

Formulation and Evaluation of Modafinil–Nicotinic Acid Cocrystal-Based Mouth Dissolving Film

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Abstract:

➤ Objective:

This work was conducted to prepare and characterize a Modafinil-nicotinic acid cocrystal loaded mouth dissolving film (MDF) through formulation-optimization approach.

➤ Methods:

Modafinil and nicotinic acid were mixed in a 1:1 molar ratio and characterized in terms of aqueous solubility, FTIR, powder x-ray diffraction (PXRD) and SEM analysis. The cocrystal was prepared in HPMC E5 films by solvent casting method. Variables including HPMC E5, PEG 400 and crospovidone were studied using three-factor three level Box–Behnken design with disintegration time as the main response variable. Optimized MDF was evaluated in terms of appearance, weight variation, folding endurance, surface pH, drug content, disintegration time, in-vitro dissolution and release kinetics.

➤ Results:

The aqueous solubility increased from 0.714 mg/mL for Modafinil to 4.003 mg/mL for the cocrystal, showing 5.61 fold increase in solubility. PXRD analysis revealed a well-defined crystalline pattern where the most intense peak was around 20.40° 2θ, whereas FTIR showed some change in N-H/O-H and fingerprint region due to modified intermolecular interaction. The optimized formulation ratio was found to be 215.3 mg HPMC E5, 2.220 mL PEG 400 and 5.990 mg crospovidone. The predicted disintegration time for the optimized film was found to be 23.93 s and the actual disintegration time was found to be 28.00 ± 1.00 s. The mean weight, folding endurance, surface pH and drug content of the film were found to be 328.23 ± 0.85 mg, 119.67 ± 1.53 folds, 6.73 ± 0.02 and 99.72 ± 0.56%, respectively. Mean cumulative drug release from the films at various times is given below: 26.28% at 1 min, 90.91% at 10 min and 100% after 30 min. First-order kinetics gave the highest value of R² (0.9960); the Korsmeyer-Peppas model provided an n value of approximately 0.56, showing anomalous release behavior. Conclusion: This study highlights the potential of combination of pharmaceutical cocrystallization technique with MDF technique to enhance the solubility and rapid release characteristics of Modafinil.

Keywords: Modafinil; Nicotinic Acid; Pharmaceutical Cocrystal; Mouth Dissolving Film; HPMC E5; PEG 400; Crospovidone; Box–Behnken Design; Dissolution Kinetics.

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I. INTRODUCTION

Mouth dissolving films (MDFs) or orodispersible films (ODFs) are film-like drug delivery systems that have been

formulated to wet, break up, and dissolve quickly once placed inside the mouth. MDFs offer many advantages over the usual tablets and capsules since their small size, flexibility, portability and non-aqueous delivery allow for an alternative

choice, especially when oral swallowing is problematic or when there is no availability of water. Oral films have gone a long way in terms of evolution from simple polymeric films to complex oral films utilizing advanced techniques such as taste masking, solid state modification, nanotechnology, multilayering, quality by design and personalized manufacturing.^{14–22}

The MDF will have to satisfy all of these factors at the same time. The polymer will need to form a continuous and structurally stable matrix, but one that hydrates and breaks up quickly in the saliva. Plasticizers may be added for making the matrix flexible and less brittle, although over-plasticizing may lead to very soft or tacky matrices. Superdisintegrants are known to speed up the process of hydration and disintegration of the matrix.^{14–18, 22}

Solvent casting continues to be one of the most common methods used for making oral films in the lab and on a development scale. This method involves dissolving or dispersing the film-forming polymer together with other ingredients in an appropriate vehicle, followed by mixing and deaeration of the mixture, and finally spreading the film-forming material in a thin layer and drying it under specific conditions. This technique is especially suitable in cases where the formulation involves hydrophilic polymers and when there is a need for a low processing temperature.^{14, 18, 27, 28, 40}

Pharmaceutical cocrystallization refers to a solid state approach where the active pharmaceutical ingredient (API) and a chosen coformer are brought together in order to create a novel crystalline solid phase through intermolecular forces and without any chemical change on the API. It involves the manipulation of solubility, dissolution, melting behavior, hygroscopicity, and other physical and chemical properties. This technique applies well to poorly soluble drugs whereby the molecule itself is fine but it poses problems in solid form.^{1–10}

Modafinil is a wake promoting medication that treats the excessive sleepiness caused by narcolepsy. The clinical and pharmacological studies demonstrate its effectiveness in improving wakefulness, although its pharmacology is related to the influence on the dopaminergic transport systems.^{11–13, 41–50} Modafinil would thus be a suitable model API for a patient-oriented rapid-dissolution dosage form, as long as the dosage form overcomes the physicochemical limitations of modafinil without altering the pharmacologically active substance.

There has been scientific evidence in the past on the possibility of forming the Modafinil-nicotinic acid cocrystals. For example, there has been scientific proof in the past on the preparation of a 1:1 ratio Modafinil-nicotinic acid cocrystal which exhibited higher aqueous solubility compared to that of Modafinil alone.³ Modafinil Cocrystals have been evaluated using an orodispersible tablet system. This is another example of the significance of cocrystals in drug formulation using fast-dissolving tablets.⁴ Here, the same idea was expanded upon in the context of thin films.

Reasons behind the combination of two techniques are complementary nature. Cocrystallization technique is employed in order to improve solid state characteristics of the drug and its aqueous solubility. However, matrix film disintegration formulation (MDF) serves the purpose of fast wetting, disintegration and drug release. Thus, the combination of these techniques will overcome drug limitation and dosage form limitation. This concept is in line with the development of patient-oriented films and quality by design concepts.^{17–22}

Even though there have been a lot of studies concerning oral films, the use of Modafinil–Nicotinic Acid cocrystal drug delivery system with solvent-casted HPMC E5 MDF along with statistical optimization of polymer concentration, plasticizer and superdisintegrants has not gained much attention yet. Thus, this study was designed for preparing and characterizing the cocrystal, formulating it into a rapidly disintegrating film, optimizing the formula with the Box–Behnken design, and characterizing the optimized formula with physiochemical and release kinetic analysis. This study is formulation-based; efficacy and pharmacokinetics are not discussed herein.

➤ Objectives:

- For preparation of 1:1 molar ratio of Modafinil and nicotinic acid cocrystal.
- For comparison of solubility of cocrystal in water with the solubility of Modafinil itself.
- For characterization of prepared cocrystal through FTIR, PXRD and SEM.
- For development of Modafinil cocrystal based mouth dissolving film through solvent casting method, utilizing HPMC E5 as film forming agent, PEG 400 as plasticizer and crospovidone as superdisintegrant.
- For optimization of HPMC E5, PEG 400 and crospovidone concentration by applying three factor-three level Box-Behnken design.
- For evaluation of optimized film formulation for its physical parameters, drug content, disintegration and dissolution study.

II. MATERIALS AND METHODS

➤ Materials:

Modafinil was acquired from SM Pharma Chemical. Nicotinic acid served as the coformer. HPMC E5 was used as the film-forming polymer; PEG 400 served as the plasticizer while crospovidone was used as the superdisintegrant. Methanol and distilled water were used in the formation of cocrystals and films. Hydrophilic film-forming polymers, plasticizers, and disintegrants were selected because they are conventional choices in oral film formulation.

Table 1 Materails and Function

Material	Function in the formulation
Modafinil	Active pharmaceutical ingredient
Nicotinic acid	Cocrystal conformer
HPMC E5	Film-forming polymer
PEG 400	Plasticizer
Crospovidone	Superdisintegrant
Methanol	Processing solvent for cocrystal preparation
Distilled water	Hydration/dispersion medium and film-processing vehicle

➤ Preparation of Modafinil–Nicotinic Acid Cocrystal:

The two substances used in the experiment, namely modafinil and nicotinic acid, were used in equal molar proportions of 1:1. From the experimental report, the process involved dissolving the weighed amount of substances in methanol and stirring to achieve a uniform preparation and subsequently isolating the solid substance. However, from the thesis record provided, the exact details on the crystallization point and drying conditions have been inadequately captured; hence, these laboratory notebook details need to be included before submission. This information is crucial considering that the cocrystallization process determines the solid-state form.^{1–10}

The prepared solid was then tested for its apparent aqueous solubility and analyzed using solid-state techniques. The utilization of such analytical techniques complementing one another was purposeful because the FTIR technique gives data about the functional group environment, the PXRD gives data on the crystalline structure, and SEM gives morphological data.^{1,2,5,6,9}

➤ UV Spectrophotometric Method:

The Modafinil stock solution was made in methanol and serial working solutions with concentrations of 2, 4, 6, 8 and 10 µg/mL were studied on a double-beam UV-Visible spectrophotometer. Absorption peak is at 259.5 nm. The calibration curve revealed that the regression equation for the range of concentrations studied is $y = 0.0072x + 0.0049$ with $R^2 = 0.9913$. This method is applied in estimating the content of the drug and the dissolution samples.

➤ Saturation Solubility:

Saturation solubility was studied using a shake flask method. An excess amount of pure Modafinil or its cocrystal was allowed to be in equilibrium with distilled water for two days at room temperature with occasional shaking. The equilibrium samples were then centrifuged for 30 minutes, and the resultant supernatant was appropriately diluted and measured at 259.5 nm. Saturation solubilities were reported as mg/mL. Cocrystallization can be employed to change the thermodynamic and kinetic parameters of dissolution.^{1–10}

➤ FTIR Characterization:

The IR spectra were obtained in the range of 4000–400 cm⁻¹. The solid compounds were studied by means of the KBr pellets technique, and PEG 400 by ATR. Comparative analysis of IR spectra of Modafinil, the Modafinil-nicotinic acid cocrystal, and certain components of formulations was performed. Modification in position, shape, and intensity of bands was discussed on the basis of modification of the

intermolecular environment, but not on the basis of the hypothesis of the formation of a new covalent bond.^{1,2,5,9}

➤ SEM Characterization:

The morphology of the surface of the formed cocrystal was characterized by SEM at various magnifications. The qualitative characterization was made based on the particle shape, surface roughness, heterogeneity of size and agglomeration of particles. SEM was employed as additional evidence of change in morphology but not as a direct confirmation of the formation of a cocrystal.

➤ PXRD Characterization:

The method of PXRD was employed in the analysis of the crystal nature and diffraction features of the synthesized Modafinil-nicotinic acid cocrystal. The diffractogram was analyzed for sharp peaks and variation in diffraction features compared to the starting compounds. The peak positions were determined based on the 2θ value and intensity in cps (counts per second). Both FTIR and PXRD analyses were taken into account for proof of the crystallization of the unique compound. The importance of the PXRD technique lies in pharmaceutical cocrystal research as it enables the identification of a new diffraction pattern.^{1–10}

➤ Preparation of Mouth Dissolving Film:

The MDF using cocrystals as the basis was prepared using the solvent casting method. Firstly, HPMC E5 was hydrated with distilled water to make up the polymeric phase. Secondly, PEG 400 was introduced as plasticizer and crospovidone was mixed into the system through stirring. Thirdly, the prepared cocrystals of Modafinil and nicotinic acid were added slowly to the mixture while being stirred to make up a uniform casting solution. Finally, the solution was left to deaerate before being cast. The solution was casted on a 6cm diameter Petri dish and kept at room temperature for about 24 hours for drying. The resulting film was then carefully taken out and cut into pieces of 3x3cm size. Each of the films was intended to contain 50mg of Modafinil.^{14, 18, 27, 28, 38–40}

Choice of HPMC E5 was done because hydrophilic derivatives of cellulose are able to form a cohesive film matrix along with fast hydration property. Choice of PEG 400 was done in order to enhance flexibility of the system and minimize its brittleness. Crospovidone was added to facilitate fast water absorption and fragmentation of the matrix.^{17, 22, 38, 39}

➤ Design of Experiments:

The design chosen in this study was a Box-Behnken with three factors and three levels and this was done using Design Expert® software. The independent variables were HPMC E5 (A), PEG 400 (B) and crospovidone (C). These

variables were tested at low, mid and high levels. The number of experimental runs done was 15. Disintegration time was the variable chosen as a response and this was optimized. The response was modeled using a quadratic polynomial regression and analysis of variance (ANOVA) was used.^{51–53}

Table 2 DoE Factors and Level

Factor	Symbol	Low level	Middle level	High level
HPMC E5	A	200 mg	300 mg	400 mg
PEG 400	B	1 mL	2 mL	3 mL
Crospovidone	C	2 mg	4 mg	6 mg

Table 1 shows the 15 experiments and disintegration times recorded. The model adequacy has been evaluated in terms of model significance, lack of fit, adjusted R^2 , predicted R^2 , and adequate precision. The numerical optimization was done via a desirability function that minimizes the disintegration time while ensuring all the factors remain within the experimental range. Response surface methodology similar to the one used here has been used in other formulations.^{51–53}

➤ Evaluation of the Optimized Film:

Assessment of physical appearance, weight variation, folding endurance, surface pH, drug content, disintegration time, and in vitro dissolution was done on the optimized film. These parameters provide an account of the physical characteristics, mechanical properties, oral compatibility, dosing uniformity, and release characteristics of the MDFs.^{14–22}

Determination of weight variation was done by using three single 3×3 cm films. Weight was determined for each film using an analytical balance, and mean, standard deviation, and percent deviation from mean were calculated. Folding endurance was tested by folding the same film at the same place until a crack or break occurs in the film. No. of folds were noted. Surface pH determination was done after

moistening the film with a small amount of aqueous medium. Drug content was determined by dissolving single films and absorbance was measured at 259.5 nm. Disintegration time was determined for 3×3 cm film pieces in simulated saliva fluid at $37 \pm 0.5^\circ\text{C}$.

Dissolution studies were conducted using the USP type I basket apparatus, which had 900 mL of phosphate buffer pH 6.8 with a temperature of $37 \pm 0.5^\circ\text{C}$ and agitation speed of 50 rpm. A film made of 50 mg Modafinil was put into the basket. Dissolution samples were collected after 1, 2, 3, 4, 5, 6, 8 and 10 minutes, and each sample was immediately replaced by fresh dissolution media. Diluted samples were measured for their absorbance at 259.5 nm. The % release was computed using the calibration curve.^{54–58}

III. RESULTS

➤ Saturation Solubility of Modafinil And Cocrystal:

The aqueous solubility of the pure Modafinil was 0.714 mg/mL, while that of the Modafinil-nicotinic acid cocrystal was 4.003 mg/mL. This gave a solubility enhancement of $4.003/0.714 = 5.61$ fold, which is equivalent to a 460.5% increase in solubility compared to the parent drug. This indicates that the change in solid form significantly influenced its aqueous dissolution profile.

Table 3 Saturation Solubility

Sample	Apparent solubility (mg/mL)	Fold change vs Modafinil
Pure Modafinil	0.714	1.00
Modafinil–nicotinic acid cocrystal	4.003	5.61

The direction of change is in agreement with the previously published literature of Modafinil-nicotinic acid cocrystals, where the cocrystallization led to enhanced aqueous solubility and dissolution.³ Nevertheless, the numerical value from this study should be considered study specific due to the dependence of solubility on the medium of study, temperature, time for equilibration, form of the solid, physical properties of the solid, and methodology used for the determination of solubility.^{1–10}

➤ FTIR Characterization:

Characteristic absorption peaks of Modafinil FTIR were identified at 3309.25 cm^{-1} and 1686.44 cm^{-1} . On the other hand, the absorption peaks of the cocrystal included 3432.67 , 1686.44 , 1402.00 , 1322.93 , 1033.66 and 747.28 cm^{-1} . Changes in the N-H/O-H region and fingerprint region

indicated modifications in the intermolecular environment due to the presence of nicotinic acid.

Spectral results were conservatively analyzed. The retention of the main functional groups of Modafinil suggests that there is preservation of the main functionalities in the active pharmaceutical ingredient, but changes may occur due to hydrogen bonding or interaction between molecules. However, FTIR spectroscopy alone is not sufficient for defining crystal structure; therefore, the data were compared with PXRD and SEM results.

➤ SEM Morphology:

In the SEM test, it was observed that there were irregular and heterogeneously shaped particulates of varying size. These are signs that the material has undergone changes in its solid form post-cocrystallization process. However,

particle agglomeration does not indicate the formation of cocrystals; rather, these observations provide further evidence in support of the spectroscopic and diffraction tests.

➤ *PXRD Pattern:*

Sharp reflections were obtained from the PXRD pattern, meaning that the compound was a crystal. The experimentally

found reflections were present at 8.99°, 10.15°, 12.85°, 15.44°, 15.74°, 18.20°, 19.24°, 20.40°, 23.14°, 24.76°, ~25.91–25.92°, ~26.84–26.85°, 27.92°, 32.96°, 33.63°, 38.32° and 41.42° 2 θ . The strongest reflection was found to be at ~20.40° 2 θ with a value of 77,846.51 cps.

Table 4 PXRD Pattern

2 θ (°)	Intensity (cps)	Observation
8.99	9,236.71	Moderate
10.15	9,436.02	Moderate
12.85	9,443.08	Moderate
15.44	38,018.13	High
15.74	24,305.95	High
18.20	17,312.42	Moderate
19.24	26,428.55	High
20.40	77,846.51	Major peak
23.14	12,727.10	Moderate
24.76	21,463.04	High
25.91–25.92	~26,628–28,376	High
26.84–26.85	~29,267–29,416	High
27.92	15,168.96	Moderate
32.96	9,802.96	Moderate
33.63	6,030.75	Low–moderate
38.32	5,727.62	Low–moderate
41.42	5,449.36	Low–moderate

The highly reflective patterns clearly indicate that the prepared substance was still in the crystalline state. In light of the current study, the combination of the modified diffraction pattern, along with changes in the FTIR spectra, was taken to be evidence that suggested the formation of a new solid form.

The definitive identification of the crystal structure would need to be done by comparing with authentic reference patterns and structural analysis.^{1–10}

➤ *Box–Behnken Experimental Design and Model:*

Table 5 Box–Behnken Experimental Design and Model

Standard	Run	HPMC E5 (mg)	PEG 400 (mL)	Crospovidone (mg)	Disintegration (s)
15	1	300	2	4	36
9	2	300	1	2	48
13	3	300	2	4	37
11	4	300	1	6	39
3	5	200	3	4	27
2	6	400	1	4	56
4	7	400	3	4	44
10	8	300	3	2	40
6	9	400	2	4	49
1	10	200	1	4	35
14	11	300	2	4	36
8	12	400	2	6	40
12	13	300	3	6	29
7	14	200	2	6	25
5	15	200	2	2	34

The disintegration time was between 25 seconds to 56 seconds in the 15 experiments. The lowest disintegration time recorded was 25 seconds in Experiment 14 (200 mg HPMC E5, 2 mL PEG 400 and 6 mg crospovidone), while the highest disintegration time was 56 seconds in Experiment 6 (400 mg HPMC E5, 1 mL PEG 400 and 4 mg crospovidone).

It was found to be statistically significant (model $F = 56.53$, $p = 0.0002$). Linear terms for HPMC E5, PEG 400 and crospovidone were found to be significant ($p \leq 0.0002$), while the quadratic term for PEG 400 was also significant ($p = 0.0080$). Lack of fit test was not found to be significant ($F = 9.00$, $p = 0.1016$). Adjusted R^2 was 0.9728 and predicted R^2 was 0.8535, and the adequate precision was 27.3057. Overall,

these statistical results indicate that the response surface equation fitted the disintegration response well.

Coded factor regression equation was as follows:
Disintegration time = $36.33 + 8.50A - 4.75B - 4.75C - 1.00AB + 0.00AC - 0.50BC + 1.08A^2 + 3.08B^2 - 0.4167C^2$, where A, B and C stand for HPMC E5, PEG 400 and crospovidone

concentration codes respectively. Positive co-efficient of HPMC E5 shows that with increase in polymer level within design space range there is an increase in disintegration time while negative linear coefficients of PEG 400 and crospovidone show a tendency towards fast disintegration with their increasing levels.

Table 6 Box–Behnken Experimental Design and Model

Model statistic	Value
Model F-value	56.53
Model p-value	0.0002
R ²	0.9903
Adjusted R ²	0.9728
Predicted R ²	0.8535
Adequate precision	27.3057
Lack of fit p-value	0.1016
Coefficient of variation	3.63%

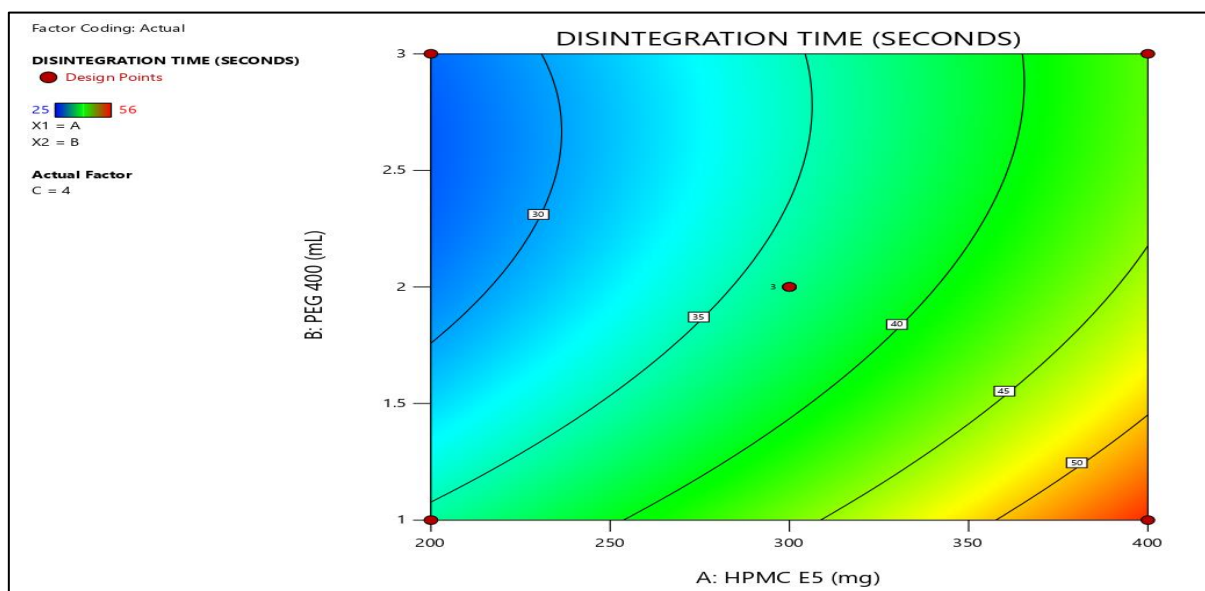


Fig 1 Model Staistic and Value

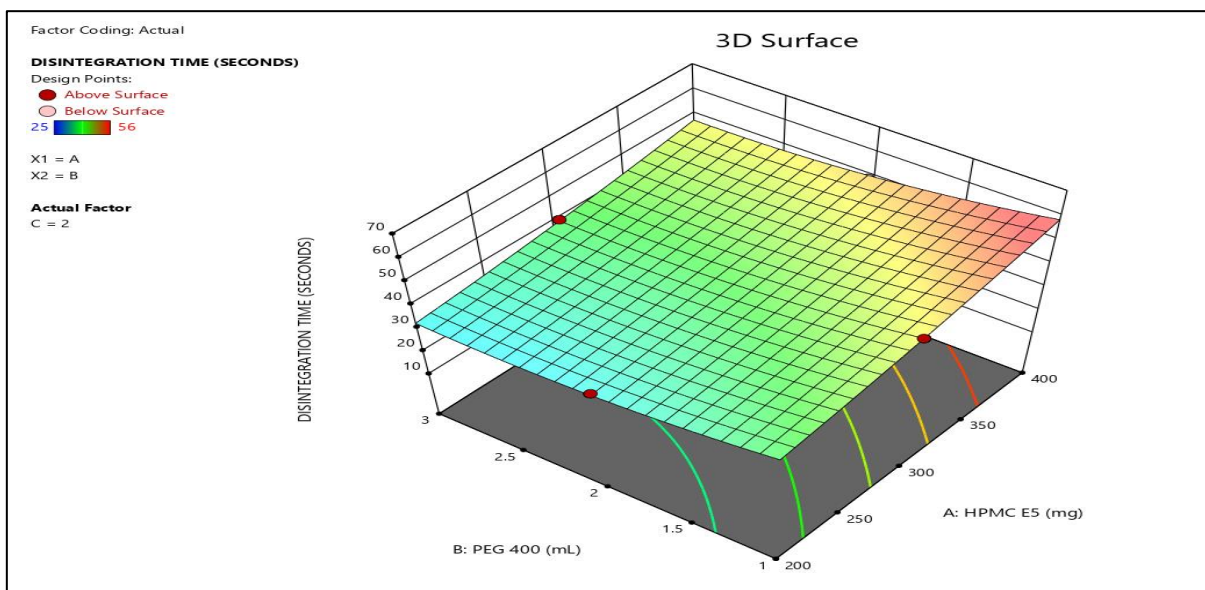


Fig 2 Graph of Disintegration Time and 3D Surface

➤ *Numerical Optimization:*

Optimization process involved numerical optimization of the desirability function where the response to be minimized is the disintegration time. The optimized film formulation consisted of 215.3 mg HPMC E5, 2.220 mL PEG 400, and 5.990 mg crospovidone. The predicted

disintegration time for the optimized film formulation by the model was 23.927 s with an overall desirability value of 1.000. The observed disintegration time for the experimentally developed optimized film fell within the 95% prediction intervals of 19.40 to 28.46 seconds.

Table 7 Numerical Optimization

Optimized factor/response	Predicted or selected value
HPMC E5	215.3 mg
PEG 400	2.220 mL
Crospovidone	5.990 mg
Predicted disintegration time	23.93 s
Experimental mean disintegration time	28.00 ± 1.00 s
95% prediction interval	19.40–28.46 s
Desirability	1.000

➤ *Physicochemical Evaluation of Optimized Film:*

Table 8 Physicochemical Evaluation of Optimized Film

Parameter	Result
Appearance	Smooth, uniform, transparent to slightly translucent; flexible; no visible cracks or air bubbles
Weight variation	328.23 ± 0.85 mg; maximum deviation 0.26%
Folding endurance	119.67 ± 1.53 folds
Surface Ph	6.73 ± 0.02
Drug content	99.72 ± 0.56% (49.86 ± 0.28 mg/film)
Disintegration time	28.00 ± 1.00 s

The optimal film appeared to be consistent in appearance without any presence of cracks or bubbles. Mean weight was 328.23 ± 0.85 mg with the highest percent deviation of 0.26% denoting a close range of weights between the three tested units. Folding endurance was 119.67 ± 1.53 folds, proving that the film could be folded repeatedly without any observable damage under the set test conditions. Mechanical properties are an important aspect of oral films due to their requirement during processing, administration and handling.^{14–22}

In addition, the surface pH of the film was 6.73 ± 0.02, which was quite close to the physiological level of the oral environment, and consequently did not present a possibility of irritation due to low or high pH level in vitro test conditions. The content of the drug was 99.72 ± 0.56%, equal

to 49.86 ± 0.28 mg Modafinil per film. This data shows that the drug was evenly distributed in the films. It is especially crucial in case of unit-dose oral films.^{15, 25}

Disintegration times of 27, 28, and 29 seconds respectively have been achieved for the optimized film with an average value of 28.00 ± 1.00 seconds. Quick disintegration is desirable for such a mouth-dissolving film since it would aid in quick disintegration of the matrix along with easy exposure of the entrapped drug into the aqueous environment. The obtained result is in conformity with the designed formulation where the inclusion of hydrophilic polymers like HPMC, PEG 400, and crospovidone was done.^{14–22, 38–40}

➤ *In-Vitro Drug Release:*

Table 9 In-Vitro Drug Release

Time (min)	Mean cumulative drug release (%)
0	0.00
1	26.28
2	38.43
3	50.64
4	60.52
5	69.25
6	76.83
8	84.45
10	90.91

It is evident from the graph that the MDF had a rapid and progressive release pattern. Cumulative mean release of 26.28%, 38.43%, 50.64%, 60.52%, 69.25%, 76.83%, 84.45%

and 90.91% were recorded at 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 6 minutes, 8 minutes and 10 minutes

respectively. There was very little variation between the three different trials carried out.

This rapid release may be considered as a result of multiple factors of the formulation design. First, the thin film shape creates a lot of surface to interact with the dissolution media. HPMC E5 is hydrophilic and it quickly swells, while PEG 400 changes properties of the polymers with regard to

their flexibility and wetting characteristics. Crospovidone helps with fast liquid absorption and disintegration of the film matrix. Besides, the cocrystal showed significantly increased solubility compared to Modafinil itself, which helps to overcome the limitation associated with dissolution of this drug.^{14–22, 26–37}

➤ Release-Kinetic Analysis:

Table 10 Release-Kinetic Analysis

Model	R ²	Interpretation
Zero-order	0.7493	Moderate/poor fit
First-order	0.9960	Best fit among tested models
Higuchi	0.9914	Good fit; diffusion contribution
Korsmeyer–Peppas	0.9918	Good fit; $n \approx 0.56$, anomalous/non-Fickian

The following four mathematical models were used to fit the dissolution data. For the zero-order model, the value of R² was found to be 0.7493, which indicates that the process was not a constant rate one. For the first-order model, the maximum value of R² was 0.9960, which was the highest for all the models considered. For the Higuchi model, R² was 0.9914.^{54–58}

For the Korsmeyer–Peppas equation, an R² value of 0.9918 and n value of 0.56 were obtained. In the current study, this n value is indicative of an anomalous drug delivery pattern, where more than one physical process is responsible for drug release, for example, the drug is delivered through diffusion along with polymer relaxation and swelling. The n value needs to be interpreted carefully since the equation provides more insight into an appropriate fraction of early drug release and also the current film may involve more than one mechanism of action.^{55–58}

IV. DISCUSSION

The key idea behind this study's formulation concept lies in combining solid-state engineering with a drug delivery dosage form. The process of cocrystal synthesis takes care of the physical and chemical behavior of the API, while the MDF technology focuses on administration and rapid release. This approach is fundamentally different from adding more of the regular excipient in the film since first, the API has to be transformed into a new crystalline structure. Pharmaceutical cocrystal research confirms that this approach can be used to modify the API properties without covalent modification of its molecular structure.^{1–10}

The factor of 5.61 in terms of increasing apparent aqueous solubility measured here is especially significant in view of the fact that rapid delivery performance of oral films is dependent on the capability of the drug to dissolve in a small amount of aqueous solution. If an insoluble crystalline API remains in its solid form, even though the film quickly disintegrates, then clearly rapid film disintegration is not enough to ensure rapid dissolution. From this study, it can be concluded that the formation of cocrystals and film formulation had a synergistic effect on each other.

The magnitude of solubility enhancement in this case is directionally consistent with prior Modafinil-nicotinic acid cocrystals studies. Ghosh et al. have identified a 1:1 ratio Modafinil-nicotinic acid cocrystal system and showed significant enhancement of solubility and dissolution along with improved pharmacokinetic behavior in their study.³ But this work should not be viewed as independent confirmation of increased bioavailability since no pharmacokinetics study has been done. This work adds to prior research by presenting an MDF based on a cocrystal system.

However, the results of FTIR analysis indicate that there is no derivatization of Modafinil, but only a modification in its molecular environment. The shift and broadening that have been seen in the N-H/O-H zone and also modifications in the bands in the fingerprint zone may be linked to interactions between molecules involving the active pharmaceutical ingredient and the coformer. These are consistent with crystal engineering through hydrogen bonding but do not define any specific supramolecular architecture through spectra alone.^{1, 2, 5, 6, 9}

PXRD spectrum in this study consists of many strong sharp peaks and a prominent peak at around 20.40° 2θ. The strength of the peak is 77,846.51 cps. The formation of a clear diffraction spectrum indicates the crystalline nature of the synthesized compound. For the design of pharmaceutical cocrystals, the most convincing proof can be generated by the integration of diffraction techniques with spectroscopic, thermal, and when needed, structural techniques. Therefore, the current FTIR/PXRD/SEM technique set should be considered as supporting characterization rather than crystal structure determination.^{1–10}

Additional evidence from DoE experiment results that the film response was sensitive to the proportions of chosen excipients was provided. HPMC E5 had a positive linear coefficient in the coded model, which indicates that an increased amount of the polymer contributed to the increased disintegration time in the considered range. Mechanistically, the effect can be explained by the denser formation of the hydrated matrix due to the increased proportion of film-forming polymers that disintegrate for a longer period of time. On the other hand, PEG 400 and crospovidone demonstrated negative linear coefficients that correspond to the role of

these substances in changing the properties of the hydrated matrix. The relationship between the excipients and mechanical/dissolution properties of the matrix is similar to those observed in the literature for oral films.^{17, 22, 29–40}

For the Box–Behnken design, there was a statistically significant effect with a very high adjusted R^2 of 0.9728. The lack-of-fit statistic, which was found to be 0.1016, was not statistically significant and thus implied that the quadratic model was a good fit to the response surface. The predicted R^2 of 0.8535 is smaller than the adjusted R^2 but is still positive, and thus provides reasonable evidence in favor of predictive power. The adequate precision was found to be 27.3057 and thus much larger than the recommended value of 4.^{51–53}

Optimized mixture composition was derived from the response surface rather than just the formula that had the lowest observed disintegration time from the first 15 experiments. In this regard, the optimization process using numerical optimization method yielded the formula consisting of 215.3 mg HPMC E5, 2.220 mL PEG 400 and 5.990 mg crospovidone, which produced a predicted disintegration time of 23.93 s and desirability of 1.000. The experimentally obtained mean value of 28.00 ± 1.00 s falls within the 95% prediction interval of 19.40–28.46 s. It confirms the ability to apply the model for the selection of a suitable formula within the tested design space, as well as shows the normal deviation of the model prediction from an independent experimental batch.

From the optimized film results, the low average weight and minimal deviation of weight imply excellent consistency of the cast film based on the reported preparation method. The high folding endurance also implies that the film is not brittle. Such characteristics are important because oral films which hydrate quickly but easily break while being cut, packed, or handled are not practically useful. In literature dealing with oral films, there is a need for achieving a compromise between mechanical strength and fast hydration/dissolution and not focusing on one aspect.^{14–22, 25, 27}

The near neutral surface pH value of 6.73 ± 0.02 is also an additional in-vitro property. The pH test does not serve as a substitute for an irritation test on mucous membrane; however, it shows that the surface of the film does not have any highly acidic or basic properties during the test procedure. Similarly, the drug content value of $99.72 \pm 0.56\%$ also shows good homogeneity amongst the films. This is particularly important in the case of oral films as they provide a unit dose of the drug.

Dissolution behavior is thus the key performance measure that can be attributed to the developed formulation. More than a quarter of the drug is dissolved within 1 min, whereas 90.91% of the drug is dissolved in 10 min based on the USP Type I conditions. The dissolution profile is characteristic of a fast-dissolving film. However, comparisons with other oral films in the literature must be conducted with caution due to the variability among different studies.^{14–22, 26–37}

Upon analyzing the data for drug release, it was seen that first-order kinetics gave the best correlation among all four models used. The high Higuchi R^2 and Korsmeyer-Peppas value of n of about 0.56 support the involvement of diffusion and polymer relaxation or swelling in drug release. As this film swells and then breaks down during the whole process of dissolution rather than maintaining a constant matrix form, these mathematical models can only be considered as descriptive.^{54–58}

The strategy of formulation has further implications for its development. The oral films are susceptible to residual moisture and humidity, as well as the ratio of polymers to plasticizers. The process of manufacturing may influence the physical stability and in vitro biopharmaceutical performance.^{15, 17–22, 27, 40} As such, the current optimized formula should rather be seen as a development formula, which needs to undergo stability testing according to ICH guidelines for moisture barrier packaging, as well as the physical and chemical changes in storage.

Solvent casting is appealing from the manufacturing point of view in the laboratory due to the ability to easily control the composition and thickness of the resulting films. However, for scale-up it becomes necessary to control the viscosity of the casting solution, drying time, humidity, substrate properties, and the presence of residual solvent. The recent scientific publications compare solvent casting to other manufacturing techniques.^{27, 40} As such, this current study offers only a formulation basis rather than an actual manufacturing process.

Among the most significant advantages of the research can be considered the use of cocrystal characterization, optimization using the DoE approach, and comprehensive in-vitro testing of the optimized film. The main weaknesses of the research also need to be mentioned. The specific conditions of cocrystal isolation and drying need to be completed based on the lab report; the sensory/taste testing was not carried out; the stability of the developed formulation was not studied; the comparison of dissolution between pure Modafinil and cocrystal film was not done; and no pharmacokinetic, permeability, or clinical studies were conducted.

Future research needs to involve complete solid-state characterization by using an appropriate reference pattern along with DSC/TGA or single crystal analysis when required, followed by stability studies with regard to controlled temperature and humidity conditions, moisture content studies, and mechanical property determination involving tensile strength and elongation; taste and mouth feel evaluation; dissolution comparison to a suitable Modafinil reference; and in vivo pharmacokinetic study. It is important to carry out more research to see if there is any biopharmaceutical advantage obtained from the above-mentioned in vitro studies. However, considering the clinical significance of Modafinil in treating narcolepsy based on the existing literature, the current formulation study should be limited strictly to scientific facts obtained from the experiment.^{11–13, 41–50}

V. CONCLUSION

Modafinil-Nicotinic Acid cocrystal Mouth Dissolving Film (MDMF) was successfully prepared and optimized via solvent casting method. Cocrystal formulation had a 5.61 times higher apparent solubility than pure drug, 4.003 mg/mL versus 0.714 mg/mL. FTIR, PXRD and SEM analysis supported that there was modification in the solid state properties of Modafinil.

The optimized formulation consisted of 215.3 mg HPMC E5, 2.220 mL PEG 400 and 5.990 mg croscopovidone. This formulation showed satisfactory appearance, average weight of 328.23 ± 0.85 mg, 119.67 ± 1.53 folds of folding endurance, average pH value on the surface of 6.73 ± 0.02 and content of drug of 99.72 ± 0.56 %. The disintegration time of film was 28.00 ± 1.00 seconds, and under the conditions of dissolution test, 90.91% of the drug was released after 10 minutes. The first order kinetics model provided the highest R^2 , and the exponent of Korsmeyer-Peppas equation pointed out anomalous/non-Fickian release.

In conclusion, the current investigation supports the possibility of the combination of pharmaceutical cocrystal technology with mouth dissolving film technology. However, further studies in solid state, stability, sensory, comparison, biopharmaceutical and clinical are needed before reaching any conclusions on the performance, bioavailability and efficacy of the product.

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