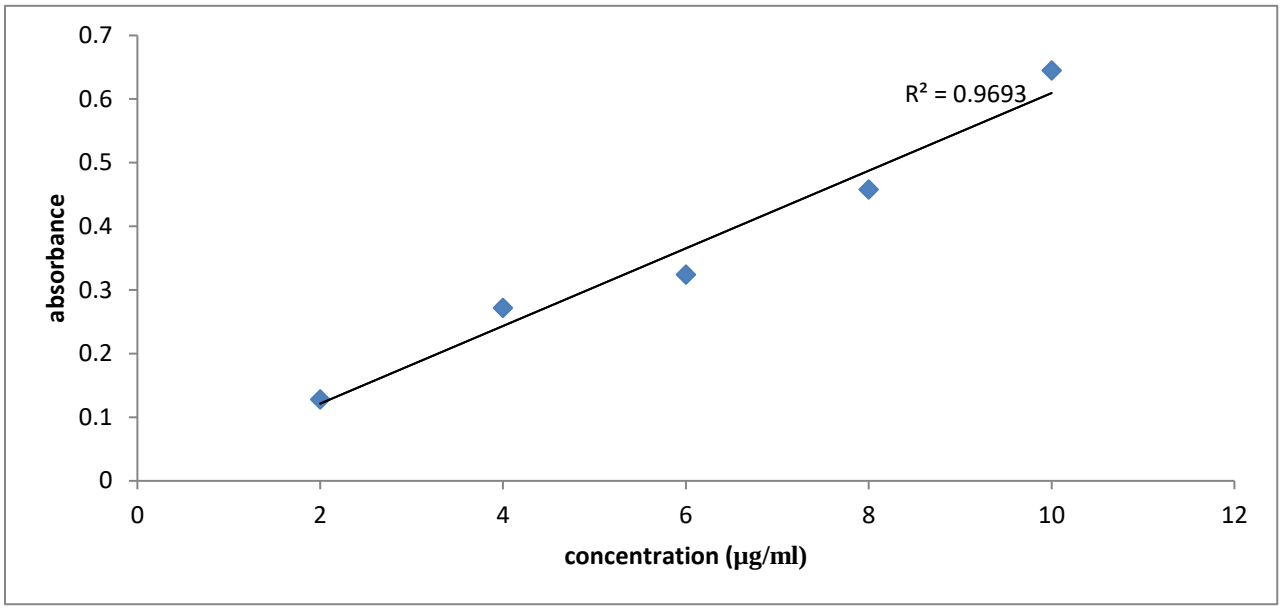


Figure 5: Calibration curve of curcumin

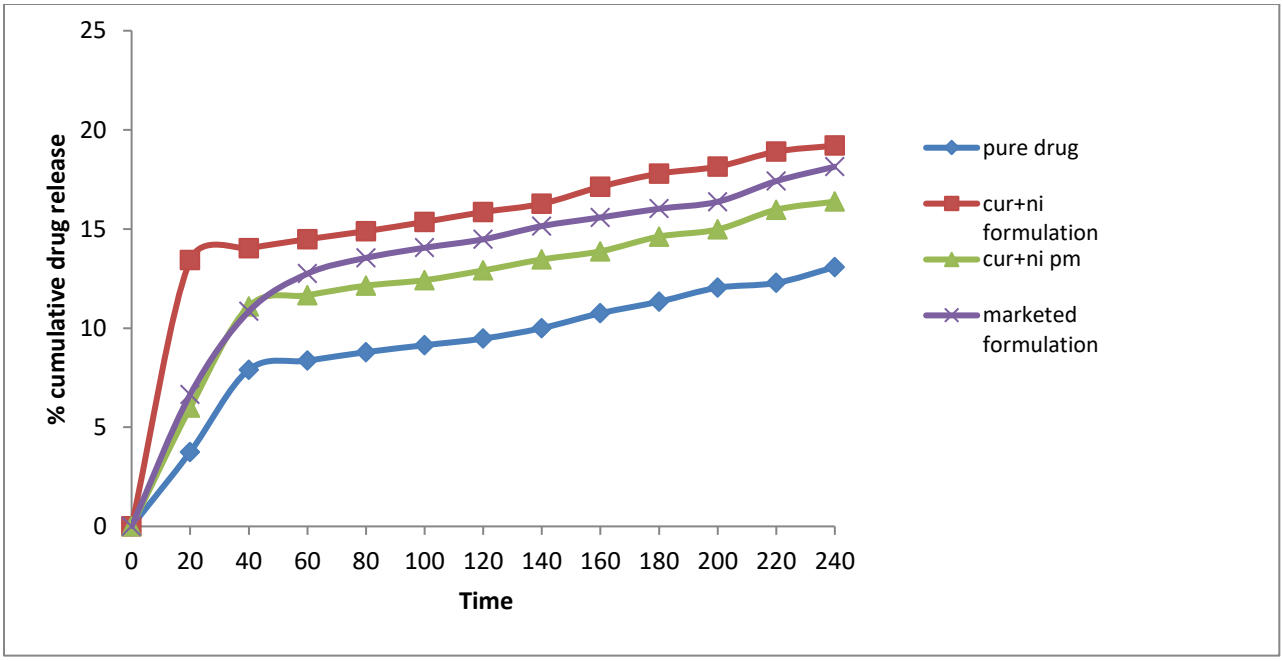


Figure 6: Percentage Drug Release Graph

Stability studies

In this investigation, rapid photodegradation was applied to the eutectic mixture (35%:65%, curcumin: nicotinamide) and pure curcumin (gram) in a photostability chamber (1.2 million lux h^{-1}). The samples were taken out at 24, 48, 72, 96, 120, 144, and 168 hours, and HPLC analysis was performed (Table 5). The eutectic combination decayed to 34% after the seventh day of the trial, which is twice as much as pure curcumin's 70.5% degradation. Figure 7 presents the findings. First-order kinetics govern the degradation, with R2 values of 0.966 for pure curcumin and 0.982 for the curcumin-nicotinamide eutectic combination.

Table 4: Concentration vs absorbance data

Conc. (µg/ml)	Abs
2	0.128±0.21
4	0.272±0.23
6	0.324±0.24
8	0.458±0.25
10	0.645±0.30

Table 5: Photostability Study of Curcumin and Curcumin-Nicotinamide Eutectic Mixture

Days	Percent degradation of eutectic mixture	Pure curcumin
0	0	0
1	0.56	11.55
2	12.58	31.30
3	16.02	41.44
4	21.36	44.82
5	27.37	58.76
6	30.52	66.87
7	34.48	70.55

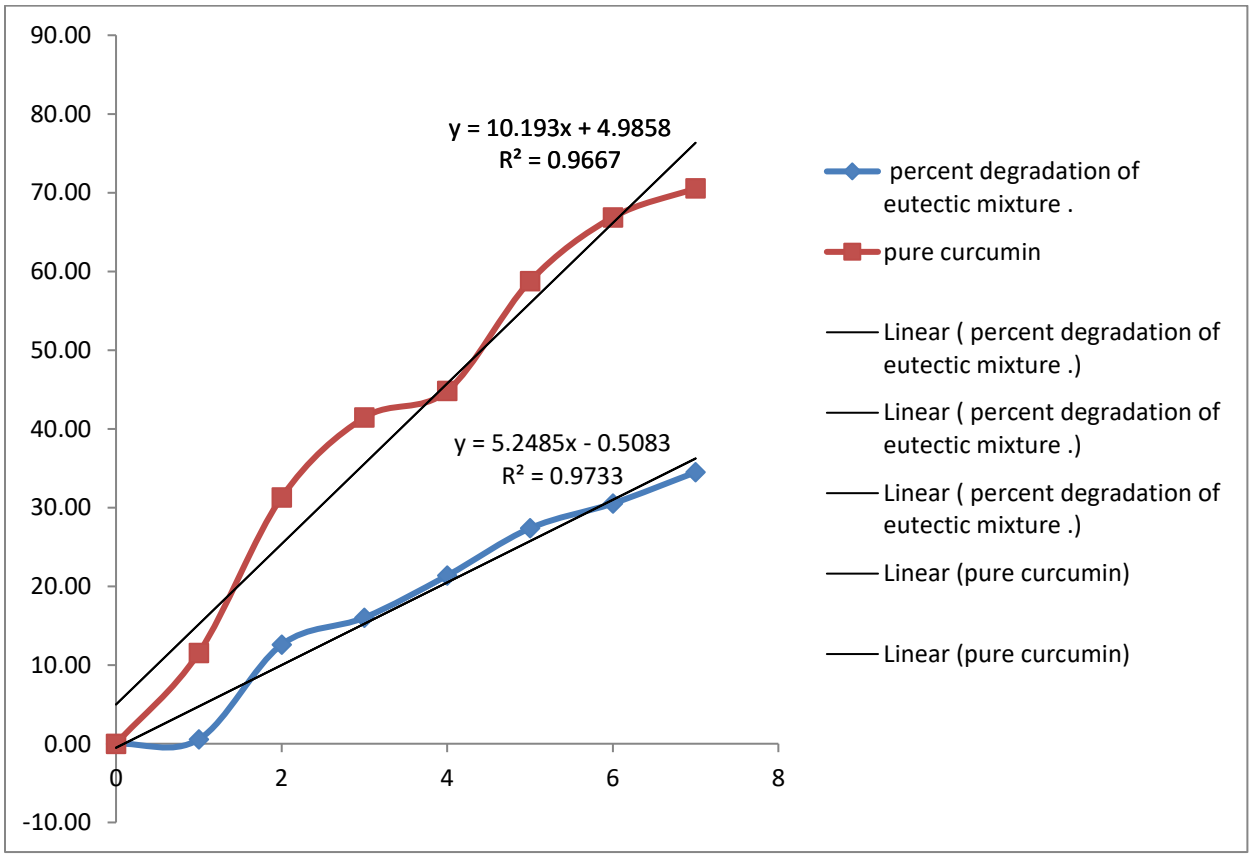


Figure 7: Drug Degradation Profile of Curcumin

Table 6: Parameters calculated during the photostability study

S No.	Parameter	Pure curcumin	Eutectic Mixture
1	K value	1.4	0.09
2	R^2 value (1st order)	0.966	0.98
3	R^2 value (zero order)	0.934	0.973
4	Shelf life	2 days	18days

In vitro anti-inflammatory activity

In vitro research has demonstrated that inflammation is primarily caused by protein denaturation. To support curcumin's anti-inflammatory action mechanism, the protein's ability to be denaturized was examined. Different dosages of a curcumin-nicotinamide eutectic combination inhibited heat-induced denaturation of protein. As seen in Table 7, 500µg/ml was found to have the highest inhibition of 70.53 ±0.2%. The IC50 value was found to be 120.35±1.97 µg/ml. Aspirin, a popular anti-inflammatory drug, had the maximum degree of inhibition at 250µg/ml, measured 76.33± 0.5%.

Table 7: %age inhibition of denaturation of protein

Concentration of sample (µg/ml)	Percentage inhibition	Control (aspirin) concentration (µg/ml)	Percentage inhibition
100	12.6±0.8	50	17.94±0.5
200	27.09±0.2	100	37.88±0.4
300	43.05±0.5	150	43.67±02
400	55.67±0.8	200	61.47±0.3
500	70.53±0.2	250	76.33±0.5

Anti -inflammatory activity (*in vivo*)

The table displays the anti-inflammatory effect of eutectic mixtures on carrageenan-induced paw edema in rats' hind paws. In group 3, the eutectic combination dosage was maintained at half that of the parent medication, curcumin, while group 4 received an equivalent dosage. In group 1, no decrease in inflammation was seen. All dose-treated groups did, however, exhibit a decrease in inflammation, with the curcumin-nicotinamide eutectic combination demonstrating the greatest reduction. As indicated in Table 8, the value of paw volume decrease in each group was determined to be.0.531±0.01, 0.363±0.05, 0.260±0.04, and 167±0.05 following five hours of carrageenan administration.

Table 8: Paw volume data of animals

Time in hr	Group 1 control	Group 2 pure drug (100mg/kg)	Group 3 EM 50mg/Kg	Group 4 EM 100mg/Kg
1	0.463±0.02	0.106±0.02	0.217±0.03	0.310±0.03
2	0.521±0.03	0.162±0.03	0.223±0.06	0.321±0.02
3	0.513±0.03	0.183±0.02	0.225±0.04	0.333±0.01
4	0.478±0.05	0.179±0.04	0.235±0.06	0.336±0.01
5	0.509±0.06	0.152±0.06	0.245±0.05	0.342±0.04
6	0.531±0.01	0.167±0.05	0.260±0.04	0.363±0.05

Conclusion

The result demonstrates that curcumin and nicotinamide can form a eutectic combination with a higher rate of dissolution. The in vivo activity backs up the theory, which states that a reduction in rat paw inflammation is correlated with an increase in the eutectic mixture's dissolution (curcumin 15% and nicotinamide 85%) as compared to pure

medication. Using GRAS coformers, curcumin was crushed mechanochemically to make binary eutectics that dissolved more quickly and had higher solubility. The formation of eutectics rather than the predicted cocrystals is not totally surprising, as mechanochemical grinding may provide long-range order, leading to eutectic compositions sustained by weak, short-range interactions. The existence of a single endotherm and a drop in melting point serve as the sole indicators of eutectic evolution in DSC. The lack of two melting peaks in the DSC study indicated that there was no additional transition to a cocrystal or unreacted solid phase. The intrinsic dissolving rates of binary eutectic mixtures were 3–11 times faster and the AUC values were 2–6 times higher than those of pure curcumin (27, 28). The current investigation yields many findings. Eutectic mixes can be prepared to enhance the physicochemical characteristics of curcumin. There are several restrictions, though, as determining the eutectic point is a difficult procedure. However, this study could help in formulation advancement in the near future.

Abbreviation

Curcumin-Nicotinamide (CN); Eutectic Mixture (EM); Physical Mixture (PM).

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Author Contributions

Sunita has completed all the evaluation parameters, Sumita Kumari has compiled the data, and Dr. Manjusha Chaudhary and Dr. Vikas Budhwar thoroughly evaluated the manuscript.

Conflict of Interest

There are no conflicts of interest.

Ethics Approval

Animals were approved in the IAEC meeting on 21/08/2023 with letter no. CAH/2023/157-162

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